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REVIEW ARTICLE

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Testosterone replacement therapy

Arcangelo Barbonetti | Settimio D'Andrea | Sandro Francavilla

Andrology Unit, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

Correspondence
Arcangelo Barbonetti, Andrology Unit, Department of Life, Health and Environmental Sciences, University of L'Aquila, Piazzale Tommasi 1, 67110, L'Aquila, Italy.
Email: arcangelo.barbonetti@univaq.it

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Abstract

Background: The aim of testosterone replacement therapy (TRT) is to improve symptoms and signs of testosterone deficiency including decreased libido, erectile dysfunction, depressed mood, anaemia, loss of muscle and bone mass, by increasing serum testosterone levels to physiologic range. TRT has been used in the last 70 years, and overtime, numerous preparations and formulations have been developed to improve pharmacokinetics (PKs) and patient compliance. The routes of delivery approved for use in the Western world include buccal, nasal, subdermal, transdermal and intramuscular (IM).

Objectives: The aim of this narrative review was to describe and compare all available and approved testosterone preparations according to pharmacology, PKs and adverse effects.

Materials and Methods: We have performed an extensive PubMed review of the literature on TRT in clinical practice. Contraindications and monitoring of TRT were analyzed by comparing available guidelines released in the last five years. We provide a review of advantages and disadvantages of different modalities of TRT and how to monitor treatment to minimize the risks.

Results: TRT is associated with multiple benefits highly relevant to the patient. However, the recommendations given in different guidelines on TRT are based on data from a limited number of randomized controlled trials (RCTs), as well as non-randomized clinical studies and observational studies. This is the case for the safety of a long-term TRT in late-onset hypogonadism (LOH). No evidence is provided indeed on the effects of TRT on endpoints such as deterioration of heart failure suggesting a cautious approach to T replacement in older men with a history of heart failure.

Conclusion: Clinicians must consider the unique characteristics of each patient and make the necessary adjustments in the management of LOH in order to provide the safest and most beneficial results.

KEYWORDS

androgen deficiency, hormonal therapy, late-onset hypogonadism, testosterone

1 | INTRODUCTION

The management of testosterone (T) deficiency aims to induce and maintain secondary sex characteristics and correct symptoms of T deficiency.[1] As late-onset hypogonadism (LOH) is considered functional in the majority of cases, the first-line treatment should remove the causing conditions such as treating obesity, type 2 diabetes (T2DM) or metabolic syndrome (MetS), with the aim to increase serum T levels according to some authors.[2] Weight loss achieved through low-caloric diet or bariatric surgery[3] and

moderate-intense aerobic exercise in obese/overweight men[4,5] is associated with an increased level of total (*t*) T and calculated free (cf) T. However, compliance for health lifestyle measures is low and their efficacy in improving LOH-related symptoms is still not well demonstrated.[6] A low level of T may contribute to fatigue or low motivation to undertake health lifestyle measures, supporting a possible still not-demonstrated benefit of T treatment in men with LOH to increase motivation to a healthier lifestyle.[2] T treatment may also augment the benefits of lifestyle interventions: T treatment of middle-aged obese men with low T level subjected to a weight loss programme prevented the diet-associated loss of lean mass, while maintaining the loss of body fat.[7] T treatment should be considered to correct symptoms of T deficiency, while restoring T serum levels.

1.1 | Testosterone preparations

Although available in the last eight decades for clinical use, only from the 1990s preparations of T resulting in physiological serum levels of the androgen entered and progressively expanded the market.[8] According to WHO 'Guidelines for the use of androgens in men',[9] the ideal androgen for replacement therapy should be safe, effective in correcting symptoms and consequences of T deficiency, inexpensive, of easy administration, with good release profile, ensuring reproducible circulating levels of T and prolonged duration of action, flexible in dosing and able to maintain normal physiologic levels of T. Preparations of natural T should be used for T replacement therapy (TRT) to guarantee total body effects of the steroid, which requires aromatization to estradiol (E) and 5-alpha reduction to dihydrotestosterone (DHT). Natural T only is converted to E and DHT at physiological rates, thus representing the first choice for TRT. The ideal T preparation should also replace T to physiologic levels to avoid excessive fluctuations.[8] A number of routes of delivery have been used in TRT over the years, but none of them fully satisfies the WHO definition of an ideal treatment[9] (Table 1).

1.1.1 | Oral testosterone

Natural T is rapidly inactivated by first-pass hepatic metabolism, making oral therapy an ineffective means of delivering unmodified T.[10] However, esterification at carbon 17-beta yields T undecanoate, preferentially absorbed into the lymphatic system when taken orally, and hydrolysed in vivo to yield native T. The efficacy of oral T undecanoate is limited because of unreliable oral bioavailability, fluctuating serum levels and short half-life, necessitating 3-4 40-mg capsules daily for full TRT[11] taken with meals to improve absorption.[12] Reported gastrointestinal and liver adverse effects[13] precluded the marketing of oral T undecanoate for TRT in the USA. Other oral T derivatives include 17-alpha-methyltestosterone and fluoxymesterolone, which are associated with hepatotoxicity[14,15] and have disappeared from the market in Europe. The DHT derivative mesterolone has only partial androgenicity[16] and is therefore unsuited for TRT.

1.1.2 | Buccal testosterone

The buccal administration for TRT was introduced in 2003 (Striant, Actient Pharmaceuticals LLC), but it is no more available in Europe. Mucoadhesive tablets applied to the gums of the mouth provide continuous release of T directly into the systemic circulation bypassing the liver, with resultant increasing bioavailability. Thirty mg T/tablet applied every 12 hours ensures circulating T peak levels within 10-12 hours of initial administration and reach steady state within 24 hours. Serum DHT levels increase parallel to serum T into the normal range. T levels drop to baseline 4-6 hours after removal of the tablet.[17-20] Buccal T was well tolerated in clinical trials lasting up to 12 months, with the most common adverse effect being gum-related and approximately 18% of subjects reported irritation, inflammation, gingivitis or dysgeusia[21] However, the effectiveness of buccal T to correct symptoms of T deficiency was not defined and few men with LOH were included in trials.[19,20]

1.1.3 | Nasal testosterone

A nasal gel formulation was approved in May 2014 by USA FDA for TRT (Natesto™, Endo Pharmaceuticals, and Malvern), and it is available in 15 European countries including Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Poland, Slovakia, Spain, Sweden and the UK. The product, self-administer into the nostrils, is based on a metered-dose pump applicator. Each pump delivers 5.5 mg of T, with the recommended dose of two pumps (one actuation per nostril) three times a day, for a total daily dose of 33 mg.[22] Absorption occurs through the nasal mucosa avoiding first-pass metabolism, and the peak concentration (C_{max}) is reached within 40 minutes.[23] Two open-label phase III trials assessed nasal T use in hypogonadal men (T < 300 ng/dL) in the USA[24] and in Canada[25] In 306 hypogonadal men treated for 90 days, 90% achieved serum T concentrations within the normal physiological range with an average level of 421 mg/dL, while 10% of patients remained at subtherapeutic concentration,mean DHT and estradiol C_{avg} levels were in the normal range.[24] Erectile function, mood, body composition and bone mineral density (BMD) improved from baseline. Treatment was generally well tolerated, but nine subjects (2.9%) discontinued the study because of drug-related adverse events including an increased level of prostate-specific antigen (PSA), headache, rhinorrhoea, nosebleed, nasal discomfort, upper respiratory tract infections, sinusitis, bronchitis and nasal scab. The study lacked a placebo or an active comparator control. The use of b.i.d. dosing of nasal gel in hypogonadal men to achieve serum T in a therapeutic range did not reduce the concentration of LH and of FSH to levels below the normal range,[26,27] and maintained sperm production.[27]

TABLE 1 Testosterone preparations

Formulation	Delivery system	Doses	Starting doses	Application site	Dose range	Advantages	Disadvantages	Testosterone levels monitoring
Oral								
Testosterone undecanoate	Capsule	40 mg/capsule	3-4 capsules daily	Oral intake	120-240 mg daily	Oral convenience; modifiable dosage; quick reversal	Fluctuating T serum level; short half-life; multiple administrations each day; taken with fatty food	Within 4 wk, 3-5 h after ingestion with fat-containing meal
Testosterone	Buccal system	30 mg/system	1 system/12 h	Upper gums above incisive	60 mg daily	Self-administration; quick reversal	Skin irritation; multiple administrations daily	4-12 wk after initiation, before or after application
Intranasal								
Testosterone nasal gel	Pump bottle	5.5 mg/pump	1 pump each nostril every 8-12 h	Nostril	22-33 mg daily	Self-administration; quick reversal; only transient inhibition of HPG axis	Multiple administrations daily; nostril irritation; contraindicated in patients with nasal diseases	Within 4 wk, 4 h after application
Pellet								
Testosterone pellet	Pellet	75 mg/pellet	10 pellets	Subcutaneous	6-12 pellets every 3-6 mo	Lower administration frequency; no risk of secondary transfer	Surgical incision; local haematoma; spontaneous extrusion	At the end of dosing interval
Topic								
Testosterone Transdermal	Patch	2 or 4 mg/patch	1 patch of 4 mg daily	Transdermal (back, abdomen, upper arms or thighs)	2-6 mg daily	Self-administration; easy application, quick reversal	Daily or 3 times a day administration; skin irritation	2 wk after initiation, morning after evening application
Testosterone gel 1%	Packet; tube; pump	50 mg/packet; 50 mg/tube; 12.5 mg/actuation	1 packet/d; 1 tube/d; 4 actuations/d	Shoulders, upper arms or abdomen	25-100 mg daily	Self-administration; quick reversal	Daily administration; skin irritation; second transfer; suboptimal response	14-28 d after initiation, prior to the morning dose
Testosterone gel 1.62%	Packet; pump	20.25 or 40.5 mg/packet; 20.25 mg/actuation	1 packet of 20.5 mg daily; 2 actuations/d	Shoulders, upper arms or abdomen	20.25-81 mg daily	Self-administration; quick reversal	Daily administration; skin irritation; second transfer; suboptimal response	14-28 d after initiation, prior to the morning dose

(Continues)

TABLE 1 (Continued)

Formulation	Delivery system	Doses	Starting doses	Application site	Dose range	Advantages	Disadvantages	Testosterone levels monitoring
Testosterone gel 2%	Pump	10 mg/actuation; 23 mg/actuation	4 actuations/d (for 10 mg pump); 1 actuation/d (for 23 mg pump)	Shoulders, upper arms or thighs	10-70 mg daily (for 10 mg pump); 23 to 69 mg daily (for 23 mg pump)	Self-administration; quick reversal; less serum testosterone level fluctuation	Daily administration; skin irritation; second transfer	14 d after initiation, 2-4 h after actuation
Testosterone solution 2%	Pump	30 mg/actuation	1 actuation for each axilla	Axilla	30-120 mg daily	Quick reversal; good skin tolerability	Suboptimal response; secondary transfer	14 d after initiation, 2 to 8 h after dose application
Intramuscular								
Testosterone cypionate	Injection	Vial 100 mg/mL; vial 200 mg/mL	1 vial 100 mg/wk or 1 vial 200 mg/2 wk	Gluteal muscle or lateral upper thigh	50-200 mg every 7 or 14 d	Affordable cost; short acting that allows drug withdrawal in case of side effects	Multiple injections; fluctuation in serum testosterone levels	1 wk after injection
Testosterone enanthate	Injection	Vial 100 mg/mL vial 200 mg/mL; vial 250 mg/mL	1 vial every 2 or 3 wk	Gluteal muscle or lateral upper thigh	100-300 mg every 2 or 3 wk	Affordable cost; short acting that allows drug withdrawal in case of side effects	Multiple injections; fluctuation in serum testosterone levels	1 wk after injection
Testosterone propionate	Injection	Vial 100 mg/mL	½ vial every 3-5 d	Gluteal muscle or lateral upper thigh	NS	Affordable cost; short acting that allows drug withdrawal in case of side effects	Multiple injections; fluctuation in serum testosterone levels	NS
Testosterone ester combinations	Injection	Vial 250 mg/mL	1 vial every 3 wk	Gluteal muscle or lateral upper thigh	NS	Affordable cost; short acting that allows drug withdrawal in case of side effects	Multiple injections; fluctuation in serum testosterone levels	NS
Testosterone undecanoate	Injection	Vial 1000 mg/4 mL; vial 750 mg/3 mL	1 vial 1000 mg at weeks 0, 6 and every 10 to 14 wk; 1 vial 750 mg at weeks 0, 4 and every 10 wk	Gluteal muscle	1000 mg; 750 mg	Steady-state serum testosterone levels without fluctuation, few injections/year	Intramuscular injection; high cost, long acting that cannot allow drug withdrawal in case of side effects	Prior to each subsequent injection

Abbreviations: HPG, hypothalamic-pituitary-gonadal axis; NS, not specified.

This is related to a transient inhibition of hypothalamic-pituitary-gonadal (HPG) axis with endogenous testosterone returning to pre-dose levels 4-6 hours after exogenous T dosing.[26] This provides a form of T replacement that does not suppress HPG axis and thus preserves spermatogenesis for fertility. T nasal gel is another non-invasive alternative with simple administration, lower dose levels because of efficient absorption and avoidance of first-pass metabolism,[23,28] and no concern for secondary transfer. T nasal gel was not specifically used in subjects with LOH.

1.1.4 | Subdermal testosterone implants

T pellet implants were the first effective formulation for TRT, developed in the 1940s.[29] T pellets of a crystalline preparation created through high-temperature moulding are designed for consistent and prolonged-release.[30] Absorption occurs through uniform erosion of the pellet's surface. Dosing varies on patient age and diagnosis and is adjusted to the patient's response and the manifestation of adverse reactions. General dosing recommendations are 150-450 mg implanted subdermally in the hip area or another fatty area at 3- to 6-month intervals.[30] T pellets are available in 12.5, 25, 37.5, 50 and 75 mg pellets. In a randomized, crossover clinical study, 43 men with primary or secondary hypogonadism received each of the following regimens: 100 mg × 6 pellets, 200 mg × 3 pellets or 200 mg × 6 pellets.[30] Each regimen was separated by at least 6 months, and the next one was not initiated until T decreased to hypogonadal levels. T serum levels peaked at approximately one month and were maintained in the normal range for 4-5 months with either 600 mg dose or for 6 months with the 1200 mg dose. The estimated half-life was 2.5 months. The most common adverse event is pellet extrusion, with an incidence of 8.5% reported in a large retrospective analysis of 973 implant procedures using fused crystalline T implants performed in 221 subjects.[31] Other rare adverse events included site infections, bleeding or fibrosis in the site of implants, and the overall continuation rate was 92.7%.[31] The clinical efficacy and patient-reported outcomes were assessed in a small group of 15 men with T deficiency (T < 300 ng/dL) who received implantation of 12 T pellets (900 mg) in an open-label study.[32] Male functioning (IIEF score), depression (CES-D total score) and androgen deficiency symptoms (qADAM total score) improved from baseline. Most patients were 'very satisfied' (40.0%) or 'quite satisfied' (26.7%) with treatment. Pellet extrusion and polycythaemia occurred in one patient each. Potential advantages of pellet usage include the infrequency of dosing, guaranteed compliance and lack of transference. However, the administration is invasive requiring skin incision and local anaesthesia. There are also concerns regarding pellet removal for patients experiencing T-related side effects such as increased haematocrit (>50%). Accordingly, its use is not indicated in LOH. A retrospective analysis of 228 subjects reported an estimated rate of increased haematocrit at 6 months of 10.4%, at 12 months of 17.3% and at 24 months of 30.2%.[33] BMI, but not haematocrit at baseline, age and smoking status were significantly associated with increased polycythaemia rates.[33] The use of T implants is not substantially reported in men with LOH, and it is available in the USA and Australia only.

1.1.5 | Transdermal testosterone

Testosterone patches

T patches applied to the scrotal skin were the first T transdermal (TTD) preparation for clinical use,[34,35] However, although physiological serum levels could be achieved,[36] application to the hair rich scrotal area was not well accepted and favoured the development of subsequent non-scrotal systems that replaced scrotal patches. Non-scrotal transdermal patches were approved by USA FDA in 1995. The patches are available in 2 or 4 mg/d formulations. The recommended starting dose is one 4 mg/d patch every 24 hours applied nightly to the back, abdomen, upper arms or thighs.[37] Sites should be rotated and not re-used for 7 days. Two weeks after initiation of therapy, a serum T level should be measured (early morning after patch application the night before). Levels < 400 ng/dL require a dose escalation to 6 mg/d, while levels > 930 ng/dL should require a dose reduction to 2 mg/d.[22] The pharmacokinetics, efficacy and safety of the Androderm system and intramuscular (IM) T enanthate injections for the treatment of male hypogonadism were compared in a 24-week multicentre, randomized, parallel-group study.[38] Sixty-six adult hypogonadal men (22-65 years of age) were withdrawn from prior IM treatment for 4-6 weeks and then randomly assigned to treatment with TTD (two 2.5-mg systems applied nightly) or IM (200 mg injected every 2 weeks). TTD treatment produced circadian variations in the levels of total bioavailable T, DHT and E within the normal physiological ranges. IM treatment, on the contrary, produced supraphysiological levels of T, bioavailable T and E (but not DHT) for several days after each injection. Mean morning sex hormone levels were within the normal range in greater proportions of TTD patients (range: 77%-100%) than IM patients (range: 19%-84%). Both treatments maintained sexual function and mood at the prior treatment levels. PSA levels, prostate volumes, and lipid and serum chemistry parameters were comparable in both treatment groups. Transient skin mild-to-moderate erythema or pruritus from the patches was reported by 60% of the TTD patients, but only three patients (9%) discontinued treatment because of skin reactions. IM treatment was associated with significantly more abnormal haematocrit elevations (43.8% of patients) compared with TTD treatment (15.4%). The approximate half-life of TTD is 1.3 hours, and hypogonadal concentrations are achieved within 24 hours of patch removal.[39] The efficacy of the transdermal patch is often limited by lack of adherence or discontinuation because of skin reactions. This is because of permeation enhancers included in the transdermal system that are necessary to increase absorption.[8] Size and the intrusive nature of the patches is also a concern. Advantages of transdermal patch use include non-invasive easy application, quick reversal after removal and normal circadian

pattern of T. The risk of transference to others is not a concern, and however, the patches were discontinued in Europe.

Testosterone gel/liquid solutions

Several T gels and liquids were developed for transdermal TRT since early 2000. Because of the concern for T gel or liquid being transferred to females and children who come into contact with a patient's skin after use, these formulations have received a USA Boxed Warning to be included in the package slip.[40] Patients should be reminded to wash their hands after application and to avoid skin contact with others. Recommended sites of application for these agents are areas that will be covered by clothing to minimize transfer. A 2% T gel comes in a metered-dose dispenser that includes a hands-free cap applicator for precise dispensing and application. This avoids exposure to the hands, which minimizes the risk of transfer.[41] USA Boxed Warning was hence eliminated for this product. The potential advantages of T transdermal gels and liquids include ease of application, less skin irritation than patches and more consistent serum T levels than other formulations, such as IM T.[22] Different brands are available in 1%, 1.62% and 2% solutions of native T (Table 1), representing the most popular formulations of TRT in LOH.[6]

Dosage forms for the 1% concentration include unit-dose packets that contain either 25 mg/2.5 g or 50 mg/5 g of T, or alternatively, a multi-dose metered pump that provides 12.5 mg of T per actuation. The recommended starting dose is 50 mg applied topically once daily in the morning. Areas for application include the shoulders, upper arms or abdomen.[42] Based on serum T levels, the dose can be increased in 25 mg increments up to 100 mg of T daily. The 1.62% concentration is also available in a metered-dose pump and unit-dose packets in the USA market only. The metered-dose pump provides 20.25 mg of T per actuation, while the unit-dose packets contain either 20.25 mg/1.25 g or 40.5 mg/2.5 g of T. The recommended starting dose of 1.62% gel is 40.5 mg applied topically once daily in the morning. Serum T levels should be measured 14 and 28 days after initiation prior to the morning dose. Dose adjustments between 20.25 and 81 mg increments are recommended for levels outside the range of 350-750 ng/dL.[22] The pharmacokinetic effects of 1% T gel on serum T levels were evaluated in a randomized, parallel study that compared gel (50 mg/d or 100 mg/d) and patches (5 mg/d) for 3 months in 227 hypogonadal men.[43] On day one, serum T was within physiological range in both gel groups, reaching a C_{max} after 16-22 hours, respectively, in the 100 mg/d and in the 50 mg/d group. The 1% transdermal T gel was able to increase serum T to the upper range of normal after a few days of use and maintained levels between mid to upper range of normal with repeated daily use, without relevant variation over 24 hours, with a compliance rate of approximately 90%.[43] The most common adverse effect associated with 1% T gel included application site reaction that very rarely required discontinuation after 12-month treatment in a 48-month multicentre trial of 163 hypogonadal men (19-68 years old).[19,20] Five subjects discontinued treatment because the PSA level increased above the predetermined critical value of 5.5 ng/dL; one patient discontinued treatment because of erythema and punctate rash. Gynaecomastia was observed in eight subjects during treatment (4.9%). Acne was noted in 12 subjects (7.4%).[19,20] The pharmacokinetic profile and the dose proportionality observed after T gel application indicate that this transdermal delivery system may provide dose flexibility and serum T levels from the low to the high normal adult male range.[43] Comparative analysis of the pharmacokinetic profile of 1% T gel (50 mg/d or 100 mg/d) and T patches (5 mg/d) showed accumulation ratios higher in both T gel dosage groups, consistent with the longer-lasting elevations of serum T indicating a longer effective half-life than the T patch, assuring T levels from the low to the high normal adult male range,[43] as well as less fluctuation in T levels over 24 hours.[44] DHT and estradiol concentration was maintained in the normal adult male range.[43]

A 2% T gel is available as a metered-dose pump delivering 10 mg[46] or more recently, 23 mg[41] of T per actuation. The recommended starting dose is 40 mg (four actuations)[46] or 23 mg[41] applied once daily in the morning to the thighs[46] or to the shoulder and/or upper arm.[41] The dose can be adjusted based on serum levels measured two hours after morning application 14 days after initiation or adjustments,[46] or 4 hours post-dosing on days 14, 35 and 56 from initiation.[41] Dosing range is 10-70 mg/d[46] or 23-69 mg/d.[41] The effect of 2% gel on serum T levels was evaluated in a multicentre, open-label study of 129 men with hypogonadism.[46] The subjects applied 2% gel initially at 40 mg/d for 90 days. Dose adjustments between 10 and 70 mg/d were allowed subsequently. On day 90, the C_{avg} was 438 ± 162 ng/dL with a mean C_{max} of 827 ± 356 ng/dL and 77.5% of patients had C_{avg} within the normal range at 90 days. Additionally, the 24-hour pharmacokinetic profile showed T peaked 2-4 hours after application with low risk for supraphysiologic T levels and were maintained in the physiological lower range at 24 hours.[46] The most common adverse events that patients experienced probably related to the study medication were skin reactions (16.1%); 79% were mild and the remainder were moderate. Only two patients discontinued therapy for skin-related issues.[46] Similar results were reported in a phase 3 open-label non-comparator study in 139 hypogonadal men receiving 2% T gel 23 mg/d.[45] The dose was uptitrated to 46 mg/d after 2 weeks and to 69 mg/d to reach a T concentration (C_{avg}) between 300 and 1.050 ng/dL on day 90. 76.1% of subjects meet C_{avg} criteria with a favourable local skin tolerability profile.[45]

A 2% solution of T is also available in a metered-dose pump that provides 30 mg of T per actuation. The solution is applied to the underarms using the provided applicator. The suggested starting dose of 60 mg is applied once daily in the morning, and it is adjusted according to serum T levels measured 14 days after initiation, 2-8 hours after dose application. The dose can be adjusted in 30 mg increments up to a maximum of 120 mg.[22] A multicentre, open-label study in men with documented androgen deficiency was conducted to evaluate the effects of 2% T solution at a dose of 60 mg/d, adjusted 45 and 90 days after initiation.[47] By day 120, 84.1% of patients had a C_{avg} within the normal range (300-1050 ng/mL). Adverse events included application site irritation (7%) or erythema (5%), headache (5%) and increased haematocrit (4%). A same treatment in hypogonadal men with suboptimal response to T gel reported a

normal T level (300-1050 ng/mL) after 2 weeks of treatment in 70% of patients.[48] In conclusion, transdermal T preparations show a pharmacokinetic very close to ideal substitution and upon removal T is immediately eliminated so that these preparations are particularly preferred for substitution to quickly treat side effects.[8] Transdermal T has been extensively used in hypogonadal men including in case of LOH, showing a beneficial effect on sexual desire, erectile function and sexual satisfaction,[49,50] (see specific chapter on the effect of TRT on sexual function).

1.1.6 | Intramuscular injectable testosterone

Preparations of IM T have been used since the 1950s. Natural T has an approximate half-life of 10 minutes when injected. Current formulations have a prolonged half-life through the esterification of the 17β carbon of natural T.[11] Esterification increases the solubility of T in oil, which allows for slower release once injected into the muscle. T esters are not biologically active until the ester group is cleaved off. The IM preparations approved for the treatment are T cypionate (TC), T enanthate (TE), T propionate (TP) (not approved in the USA for TRT in hypogonadism) and T undecanoate (TU). The absorption kinetics of different T esters increase when the esterified fatty acids to the 17β position of T have a longer chain,in addition, pharmacokinetics are also influenced by the oily vehicle, the injection site and the injection volume.[11] TU has the longest carbon side chain, consisting of 11 carbon atoms compared to seven and eight for TC and TE, respectively, which accounts for its longer duration of action. A disadvantage of these formulations is the necessity for IM injection. Serum T levels should be measured one week after receiving a dose of TC or TE, targeting a therapeutic level of 400-700 ng/dL. For TU, levels should be measured prior to each subsequent injection. Although the injectable preparations are generally considered very safe, pulmonary oil micro-embolism (POME), clinically characterized by brief respiratory symptoms including cough, urge to cough and dyspnoea immediately after the injection, has been observed after injection of TE in castor oil at a rate of 1.5% of injections.[51] POME may rarely occur also after IM injection of TU, requiring sometimes treatment with epinephrine.[8]

Testosterone propionate

Single-dose pharmacokinetics of 50 mg TP after IM injection resulted in maximal T levels in the supraphysiological range shortly after injection and T levels below the normal range following day 2 after injection. Therefore, the administration of TP is not suitable for substitution therapy of male hypogonadism because of its short-term kinetics resulting in wide fluctuations of T serum concentrations and maximal injection intervals of three days for the 50 mg dose.[11]

Testosterone cypionate

TC is supplied in 100 mg/mL (10 mL vial) and 200 mg/mL (1 and 10 mL vials) concentrations, prepared in cottonseed oil. The recommended starting dose for male hypogonadism is either 75-100 mg IM weekly or 150-200 mg IM every 2 weeks,[1] 50-200 mg every 1-2 weeks[52] or 200 mg every 2-3 weeks.[53] A clinical study of replacement therapy with single-dose administration of 200 mg of TC in 11 hypogonadal patients[54] showed a large fluctuation in serum T over a 2-week period illustrating the non-ideal kinetics of TC IM injections.[22] The mean C_{max} was supratherapeutic (1112 ± 297 ng/dL) and occurred between days four and five post-injection. After day 5, T levels declined, and by day 14, the mean C_{avg} approached 400 ng/dL. The fluctuation in serum T levels can result in mood swings or changes in libido, while common adverse effects with TC use are local inflammation and pain at the site of injection.[22]

Testosterone enanthate

TE is available in 100, 200 mg/mL or 250 mg/mL prepared in sesame oil. The recommended starting dose for TE is the same as TC in all guidelines. The effect of varying doses of TE on serum T was evaluated in 23 males with primary hypogonadism.[55] The average C_{max} peaked above 1200 ng/dL 24 hours and 48 hours, respectively, after the last dose of 100 mg and 200 mg and declined to slightly above 600 ng/dL after 1 week and 2 weeks, respectively. The average C_{max} peaked above 1200 ng/dL within 36-48 hours after the last dose of 300 and 400 mg. For both groups, levels plateaued below the therapeutic range (300 ng/dL) by week 3 and week 4, respectively. The authors concluded that the TE doses of 200 mg have to be injected every two weeks or doses of 300 mg every 3 weeks to guarantee effective substitution therapy.[55] TE-associated adverse events are similar to those of TC. The short-acting IM injections have the highest incidence of erythrocytosis approaching 40%.[56] It is suggested that T formulation, dose and pharmacokinetics collectively determine the risk of erythrocytosis by establishing the duration of supraphysiological T levels,[57,58] Short-acting IM T formulations (TC and TE) are associated with the most rapid and significant increases in serum T levels, with supraphysiological T levels achieved within days of an injection and a return to baseline by 10-14 days, followed by a decrease to subphysiological levels within 3 weeks if not re-dosed,[56,59] Caution should be exercised in prescribing short-acting IM formulations in at-risk populations (T2DM, smokers, obese, thrombophilic conditions).[58]

Testosterone ester combinations

T ester mixtures have been widely used for substitution therapy of male hypogonadism with the idea that a short-acting Tester (eg TP) is effective for substitution during the first days of treatment, while a longer-acting T (eg T enanthate (TE)) allows for an effective substitution for the end of injection interval. However, the pharmacokinetic parameters of the individual T esters show that both preparations cause the highest T serum concentrations shortly after injection. The addition of TP to TE only increases the initial undesired T peak producing a much wider fluctuation of T serum concentrations relative to injection of TE alone. For the treatment of male hypogonadism, there is no advantage in combining the available short- and long-acting T esters.[11]

Testosterone undecanoate

TU at a concentration of 250 mg/mL dissolved in castor oil supplied in 3- or 4-mL vials is given slowly IM in the gluteus medius. This preparation that shows a longer half-life compared to other IM preparation of T of about 34 days,[8,60] is approved in the USA at the single dose of 750 mg, followed by 750 mg 4 weeks later, then 750 mg every 10 weeks thereafter.[1] Dosage titration is not recommended. Starting at the 3rd or the 4th injection, this dosing in an open-label study of 117 hypogonadal males resulted in a mean C_{max} of 813 ng/dL reached by day seven and a mean C_{min} between 323 and 339 ng/dL by week 10 after each injection.[61] The pharmacokinetic profile of TU does not demonstrate supratherapeutic peaks, and patients maintained average T concentration DHT and estradiol levels in the adult male range throughout the 84 weeks of treatment.[61] A single dose of 1000 mg TU in castor oil (4 mL vial) has been approved for clinical use in Europe. The second 1000-mg injection is given 6 weeks later, while further injections follow 10-14 weeks later. Individual intervals are determined according to serum T levels that are measured immediately before the next injection and repeated at yearly intervals.[62] Values that are too high lead to an extension of injection intervals, those that are too low to a shortening in injection intervals.[8] In a recent meta-analysis of 33 studies including 3359 men treated with injectable TU and 478 men on placebo, treatment was associated with a significant reduction of fat mass and HbA1c in both controlled and uncontrolled trials, as well as to an improvement of erectile function.[60] In uncontrolled trials, TU ameliorated also blood pressure, lipid profile, waist circumference and body mass index, but these data were not confirmed in placebo-controlled trials.[60] A recent RCT shows that sexual function benefits are evident principally in patients with severe hypogonadism (<8 nmol/L): improvements in intercourse satisfaction and sexual desire appeared by the sixth week of treatment, while erectile function improvements appeared after at least 30 weeks of treatment with TU.[63] TU is generally well tolerated. Adverse events in the meta-analysis included a haematocrit above the physiological level in 0.02%, while PSA levels > 4 ng/mL were reported in 0.04% and 11 men in uncontrolled trials had a new diagnosis of prostate cancer during follow-up (event rate 0.03%).[60] The relatively long washout period may cause problems if complications appear. After each injection, the patient should be observed for 30 minutes because of the rare adverse reactions of POME and anaphylaxis.[22] There is a USA FDA Boxed Warning for the risk of POME and anaphylaxis,as a result, TU is only available through a restricted-use programme in the USA (Aveed REMS Program).[22] Other adverse effects reported during TU clinical trials included acne and injection site pain.[61]

2 | TESTOSTERONE REPLACEMENT THERAPY: CONTRAINDICATIONS AND MONITORING

TRT for all-cause hypogonadism including LOH has been the object of guidelines from different societies in the latest 5 years, which extensively analysed contraindications of TRT and its monitoring: Endocrine Society (USA),[1] American Urological Association (AUA),[52] European Association of Urology (EAU),[64] British Society for Sexual Medicine (BSSM),[65] Endocrine Society of Australia (ESA),[66] European Male Aging Study (EMAS) position statement,[67] The International Society for the Study of the Aging Male (ISSAM),[68] Italian Society of Endocrinology (SIE)[69] and Canadian Men's Health Foundation (CMHF).[53]

The physicians are often reluctant to prescribe TRT in elderly men because of the potential risks that are extensively treated in this special issue. In case of LOH, according to the Endocrine Society, it is recommended to treat men with symptoms of T deficiency and consistently low morning T concentrations and TRT should be offered on an individualized basis after explicit discussion of the potential risks and benefits, considering that no RCTs have been of sufficient size to evaluate the risk.

2.1 | Contraindications

2.1.1. | Prostate and breast cancer

Locally advanced or metastatic prostate cancer and breast cancer are associated with a very high risk of serious adverse outcomes, precluding the use of TRT in all guidelines (Table 2). The association between T treatment and development of breast cancer is still poorly defined and restricted to occasional observations reported in primary hypogonadism only.[70] According to the Endocrine Society, BSSM, EMAS and SIE, T treatment is also not recommended in men with a palpable prostate nodule or induration, as well as in men with a PSA level > 4 ng/mL, or a PSA > 3 ng/mL combined with a high risk of prostate cancer. According to EAU and to CMFF guidelines, TRT can be cautiously offered in selected hypogonadal men treated for a localized prostatic cancer and currently without evidence of active disease (ie measurable PSA, abnormal digital rectal examination (DRE), evidence of metastasis). Treatment should be restricted to patients with a low risk for recurrent prostatic cancer (ie Gleason score < 8, pathological stage pT1-2; pre-operative PSA < 10 ng/mL), and it should not be started before 1 year of follow-up. The recommendation on this topic is however weak in EAU guidelines because of the restricted number of available observations.[71] The Expert Opinion of AUA guidelines stated that patients with T deficiency and a history of prostate cancer should be informed that there is an inadequate evidence to quantify the risk-benefit ratio of TRT. According to Endocrine Society and AUA guidelines, before initiating TRT, a DRE and a determination of PSA level should be offered to all men 55-69 years of age and to men 40-69 years of age who are at increased risk for prostate cancer. Similarly, ESA guidelines suggest that monitoring for prostatic disease before and during TRT should be undertaken as appropriate for eugonadal men of similar age. DRE and PSA testing are therefore required before TRT when there is a reasonable possibility of pre-existing prostate disease. A routine baseline

TABLE 2 Contraindications to TRT according to guidelines

	Erythrocytosis	Prostate cancer	Breast cancer	CVD	LUTS	OSA	Fatherhood desire
CMHF[53]	TRT contraindicated in men with Hct >54% (Hct <52% would provide for a lower risk of thrombosis)	TRT contraindicated in men with metastatic PCa. TRT can be suggested in men treated for localized PCa with no evidence of active disease[a]	TRT contraindicated in men with breast cancer	In men with CVD, TRT should be restricted to those with stable disease, only after a discussion of the potential risks and benefits	In men with LUTS because of BPH, TRT should be restricted to those with mild-to-moderate symptoms	Recommendations not reported	TRT contraindicated in men more interested in maintaining fertility over symptomatic improvement
ISSAM[68]	TRT contraindicated in men with Hct >52%	If suspicion of PCa exists, TRT may be initiated in men with negative prostate biopsy	Recommendations not reported	TRT contraindicated in men with severe untreated CHF	No evidence that TRT either increases the BPH risk or contributes to LUTS worsening	TRT contraindicated in men with severe untreated OSA	Recommendations not reported
SIE[69]	TRT contraindicated in men with Hct higher than the upper limit of the normal rang	TRT contraindicated in men with PCa[b] and in those with unevaluated prostate nodule or induration and/or PSA >4 ng/mL	Recommendations not reported	Suggested caution in prescribing TRT to older men with known CVD	TRT contraindicated in men with an overt urinary tract obstruction because of BPH	TRT contraindicated in men with a known history of OSA	TRT contraindicated in men who are attempting to father a child
EMAS[67]	TRT contraindicated in men with Hct >50%	TRT contraindicated in men with metastatic PCa and in those with unevaluated prostate nodule or induration and/or PSA >4 ng/mL	TRT contraindicated in men with breast cancer	TRT contraindicated in men with uncontrolled CHF	TRT contraindicated in men with severe LUTS	The potential effects of TRT on the risk of OSA are uncertain	Recommendations not reported
ESA[66]	*Precautions:* untreated polycythemia	*Contraindications:* advanced, metastatic or incurable PCa *Precautions:* abnormal DRE, with or without elevated PSA level. TRT may be acceptable in men with organ-specific PCa after definitive or clinically adequate treatment	*Contraindication:* breast cancer.	*Precautions:* Unstable or inadequately treated cardiac disease (eg, poorly controlled cardiac failure or ischaemia, recent cardiovascular events)	*Precautions:* severe LUTS[c]	*Precautions:* untreated OSA	*Precautions:* desire of fertility
BSSM[65]	TRT contraindicated in men with Hct >54%	TRT contraindicated in men with locally advanced or metastatic PCa and in those with unevaluated prostate nodule or induration and/or PSA >4 ng/mL[d]	TRT contraindicated in men with breast cancer	TRT contraindicated in men with severe CHF (NYHA class IV)	TRT contraindicated in men with severe LUTS[c]	TRT contraindicated in men with severe untreated OSA	TRT contraindicated in men with active desire to have children
AUA[52]	TRT contraindicated in men with Hct >50%	TRT contraindicated in men with locally advanced or metastatic PCa. TRT can be considered in men who underwent radical prostatectomy with favourable pathology[e] and undetectable PSA postoperatively	Recommendations not reported	TRT should not be commenced for a period of 3 mo in men with a history of cardiovascular events	Recommendations not reported	Recommendations not reported	TRT contraindicated in men who are currently trying to conceive

(Continues)

TABLE 2 (Continued)

	Erythrocytosis	Prostate cancer	Breast cancer	CVD	LUTS	OSA	Fatherhood desire
EAU[64]	TRT contraindicated in men with Hct >54%	TRT contraindicated in men with advanced PCa. After radical prostatectomy for localized PCa, in the absence of evidence of active disease[a], TRT should be restricted (after a 1-year follow-up) to patients with a low risk for recurrent PCa[f]	TRT contraindicated in men with breast cancer	TRT contraindicated in men with severe CHF. Suggested caution in older men with known CVD. An electrocardiogram prior to TRT could be considered	Recommendations not reported	No evidence that TRT can result in the onset or worsening of OSA	TRT contraindicated in men with active child wish
Endocrine Society[1]	TRT contraindicated in men with Hct >48% (>50% for men living at high altitude)	TRT contraindicated in men with metastatic PCa and in those with unevaluated prostate nodule or induration and/or PSA >4 ng/mL[d]	TRT contraindicated in men with breast cancer	TRT contraindicated in men with uncontrolled or poorly controlled CHF	TRT contraindicated in men with severe LUTS[c]	TRT contraindicated in men with untreated severe OSA	TRT contraindicated in men with desire for fertility in the near term

Abbreviations: AUA, American Urological Association; BPH, benign prostatic hypertrophy; BSSM, British Society for Sexual Medicine; CHF, congestive heart failure; CMHF, Canadian Men's Health Foundation; CVD, cardiovascular disease; DRE, digital rectal examination; EAU, European Association of Urology; EBRT, external beam radiation; EMAS, European Male Aging Study; ESA, Endocrine Society of Australia; Hct, haematocrit; ISSAM, International Society for the Study of the Aging Male; LUTS, lower urinary tract symptoms; mo, months; NYHA, New York Heart Association); OSA, obstructive sleep apnoea; PCa, prostate cancer; PSA, prostate-specific antigen; SIE, Italian Society of Endocrinology; TRT, testosterone replacement therapy.

[a]Active disease: measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis.

[b]TRT could be considered after at least 12 mo of clinical and biochemical cure following radical prostatectomy for PCa, but only under strict monitoring.

[c]As indicated by the AUA symptom index and International Prostate Symptom Score (IPSS) higher than 19.

[d]Or >3 ng/mL in men at high risk of PCa, such as African Americans and those with first-degree relatives who have PCa.

[e]Negative margins, negative seminal vesicles, negative lymph nodes.

[f]Gleason score <8; pT1-2; pre-operative PSA <10 ng/mL; patients who underwent brachytherapy or EBRT for low-risk PCa can also be cautiously considered for TRT with a close monitoring.

prostate evaluation (DRE and PSA level) is recommended in other guidelines (SIE, EUA, CMHF, BSSM, ISSAM, EMAS).

2.1.2. | Elevated haematocrit

TRT is contraindicated in case of elevated haematocrit: >48% or 50% for men living in high altitude,[1] >50%,[52,67] >52%/>54%,[53] >54%,[64,65] haematocrit higher than the upper limit of the normal reported by the laboratory.[69] According to the Framingham Heart Study, in older men, an increased risk for cardiac disease mortality is seen in the high quintile haematocrit (49%-70%).[72] A continuous monitoring of the individual risk profile (eg dehydration, hypercoagulability and smoking) is mandatory before and during T treatment.[69]

2.1.3. | Severe chronic heart failure

Guidelines agree that T treatment should not be started in case of a severe chronic heart failure (New York Heart Association class IV), myocardial infarction or stroke within the last 6 months, or thrombophilia. In case of decision to treat, hypogonadal men with chronic heart failure should be followed carefully with clinical assessment and T and haematocrit measurements on a regular basis.

2.1.4. | Severe lower urinary tract symptoms (LUTS)/AUA/IPSS > 19)

It is suggested to avoid T treatment in men with a severe LUTS, but it is not demonstrated that T worsen LUTS.[1]

2.1.5. | Obstructive sleep apnoea

TRT is contraindicated in case of non-treated severe obstructive sleep apnoea (OSA). T treatment only transiently worsens the severity of OSA,[73]therefore, unless severe and untreated, OSA should not be considered an absolute contraindication to TRT.

2.1.6. | Active desire to have children

All guidelines report that TRT is to be avoided in men who desire fertility in the next 6-12 months.

2.2 | Monitoring

After initiation of TRT, patients are evaluated to assess symptomatic improvement, presence of adverse effects and compliance with treatment (Table 3). The time-course of the effects induced by TRT has been reviewed,[74] demonstrating an improved sexual desire appearing after 3 weeks, reaching a plateau at 6 weeks. Improved erectile function and ejaculation may require up to 6 months. The improved depressive mood may appear within 3-6 weeks, with a maximum after 18-30 weeks. Failure to benefit within a reasonable timeframe of 6 months for sexual symptoms associated with a restoration of normal T levels should prompt vs a critical risk-vs-benefit estimation on whether to continue.[52,65,67] Alternatively, it is recommended treatment with a PDE-5 inhibitor in men with persistent ED, who were adequately treated with TRT, rather than no further treatment.[53] At the same time, patients with unexplained anaemia who improve on TRT, or men with low vertebral and femoral BMD, continuation can be considered even in the absence of another symptom improvement.[52] Although there is evidence that T treatment in LOH improves sexual function, depressive mood, muscle function, anaemia, vertebral and femoral BMD, and body composition, the risks of this treatment are still poorly defined as well as the long-term efficacy of T. Therefore, a discussion of risks and benefits is warranted before continuing treatment in case of no benefit for sexual symptoms but restoration of normal T concentration after a first TRT treatment.

2.2.1. | Serum testosterone concentration

Most guidelines agree to maintain serum T concentration in the mid-normal range for healthy young men. T levels should be generally checked at 3, 6 and 12 months and then annually. T concentrations in men receiving TRT show large variations mostly related to the formulation used, and the timing of measuring T concentration should be guided from pharmacokinetics of suggested formulation with the goal being to evaluate steady-state blood levels (Tables 1 and 3).

2.2.2. | Haematocrit

TRT is associated with an increased haematocrit as reported in the specific contribution in this special issue, and this should be checked at 3, 6 and 12 months and then annually. Haematocrit during TRT should be <54% according to almost all guidelines. Dose adjustment or temporary interruption of TRT and/or periodic venesection might be required to keep haematocrit below 54%. The effects of T on haematocrit are dose dependent, while a more advanced age is also a factor.[75] The effects are apparent after 3 months, and a maximum is reached after 9-12 months.[74] It is interesting that the analysis of studies with transdermal preparations enrolling hypogonadal patients (T < 12 nmol/L) showed that the risk of elevated haematocrit (>52%) during treatment was not confirmed.[76] Transdermal T upon removal is immediately eliminated so that TD preparations are particularly preferred for substitution to quickly treat side effects such as increased haematocrit.[8] This is of particular relevance for TRT in men with LOH, transdermal T represents, indeed, the most popular formulation of TRT in this condition.[6] Special attention in haematocrit monitoring should be reserved in case of TRT in men with moderately chronic heart failure. Available

TABLE 3 Recommendations for TRT monitoring according to guidelines

	Assessment of clinical response and side effects	TT levels: timing and therapeutic target	Hct	PSA	DRE	BMD
CMHF[53]	3 and 6 mo, then annually	Baseline, 3 and 6 mo, then annually. Target: 404-505 ng/dL[a]	Baseline, 3 and 6 mo, then annually to keep Hct <52%-54%	Baseline, 3 and 6 mo, then annually	Baseline and 6 mo, then annually	NS
ISSAM[68]	3, 6 and 12 mo, then annually	NS	Baseline, 3-4 and 12 mo, then annually to keep Hct <52%-54%	Baseline, 3, 6 and 12 mo, then at least annually	Annually	Annually in hypogonadal men with lowered BMD
SIE[69]	3, 6 and 12 mo, then annually	NS	Recommended CBC monitoring (timing NS) to avoid critical elevation of Hct	Baseline, 3, 6 (or 9) and 12 mo, then at least annually[b]	Baseline, 3, 6 (or 9) and 12 mo, then at least annually	NS
EMAS[67]	3, 6 and 12 mo, then annually	Baseline, 3, 6 and 12 mo, then annually. Target: mid-normal range for healthy young men (350-750 ng/dL[a])	Baseline, 3, 6 and 12 mo, then annually	Baseline, 3, 6 and 12 mo, then annually	Baseline, 3, 6 and 12 mo, then annually	Baseline, then biannually
ESA[66]	3 mo, then annually	Timing NS. Target: within the lower part of the reference range for eugonadal men	Baseline, 3 mo, then annually to keep Hct within the normal reference range	Baseline (if increased risk for PCa[c]), then as appropriate for eugonadal men of similar age	Baseline (if increased risk for PCa[b]), then as appropriate for eugonadal men of similar age	Baseline, then annually or biannually
BSSM[65]	3, 6 and 12 mo, then annually	Baseline, 3, 6 and 12 mo, then annually. Target: 433-865 ng/dL[a]	Baseline, 3, 6 and 12 mo, then annually to keep Hct <54%	Baseline, 3, 6 and 12 mo, then annually	Baseline	Annually or biannually in hypogonadal men with abnormal BMD
AUA[52]	3, 6 and 12 mo, then annually	Baseline, 2-4 weeks (depending on type of therapy), then every 6-12 mo. Target: middle tertile of the normal reference range	Baseline, then every 6-12 mo or sooner depending on prior values, to keep Hct <54%	Baseline testing in men >40 y of age to exclude PCa. Consider biennial testing in men 55-69 y of age. Not recommended routine PSA follow-up in men 40-54 y of age unless they are at increased risk for PCa[c]	NS	Annually or biannually in hypogonadal men with BMD loss
EAU[64]	3, 6 and 12 mo, then annually	Baseline, 3, 6 and 12 mo, then annually. Target: mid-normal range	Baseline, 3, 6 and 12 mo, then annually to keep Hct <54%	Baseline, 3, 6 and 12 mo, then annually	Baseline	Recommended BMD monitoring (timing NS) only in hypogonadal men with abnormal BMD

(Continues)

TABLE 3 (Continued)

	Assessment of clinical response and side effects	TT levels: timing and therapeutic target	Hct	PSA	DRE	BMD
Endocrine Society[1]	3 and 12 mo, then annually	Baseline, 3 and 6 mo. Target: mid-normal range	Baseline, 3, 6 and 12 mo, then annually to keep Hct <54%	Baseline, 3 and 12 mo in men 55-69 y of age (and also in men 40-54 y of age if at increased risk for PCa[c]), then follow guidelines for prostate cancer screening	Baseline, 3 and 12 mo in men 55-69 y of age (and also in men 40-54 y of age if at increased risk for PCa[b]), then follow guidelines for prostate cancer screening	Annually or biannually in hypogonadal men with osteoporosis

Abbreviations: AUA, American Urological Association; BMD, bone mineral density; BSSM, British Society for Sexual Medicine; CBC, complete blood count; CMHF, Canadian Men's Health Foundation; DRE, digital rectal examination; EAU, European Association of Urology; EMAS, European Male Aging Study; ESA, Endocrine Society of Australia; Hct, haematocrit; ISSAM, International Society for the Study of the Aging Male; mo, months; NS, not specified; PCa, prostate cancer; PSA, prostate-specific antigen; SIE, Italian Society of Endocrinology; TT, total testosterone; TRT, testosterone replacement therapy.

[a]To convert values to nmol/L, multiply by 0.03467.

[b]The Italian Society of Endocrinology also includes free PSA in TRT monitoring.

[c]Positive family history and/or African American population.

few data with a prolonged TRT (12 months) in men with moderately severe CHF including some hypogonadal men (total T < 7.5 nmol/L or bioavailable T < 2.5 nmol/L) suggested that transdermal T treatment was safe with no excess of adverse events including no significant change in haematocrit.[77] However longer, larger trials should provide information on the effects of TRT on endpoints including hospitalization, deterioration in CHF and death.[77]

2.2.3. | Prostate safety

Guidelines suggest prostate monitoring in case of TRT including PSA and DRE 3-12 months after treatment initiation. After 1 year, with T serum level in the normal range, Endocrine Society and AUA suggest that prostate monitoring should follow guidelines for prostate cancer screening.[78] Specifically, these guidelines do not recommend routine PSA testing in men 40-54 years of age unless they are at higher risk (eg positive family history, African American populations). In men 55-69 years of age, biannual PSA testing should be considered. AUA, according to prostate cancer screening,[78] does not recommend routine PSA screening in men aged 70 years or more, or any man with less than a 10-15 years life expectancy. Annual evaluation for prostate safety is on the contrary suggested after the first year of treatment by EAU, SIE, CMHF, ISSAM, BSSM and EMAS. It is interesting to note that DRE, in a large nationally representative cohort in the USA, demonstrated a prognostic usefulness to detect a clinically significant prostate cancer only when PSA was greater than 3 ng/mL.[79] Subjects with substantial or continuous increase in PSA level need to be investigated to exclude prostate cancer. PSA increases greater than 1-1.4 ng/mL above baseline during any period after initiation of T therapy, or PSA velocity increases greater than 0.35-0.4 ng/mL per year during sequential PSA measurements, over more than 2 years or a confirmed PSA >4.0 ng/mL, or a prostatic abnormality detected on DRE warrants a urologic evaluation and more intensive surveillance for prostate cancer thereafter.[1,65,68] Transient PSA elevations are common and may be because of test-retest variability[80] or other disorders, such as prostatitis, benign prostatic hyperplasia, prostate trauma, urinary tract infections or assay variability. Elevation of PSA should therefore be confirmed by repeating the test.

2.2.4. | Bone mineral density

Bone mineral density should be monitored after 1-2 years of TRT only in men with abnormal BMD at baseline. Lumbar spine BMD eventually starts to increase after 6 months of treatment and may continue for 3 years of treatment.[74] This helps to decide whether the patient needs additional treatments.

2.2.5. | Sleep apnoea

T treatment may transiently worsen the severity of OSA.[73] A meta-analysis has shown that the frequency of men with a new diagnosis

of sleep apnoea during treatment was not significantly different in TRT compared to placebo groups.[81]

3 | CONCLUSIONS

Different formulations of T are available for replacement therapy to relieve symptoms and signs of androgen deficiency in men with LOH.

T therapy is associated with multiple benefits highly relevant to the patient including amelioration of sexual function, depressive mood, muscle function, anaemia, vertebral and femoral BMD, and body composition. The recommendations given in different guidelines on TRT are based on data from a limited number of RCTs, as well as on non-randomized clinical studies and on observational studies. This is the case for the safety of a long-term TRT in LOH. No evidence is provided indeed on the effects of TRT on endpoints such as deterioration of heart failure suggesting a cautious approach to T replacement in older men with a history of heart failure. Clinicians must consider the unique characteristics of each patient and make the necessary adjustments in the management of LOH in order to provide the safest and most beneficial results.

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AUTHOR CONTRIBUTIONS

AB and SD performed the literature research and analysed the data; AB and SF wrote the manuscript; SF performed a critical revision.

ORCID

Arcangelo Barbonetti https://orcid.org/0000-0002-6888-9585
Settimio D'Andrea https://orcid.org/0000-0002-5031-031X

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