Testosterone Replacement Therapy

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Introduction

The male gonadal gland produces sex steroids and sperms under the regulation of a complex network including intratesticular factors and extra-testicular trophic hormones. The pituitary gland regulates gonadal activity, through the secretion of luteinizing hormone (LH), which mainly regulates testosterone (T) production in Leydig cells (micromoles/day), and follicular stimulating hormone (FSH), which mainly controls sperm production in seminiferous tubules (millions/day) [1, 2]. The production and secretion of gonadotropins by the pituitary gland are stimulated by the gonadotropin-releasing hormone (GnRH) produced by the hypothalamus and inhibited by a negative feedback mediated by the central action of sex steroids and inhibin B [1, 2]. Male hypogonadism (HG) is a clinical condition due to a partial or total communication breakdown of the hypothalamus-pituitary-testis (HPT) axis. Hence, HG is a condition characterized by the impairment of testicular production of both sex steroids and sperms. The term, however, is rarely used to identify abnormalities in sperm production, while it is often applied to describe T deficiency [3].

Based on a pathogenetic classification, HG can be considered as primary (pHG) when caused by any diseases affecting the testes, and as secondary (sHG) when

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due to a pituitary or hypothalamic dysfunction. In the former condition, both sex steroids and sperms are impaired despite a super-stimulation of the pituitary (hypergonadotropic hypogonadism), whereas in sHG the testis is normal, but inadequately stimulated by gonadotropins (hypogonadotropic hypogonadism). In addition, another condition, known as compensated hypogonadism (normal T serum levels and elevated LH), has also been described, although its clinical significance is still debated [4, 5].

The aforementioned classification of HG, based on its etiology, presents a practical utility for didactic and treatment purposes. In fact, patients with sHG can be successfully treated by removing the precipitating cause (for example: prolactinoma) and/or by appropriate endocrine therapy (i.e., gonadotropins or GnRH if fertility is an issue or T for virilization, if fertility is not desired). Conversely, only T treatment can be offered to patients with pHG [1, 2]. However, it is important to recognize that the phenotype of the hypogonadal patient is more often affected by the age of hypogonadism onset regardless of the site of origin. If the problem occurs very early on in fetal life, symptoms can be dramatic, spanning from an almost complete female phenotype to various defects in virilization. When the problem manifests during pre- or peripubertal age, symptoms and signs are milder including a delay in the onset of puberty with an overall eunuchoidal phenotype [6, 7]. Finally, when hypogonadism develops after puberty and especially with aging (adult-onset or late-onset hypogonadism, LOH), symptoms will be relatively mild, insidious and difficult to recognize. The European Male Aging Study (EMAS), a population-based survey performed on more than 3400 men recruited from eight European centers, clearly showed that sexual symptoms—particularly erectile dysfunction (ED) and decreased frequency of sexual thoughts and morning erections—are the most sensitive and specific symptoms in identifying adulthood patients with low T [8]. Similar results were recently reported by us in a large cohort ($n = 4890$) of subjects consulting for ED [9]. In contrast, psychological and physical symptoms were less informative [8].

Finally, more recently the concept of *organic* versus *functional* HG has been introduced [10]. The former is an irreversible condition due to congenital or acquired perturbation to the HPT axis [10]. Conversely, *functional* HG is a potentially reversible condition characterized by "no recognizable structural intrinsic HPT axis problems," frequently associated with an age-dependent accumulation of morbidities impairing the HPT axis function [10]. In particular, metabolic disturbances such as type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome (MetS) are the conditions most frequently associated with functional HG [10–13]. Interestingly, we recently reported that in a large series ($n = 4220$) of subjects seeking medical care at our unit for sexual dysfunctions only a minority of patients satisfied the criteria of organic hypogonadism (15%) whereas the majority, i.e., 85%, were allocated to the functional category. In the latter group, metabolic impairment was present in 2/3 of the subjects [14].

In the following sections, the criteria defining LOH and the available T formulations along with their outcomes are analyzed in detail.

Criteria for Starting Testosterone Replacement Therapy (TRT)

Although there is no general agreement among the different andrological societies on T thresholds for initiating TRT in LOH, the most widely shared consensus is that TRT may be beneficial when total T is below 8 nmol/L (231 ng/dL) in two different measurements [15–17]. In addition, there is also general agreement that a total T level above 12 nmol/L (346 ng/dL) does not require substitution. When T levels are in the "gray area," between 8 and 12 nmol/L, TRT should be offered only to symptomatic men [15–17]. As previously reported, sexual symptoms of erectile dysfunction and decreased mood/libido and/or decreased sexual thoughts are the most specific indicators for TRT [8, 9].

Available Testosterone Preparations

The first androgenetic steroid, *androsterone*, was chemically isolated and purified from urine by Butenandt in 1931. Some years later, in 1935, Karoly Gyula David and Ernst Laqueur extracted and purified a stronger androgenic steroid from bull testes and termed it as T. In the same year, Butenandt group in Gottingen and Ruzicka and Wettstein in Basel simultaneously published the T chemical synthesis [18]. Soon after its synthesis, it became apparent that T could not be given effectively by oral or parenteral route, because of a prompt hepatic metabolism causing only a small portion of the hormone to reach systemic circulation. Hence, a series of chemical modifications were introduced to improve T bioavailability and pharmacokinetics, essentially retarding the rate of liver catabolism or enhancing its availability. The first T ester introduced on the market was a very-short-acting formulation (T propionate) which requires two to three injections per week to maintain normal T levels (see below [18]). In 1935, a 17α-methyl-T was also synthesized for oral use. However, now it is clear that this compound along with all other T-methyl derivatives is associated with an increased liver toxicity and for these reasons these formulations are no longer recommended for clinical use [18]. Unfortunately, these products are still present on the black market and abused as anabolic steroids [19]. In the mid-1950s a longer acting T formulation (T-enanthate) became available and has remained the major T preparation for more than half a century. In the late 1970s a new orally effective T formulation based on esterification of T ring in position 17β with undecanoic acid (oral T undecanoate, TU) was introduced on the market. This chemical modification allows absorption via lymphatic system avoiding the first-pass effect in the liver [18]. In the mid-1990s, transdermal scrotal and non-scrotal T patches became available and in 2000 the more manageable transdermal T preparations (T gels) were approved for the treatment of male hypogonadism, first in the USA and later on also in other countries. In 2004, the injectable long-acting TU entered the market allowing a dosing regimen of 1000 mg every 12 weeks following a 6-week loading dose [18].

The specific characteristics of all the aforementioned T preparations are analyzed in detail (Table 8.1).

Table 8.1 Testosterone preparations

Formulation	Trade names	Chemical structure	T 1/2	Standard dosage
		Oral		
Testosterone undecanoate	Andriol®	17-α-Hydroxyl-ester	4 h	120–240 mg 2–3 times daily
	Andriol Testocaps®			
Mesterolone	Proviron®	1α-Methyl-4,5α-dihydrotestosterone	NA	50–100 mg 2–3 times daily
		Parental		
Testosterone enanthate	Testoviron Depot®	17-α-Hydroxyl-ester	4–5 days	250 mg every 2–3 weeks
	Delatestryl®			
	Testoenant®			
Testosterone cypionate	Delatestryl®	17-α-Hydroxyl-ester	8 days	200 mg every 2–3 weeks
Testosterone propionate	Testovis®	17-α-Hydroxyl-ester	20 h	100 mg every 2 days
Testosterone undecanoate in castor oil	Nebido®	17-α-Hydroxyl-ester	34 days	1000 mg every 10–14 weeks
	Aveed®(USA)[a]			750 mg every 10 weeks[a]
Surgical implants	Testopel®	Native testosterone	–	4–6200 mg implants lasting up to 6 months
	Testoimplant®			
		Transdermal		
Testosterone patches	*Not scrotal:*	Native testosterone	10 h	50–100 mg/day
	Androderm®			
	Andropatch®			
	Testopatch®			
Testosterone gel 1–2%	*1% Gel:*	Native testosterone	6 h	50–100 mg/day
	Androgel®			
	Testogel®			
	Testim®			
	2% Gel:			
	Testostop®			
	Tostrex® (also known as Fortesta®, Tostran®, and Itnogen® available only in Europe)			
	1.6% Gel			
	Androgel (available only in the USA)			
Dihydrotestosterone gel 2.5%	Andractim®	5α-Dihydrotestosterone		5 or 10 g/day
Underarm testosterone (testosterone solution 2%)	Axiron®	Native testosterone	NA	60–120 mg/day
		Transmucosal		
Buccal testosterone	Striant®	Native testosterone	12 h	30 mg/twice daily
Intranasal testosterone	Natesto®[b]	Native testosterone	NA	11 mg 2–3 times daily

[a]Available only in the USA
[b]Available only in the USA and Canada
NA not available

Oral Testosterone Preparations

Testosterone Undecanoate

As reported above, T undecanoate (TU) is a long-chain fatty acid ester of T, absorbed by the intestines into lymphatic system lacteals, therefore bypassing the liver and enabling T delivery into the systemic circulation. The recommended dosage is one or two 40 mg caps twice or thrice daily during meals (Table 8.1). However, it is important to recognize that this formulation is characterized by an unpredictable absorption depending on the dietary fat content of food intake limiting its clinical use [15–17, 20].

Mesterolone

Mesterolone is a 1α methyl derivative of 5α-dihydrotestosterone (DHT). This chemical modification allows resistance to hepatic metabolism. Mesterolone is prescribed at a daily dose of 50–100 mg and should be taken in two to three spaced dosages [15–17, 20] (Table 8.1). However, as DHT, mesterolone cannot be converted to estrogen strongly limiting its attractiveness.

Injectable Testosterone Preparations

Subdermal Implantation of T Pellets

The subdermal implantation of T pellets was introduced on the market in the first half of the last century. This formulation is still available for clinical use only in few countries, such as the USA, the UK, and Australia. The pellets consist of pure crystals of T compressed into short rods, which are implanted under local anesthesia into the subdermal fat layer of the skin. Recommended dosage includes two to six pellets (150–450 mg) subcutaneously every 3–6 months (Table 8.1) [15–17, 20]. This formulation is still the T preparation with the longest duration of action; however, the procedure is invasive and may be unattractive to patients.

Intramuscular Injectable Preparations

According to their half-lives these formulations can be classified into short-, mid-, and long-lasting preparations (Table 8.1) [15–17, 20].

T propionate is a short-acting T formulation requiring the administration of two to three fractionated doses weekly (usually 50 mg every 2–3 days) which limits its attractiveness, although it is still present on the market worldwide (Table 8.1) [15–17, 20]. In addition, the use of this preparation determines a wide fluctuation of circulating T levels often reaching supraphysiologic levels after 24 h, followed by a gradual decline to hypogonadal levels before the following administration [15–17, 20]. This phenomenon can be recognized as unpleasant by the patients who complain of variations in well-being and also increasing the risk of erythrocytosis [21].

The longer aliphatic chain in 17β-position allows *T cypionate and enanthate* to have a longer half-life requiring it to be injected every 2–4 weeks at a dose of 200–250 mg (Table 8.1) [15–17, 20]. However, the two compounds present similar

limitations as previously described for T *propionate* including wide plasma fluctuation and higher risk of erythrocytosis.

In 2004, a new, long-lasting injectable formulation of T undecanoate (TU) was introduced [15–17, 20]. In the majority of countries, this preparation is available as a depot of 1000 mg in 4 mL requiring it to be administered every 12 weeks following a booster 6-week loading dose. In the USA, a 3 mL ampoule containing 750 mg is available. The latter formulation is recommended to be injected once at initiation of therapy, at 4 weeks, and then every 10 weeks thereafter [15–17, 20]. A recent meta-analysis of all available evidence documented that this preparation shows a very good safety and benefit profile [22].

Transdermal Testosterone Preparations

Testosterone Gels

Transdermal T gels are available at different concentrations (1%, 1.62%, and 2%) and nowadays represent the most popular T formulations for the treatment of LOH along with long-acting TU (Table 8.1) [15–17, 20]. The applied gel is quickly absorbed by the skin that forms a sort of reservoir for continuous delivery to the systemic circulation. Only about 8–14% of the applied gel is usually transdermally absorbed. Considering the T production rate of 5–8 mg/day the recommended dosage of T gels is 50–100 mg daily. Local side effects such as skin irritation and erythema are seldom observed. However, the most important side effect related to the use of T gels is the possibility to transfer some amount of T to others during contact with the skin's surface. In order to overcome this possibility, newer T gel formulations at higher concentrations (1.62–2%) have been developed [15–17]. Similar effects can be obtained using the *alcohol-based T (2%) solution* which requires a daily underarm application [15–17, 20]. Unfortunately, this formulation is available only in a limited number of countries.

Testosterone Patches

Self-adherent skin patches were the first T transdermal formulation introduced on the market, firstly using scrotal systems and, later on, through non-scrotal ones (Table 8.1) [15–17, 20]. These formulations, however, are frequently associated with adverse skin reactions at the application site limiting their use [15–17, 20].

DHT Gels

In some European countries, DHT is available as a hydroalcoholic 2.5% gel requiring a dosage of 5 or 10 g/day (Table 8.1) [15–17, 20]. The gel is rapidly absorbed by the skin reaching a steady state in 2–3 days. However, similar to what was reported for mesterolone, this preparation cannot be aromatized and works as a partial androgen. Hence, this formulation can be used only for limited periods in particular conditions, such as gynecomastia and microphallus [23–25].

Transmucosal Testosterone Preparations

Transbuccal Testosterone Preparations

A T transbuccal formulation is available in several countries. This administration allows avoiding intestinal pass and liver inactivation providing the absorption of T through the oral mucosa (Table 8.1) [15–17, 20]. The system adheres to the gum or inner cheek gradually releasing medication. However, this formulation does not dissolve completely and requires removal after 12 h. This formulation is able to restore physiological T levels with minimal or transient local problems, including gum edema, blistering, and gingivitis [15–17, 20].

Transnasal Testosterone Preparations

A gel containing 5.5 mg of T in 122.5 mg for intranasal administration has been developed and available in some countries, including the USA and Canada (Table 8.1) [15–17, 20]. The recommended dosage is 11 mg of T administered intranasally three times daily (Table 8.1) [1–3, 5, 26]. The nasal gel is available as a metered-dose pump containing 11 g of gel dispensed as 60 metered pump actuations. The application is rapid, noninvasive, and convenient, and avoids secondary transference.

Testosterone Preparation Outcomes

Sexual Function

From 2005 to today, six systematic meta-analyses evaluating the effect of TRT versus placebo on sexual function have been published [26–31]. By considering all the studies reporting outcome data as effect size [29–31] and limiting the analysis only to hypogonadal patients, TRT was associated with an improvement of all sexual parameters evaluated (Table 8.2) [32]. Conversely, no effect was observed when eugonadal patients were considered (Table 8.2). According to Cohen [33], a small treatment-effect size is considered to be about 0.2, a medium effect size to be about 0.5, and a large effect size to be about 0.8. Only our study reported data categorized according to the T preparation used [29]. Interestingly, when the data on erectile function and libido outcomes were considered and studies enrolling only eugonadal patients were excluded, oral preparations did not show a positive effect, when compared to placebo, on erectile function whereas only a small effect on libido was detected (Table 8.2) [32]. Conversely, no difference in the positive efficacy of both transdermal and parental testosterone preparations was documented (Table 8.2) [32]. Finally, no sufficient data were available to evaluate possible differences among specific transdermal and parenteral preparations (not shown).

Table 8.2 Standardized mean [95% CI] for different sexual function parameters as derived from available meta-analyses

Meta-analyses considered	Overall			
	Erectile function	*Libido*	*Orgasmic function*	*Sexual satisfaction*
Isidori et al. [31]	1.87 [0.31;3.43]	1.60 [0.29;2.92]	–	1.16 [0.04;2.29]
Bolona et al. [30]	0.80 [−0.10;1.60]	1.31 [0.4;2.22]	–	–
Corona et al. [29]	1.21 [0.65;1.78]	0.95 [0.41;1.50]	0.74 [0.35;1.21]	0.86 [0.40;1.32]
	Data according to testosterone formulations (Corona et al. [29])			
	Erectile function		*Libido*	
Oral	1.77 [−0.19;3.73]		1.41 [0.14;2.68]	
Transdermal	0.31 [0.04;0.59]		0.32 [0.14;0.51]	
Injectable	0.46 [0.18;0.74]		0.81 [0.31;1.32]	

Body Composition and Glycometabolic Control

Much evidence has documented a possible association between low T and metabolic impairment [34–36]. Since 2005, four systematic meta-analyses have evaluated the effect of TRT on different parameters related to body composition and glycometabolic profile [37–40]. The meta-analyses differed in body composition and metabolic outcomes considered [37–40]. By comparing all the available data and when only hypogonadal patients were considered, TRT caused similar modifications in fat mass and lean mass without any changes in BMI (Table 8.3) [32]. Similar results were observed when fasting glycemia was considered (Table 8.3) [32]. Conversely, more conflicting results were detected when lipid profile was analyzed (Table 8.3) [32]. Finally, when body composition and metabolic profile outcomes were evaluated according to the use of the different T preparations, oral preparations did not show a positive effect on lean mass and glycometabolic profile whereas no difference in the positive efficacy of both transdermal and parental testosterone preparations on the other outcomes considered was documented (Table 8.3) [32].

Osteoporosis

The specific role of T in the regulation of bone health and its contribution to the development of male osteoporosis are conflicting [41]. Only two independent meta-analyses evaluated the effect of TRT versus placebo in RCTs [37, 42]. Both studies reported a positive effect of TRT on bone mineral density at lumber site but the effect was not documented at the femoral site [37, 42]. However, insufficient data are available to evaluate the contribution of TRT on the risk of bone fractures [41].

Table 8.3 Mean [95% CI] for different body composition parameters as derived from available meta-analyses

Meta-analyses considered	Overall							
	BMI	*Fat mass*	*Lean mass*	*Fasting glycemia (mmol/L)*	*Total cholesterol (mmol/L)*	*Triglycerides (mmol/L)*	*HDL (mmol/L)*	*LDL (mmol/L)*
Isidori et al. [37]	–	−1.46 [−3.01;0.09]	1.16 [−0.49;2.80]	–	−0.42 [−0.65;−0.19]	–	0.01 [−0.05;0.07]	−0.33 [−0.80;0.14]
Haddad et al. [47]	–	–	–		−0.22 [−0.71;0.27]	−0.27 [−0.61;0.01]	−0.04 [−0.39;0.30]	0.06 [−0.30;0.42]
Fernandez-Balsells et al. [48]	–	–	–	–	–	–	–	–
Corona et al. [49]	−0.01 [−0.45;0.42]	−0.39 [−0.61;−0.17]	0.45 [0.26;0.73]	−0.37 [−0.65;−0.09]	−0.35 [−0.61;−0.01]	−0.18 [−0.33;−0.04]	0.03 [−0.05;0.11]	–
	Data according to testosterone formulations (Corona et al. [29])							
	Fat mass		*Lean mass*		*Fasting glycemia (mmol/L)*	*Total cholesterol (mmol/L)*		
Oral	−0.26 [−0.47;−0.04]		1.28 [−0.28;2.67]		−1.19 [−2.76;0.37]	−1.19 [−2.76;0.37]		
Transdermal	−0.14 [−0.25;−0.03]		0.31 [0.21;0.41]		−0.22 [−0.40;−0.04]	−0.22 [−0.40;−0.04]		
Injectable	−0.65 [−0.96;−0.34]		0.61 [0.37;0.86]		−0.36 [−0.62;−0.10]	−0.36 [−0.62;−0.10]		

BMI body mass index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

Mood and Cognition

Much evidence suggests a possible relationship between depressive symptoms and LOH; however, the relationship between low T levels and incidence of clinical depression and the effect of TRT on depressive symptoms are still unclear [43]. Similar considerations can be drawn for the relationship between reduced levels of T and age-dependent cognition deterioration or the risk of developing Alzheimer's disease [44, 45].

Potential Side Effects

Cardiovascular Risk

CV risk is still a hot topic regarding TRT safety. Interestingly, the major problems related to this issue come from limited evidence including one RCT [46], two retrospective pharmaco-epidemiological papers [47, 48], and one meta-analysis [49] published between 2013 and 2014. All these studies present important methodological limitations, which have been discussed elsewhere [50–53]. In addition, it is important to recognize that the largest observational study published so far, including almost 45,000 male patients, showed a protective effect and not an increased risk related to TRT after a median follow-up of 3.4 years [54]. In addition, besides the Xu et al.'s [49] meta-analysis, seven other meta-analyses [38, 39, 55–59] published either before or after Xu et al. [49] did not support an increased CV risk related to TRT either when aggregated or disaggregate CV events were evaluated. Similar consideration can be drawn when venous thromboembolism risk was considered [60].

Prostate Safety

Among the scientific and nonscientific community, prostate cancer (PC) or a possible exacerbation of symptoms due to benign prostatic hyperplasia (BPH) has been considered the worst complication of TRT for a long time. However, data published in the two last decades has substantially modified this position [61–63]. Accordingly, the available meta-analyses [39, 55, 64–68] showed that TRT is associated with a short-term (<12 months) increase in PSA levels, which has not been confirmed in longer trials. Conversely, no risk of prostate cancer or BPH symptoms has been documented [39, 55, 64–66]. Accordingly, almost 10 years ago, Morgentaler and Traish speculated that ("saturation hypothesis") in a physiological condition, the human prostate androgen receptors are "saturated" by the circulating androgens and therefore rather insensitive to further T increase [69]. This hypothesis was later on confirmed in both preclinical [62] and clinical studies [70–72].

Erythrocytosis

Erythrocytosis is the most common side effect related to TRT [21]. Several mechanisms could be underlying this phenomenon. First of all, T plays a direct action in stimulating endogenous erythropoietin (EPO) secretion and bone marrow erythroid progenitor cells [21]. In addition, more recent evidence suggests that T can be involved in the regulation of hepcidin metabolism resulting in an increased iron absorption, increased systemic iron transport, and erythropoiesis [21]. Finally, a possible role of T metabolites such as estradiol or dihydrotestosterone, as well as the contribution of genetic factors (androgen receptor CAG repeats), has also been considered [21]. However, it is important to recognize that several uncontrolled studies have documented that the risk of polycythemia related to TRT is higher in subjects treated with short-acting T formulations [21]. Conversely, the use of transdermal T preparations or long-acting injectable TU is associated with lower risk [21].

Conclusion

In conclusion, the treatment of hypogonadal subjects requires adequate preparation and skill. Available evidence has documented that TRT in hypogonadal subjects is able to improve sexual function and ameliorate body composition. When prescribed according to current guidelines no CV risk or risk of prostate health has been reported. Older injectable preparations are associated with a higher risk of polycythemia.

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