SEXUAL MEDICINE REVIEWS REVIEW

Testosterone Replacement Therapy for Sexual Symptoms

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ABSTRACT

Background: Several data have clearly shown that the endocrine system—and androgens in particular—play a pivotal role in regulating all the steps involved in the male sexual response cycle. Accordingly, testosterone (T) replacement therapy (TRT) represents a cornerstone of pharmacologic management of hypogonadal subjects with erectile dysfunction.

Aim: The aim of this review is to summarize all the available evidence supporting the role of T in the regulation of male sexual function and to provide a comprehensive summary regarding the sexual outcomes of TRT in patients complaining of sexual dysfunction.

Methods: A comprehensive PubMed literature search was performed.

Main Outcome Measure: Specific analysis of preclinical and clinical evidence on the role of T in regulating male sexual function was performed. In addition, available evidence supporting the role of TRT on several sexual outcomes was separately investigated.

Results: T represents an important modulator of male sexual response function. However, the role of T in sexual functioning is less evident in epidemiologic studies because other factors, including organic, relational, and intrapsychic determinants, can orchestrate their effect independently from the state of androgens. Nonetheless, it is clear that TRT can ameliorate several aspects of sexual functioning, including libido, erectile function, and overall sexual satisfaction. Conversely, data on the role of TRT in improving orgasmic function are more conflicting. Finally, further controlled studies are needed to investigate the combination of TRT and PDE5 inhibitors.

Conclusion: Positive effects of TRT are observed only in the presence of a hypogonadal status (ie, total T $<$ 12 nmol/L). In addition, TRT alone can be effective in restoring only milder forms of erectile dysfunction, whereas the combined therapy with other drugs is required when more severe vascular damage is present. **Rastrelli G, Guaraldi F, Reismann Y, et al. Testosterone Replacement Therapy for Sexual Symptoms. Sex Med Rev 2019;XX:XXX–XXX.**

Key Words: Testosterone; Testosterone Replacement Therapy; Sexual Desire; Erectile Dysfunction; Ejaculation

INTRODUCTION

According to Masters and Johnson's[1] linear model, male sexual response is based on 4 stages defined as the human sexual response cycle. The *excitement phase* represents the first stage of sexual response, and it is a consequence of physical or mental erotic stimuli resulting in sexual arousal. *The plateau phase* follows the latter stage and precedes sexual orgasm. In this stage, penile erection reaches the highest rigidity, and the male urethral sphincter contracts to prevent retrograde ejaculation and urospermia. The plateau phase usually ends with *orgasm,* which is often characterized by anterograde ejaculation. Finally, the *resolution phase* permits reaching the baseline condition and the return of the penis to a flaccid state. In 1979, Kaplan[2] added the concept of desire, and the model of sexual response was condensed into 3 phases: desire, arousal, and orgasm. Over the last decade, the validity of the linear models has been questioned. In particular, Basson[3] proposed a non-linear model of sexual response emphasizing that desire can come either before or after arousal and that orgasm may contribute to, but is not necessary

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for, satisfaction and resolution. Accordingly, for example, a reduction of ejaculatory/orgasmic reactions might reflect a lack of sexual motivation; hypoexcitability of subjects with delayed ejaculation[4] or with a decreased ejaculate volume[5] may stem from a disjunction between genital and subjective arousal,[6] generating a vicious cycle.[7]

Despite the model of sexual response considered, much evidence, coming from either basic science or clinical studies, has clearly shown that the endocrine system plays a pivotal role in regulating all the steps involved in sexual activity.[8] Adrenal pathway and growth hormones are involved in the mechanisms supporting the arousal phase, contributing to the increase in heart and breathing rate and to the rise in blood pressure, which are essential for penis tumescence and pelvic vaso-congestion.[8] Thyroid hormones are involved in the regulation of sexual desire and contribute to ejaculation control.[8–10] Finally, androgens, and testosterone (T) in particular, are involved in the regulation of all steps of the sexual response cycle.[8,9] Accordingly, T replacement therapy (TRT) represents a cornerstone of pharmacologic management of hypogonadal subjects with erectile dysfunction (ED) or desire disorders.[8,9,11,12] The aim of this review is to summarize all the available evidence supporting the role of T or its metabolites in the regulation of male sexual function and to provide a comprehensive summary regarding the sexual outcomes of TRT in patients complaining of sexual dysfunction.

METHODS

A comprehensive Medline, Embase, and Cochrane search was performed including the following words: ("testosterone"[MeSH Terms] OR "testosterone"[All Fields]) AND ("sexual behavior"[MeSH Terms] OR ("sexual"[All Fields] AND "behavior"[All Fields]) OR "sexual behavior"[All Fields] OR "sexual"[All Fields]) AND ("physiopathology"[Subheading] OR "physiopathology"[All Fields] OR "dysfunction"[All Fields]). Publications from January 1, 1969, up to August 1, 2018, were included.

ROLE OF TESTOSTERONE IN PHYSIOLOGICAL REGULATION OF SEXUAL RESPONSE

Sexual Desire

Sexual desire can be considered as the result of the interaction among internal cognitive processes (thoughts, fantasy, and imagination), neurophysiological mechanisms (central arousability), and affective components (mood and emotional states), the biological basis of which is still mainly derived from animal models.[13–15]

Animal Studies

Brain areas involved in the regulation of sexual excitation and desire include the medio-basal hypothalamus and the limbic system. Multiple lines of evidence indicate that androgen receptors (AR), along with other sex steroid receptors, are expressed in several distinct areas of the human brain, including the temporal, preoptic, hypothalamus, amygdala, midbrain, and frontal and prefrontal areas and cingulated gyrus (Brodman area 24 [BA 24]).[16] However, the hypothalamic and limbic regions express the highest AR concentrations, confirming the role of T in regulating sexual behavior in these areas. Accordingly, mice with reduced or absent T signaling due to mutations in AR, as well as AR knockout mice, show impaired sexual behavior.[16] Similar findings have been observed in castrated rats, where restoring androgen levels has been demonstrated to be effective in re-establishing sexual behavior.[16] In addition, it is important to recognize that androgens can modulate the mesocorticolimbic system also through indirect mechanisms. First, hypothalamic nuclei that have high concentrations of ARs directly innervate mesocorticolimbic nodes influencing dopamine release, which is considered the main important neurotransmitter involved in sexual excitation.[13–15] Second, some C19 steroids can rapidly modulate neuronal excitability via allosteric binding sites, including the γ-aminobutyric acid–gated chloride channel GABA receptor, another sexual stimulating pathway.[16] Third, recent studies, performed in rodents, have documented that androgens can be directly synthesized or metabolized in the brain in either female or male rats.[16] Little is known about the androgenic capacity of the mesocorticolimbic system; however, it is assumed that the local production of neurosteroids modulates gene expression or neuron excitability in an intracrine, paracrine, autocrine, or synaptocrine manner under normal physiological conditions and serves as a compensatory mechanism when circulating steroid levels are reduced.[16] Finally, T can be locally aromatized to estradiol (E2), which can bind estrogen receptors (ERs) in the mesocorticolimbic system.[16] The role of E2 in mediating the effects of T on the brain structures involved in regulating sexual desire is proven by the impaired sexual behavior occurring in aromatase knock-out mice,[17] which is restored by the administration of E2.[18] Interestingly, similar to what has been observed for ARs, even the activation of mesolimbic ERs can modulate the dopamine pathway.[16]

Human Studies

Only a little direct and indirect evidence, obtained in humans, can support the data observed in animal models. The BA 24 area, a part of the limbic cortex deeply involved in balancing emotional behavior and generalized arousal reaction, has been found to be activated by explicit erotic films in two different studies by using both positron emission tomography[19] and functional magnetic resonance imaging.[20] Furthermore, TRT in symptomatic hypogonadal men increased blood perfusion (as assessed by single-photon emission-computed tomography), in BA 24, in the midbrain and superior frontal gyrus, along with an improvement in hypogonadal symptoms.[21] Further support is derived from data obtained in a large sample of subjects seeking medical care for sexual dysfunction at our unit between 2000–2015. Figure 1, panel A, shows that T levels are inversely related to the presence of hypoactive sexual desire, as assessed by question 14 of the Structured Interview on Erectile Dysfunction structured interview,[14]

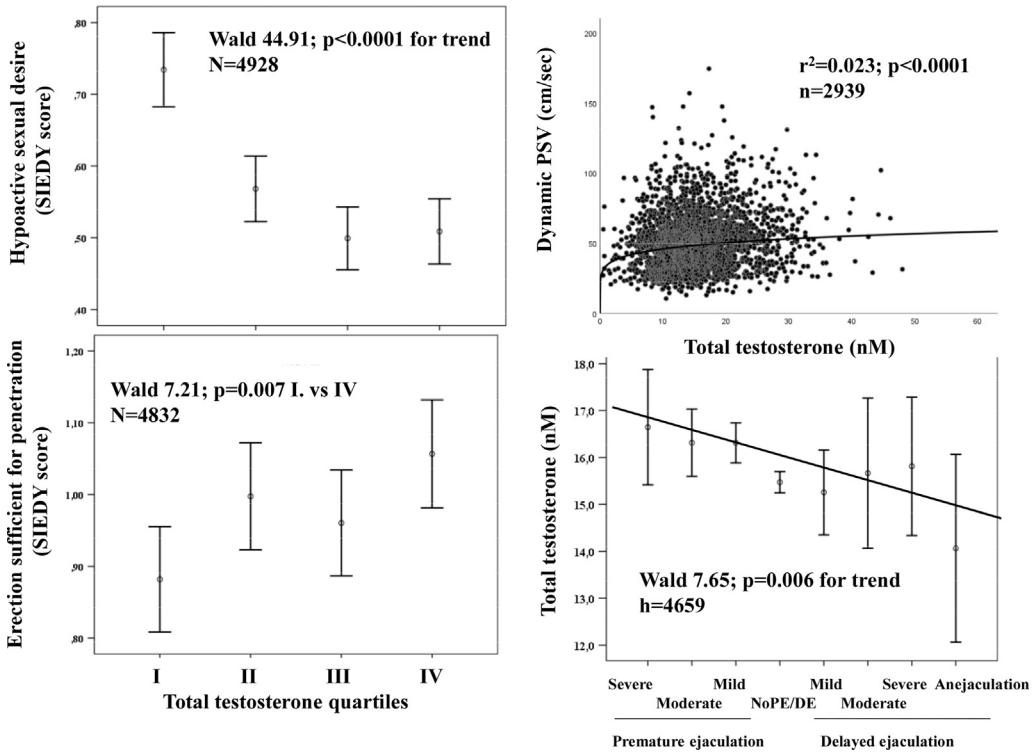

Figure 1. Severity of sexual symptoms and dynamic peak systolic velocity (PSV) according to total testosterone levels. Data derive from ordinal logistic and linear regressions adjusted for age. Abbreviations: SIEDY = structured interview on erectile dysfunction; PE = premature ejaculation; DE = delayed ejaculation.

even after adjustment for age. Despite this evidence, more conflicting data are derived from epidemiologic studies evaluating the relationship between circulating T levels and reduced libido in aging men. Only a weak association between total T and sexual desire was reported by the Massachusetts Male Aging Study.[22] In contrast to this study, the Concord Health and Aging in Men Projects, a prospective study including 1,226 elderly dwelling men in Australia, found a close association between the decline in T >2 years of follow-up and the reduction of libido.[23] Similarly, the European Male Aging Study, involving more than 3,400 men from 8 European centers, documented that decreased sexual thoughts are one of the most specific symptoms related to T deficiency in the cross-sectional evaluation.[24] Later on, these data were confirmed in a prospective analysis of the same study.[25] Similar results were more recently reported in a population of ≤5,000 men consulting for sexual dysfunction at our Unit[26] and in the baseline analysis of the data derived from the Testosterone Trials (TTrials), a survey performed in ≤800 community-dwelling men recruited from 12 sites in the United States.[27] Besides hormones, several other factors, including psychiatric, relational, or pharmacologic conditions, can influence sexual desire.[12] All of these factors can influence the role of T in regulating sexual desire and explain, at least partially, the aforementioned conflicting data reported in the epidemiologic surveys.

The contribution of E2 in the regulation of male sexual behavior, in humans, has also been confirmed. In particular, an unexpected improvement of sexual desire and frequency of sexual activity has been observed during transdermal E2 treatment, in some cases of subjects with aromatase deficiency.[28,29] In addition, a study performed in healthy men with experimentally induced hypogonadism documented that the simultaneous administration of anastrozole prevented the TRT-observed restoration of sexual desire.[30]

Finally, a role for a local androgen metabolism within the central nervous system, that is, neurosteroids, in the control of sexual behavior, is derived from data obtained in patients with benign prostate hyperplasia treated with 5-α reducatase inhibitors (5ARI) to decrease prostatic dihydrotestosterone levels. A recent meta-analysis of the available placebo-controlled trials documented that the use of 5ARI resulted in up to a 2−fold increased risk of reduced libido when compared to placebo.[31] Interestingly, in some cases the reduction of sexual desire persisted even after 5ARI were withdrawn.[32] A possible explanation is that blocking 5α-reductase within the brain could impair other 5α-reduced steroid metabolites, acting as neurosteroids.[32]

Erectile Function

A large body of evidence documented that androgens modulate nearly every factor involved in regulating penile erection at a local level. In particular, corpora cavernosa structure, function, and innervation, as well as intercellular mechanisms involved in the regulation of erection and detumescence, are under androgen control.[33−35]

Animal Studies

The main limitation regarding the analysis of the data derived from animal models deals with the fact that the vast majority of early studies used experimental conditions characterized by a severe hypogonadism, that is, obtained through surgical or medical (gonadotropin-releasing hormone) castration. These data can hardly be transferred to the human physiology of erection, with few exceptions, including bilateral orchiectomy for testis cancer and androgen deprivation for prostate cancer. More recent studies, however, have applied a model of high-fat diet—induced hypogonadism. This model is more closely linked to the hypogonadism of everyday clinical practice. Results have essentially confirmed findings from castration studies.[33–35]

Penile Structure. Androgens are critical for maintaining the right balance between trabecular smooth muscle and connective tissue. Androgen deprivation is characterized by the reduction in the content of trabecular smooth muscle cells and by the increase in the extracellular matrix along with the accumulation of fat cells (fibroblasts or preadipocyte-like cells), especially in the subtunical region of the corpus cavernosum.[33–35] The working hypothesis (*neuronal circuitry hypothesis*) supports the idea that androgens play a crucial role in maintaining the adequate penile neuronal stimulation of the corpora cavernosa, required for maintaining tissue structural integrity.[33–35]

Regulation of Nitric Oxide Pathway. Nitric oxide (NO) is the most important mediator of the erectile process. NO is synthetized upon cholinergic stimulation by the enzymes NO synthase (NOS), in the endothelial cells (eNOS) and in non-adrenergic/non-cholinergic (NANC) nerves (nNOS). After its production, NO diffuses into penile smooth muscle cells where it stimulates the formation of cyclic guanylate monophosphate (cGMP), which in turn, promotes their relaxation.[33–35] Several animal models have documented that both eNOS and nNOS, as well as their pathways downstream, are positively modulated by androgens.[33–35]

Regulation of Phosphodiesterase Type 5. The type 5 phosphodiesterase (PDE5) is the molecular mechanism involved in the conclusion of erection. A putative androgen response element is present in the PDE5 gene, which would suggest the possibility of direct androgenic regulation.[33–35] In vitro and in vivo rat and rabbit models have documented a reduction of PDE5 expression with reduced T levels, restored with T administration.[33–35] Although androgens are considered the main regulators of PDE5, more-recent evidence has emphasized a possible inhibitory role of estrogens.[36] Hence, the androgens/estrogens ratio rather than the androgens alone seems to represent better the regulator of PDE5 expression and function.[33–36]

Regulation of Contractile Pathways. T down-regulates the activity of RhoA-ROCK (Ras homolog gene family member A-Rho-associated, coiled coil containing protein kinase) pathway, which is involved in the sensitization to calcium of penile smooth muscle cells, allowing prolonged relaxation.[33–35] In addition, androgens regulate α1-adrenergic responsiveness of smooth muscle cells. In particular, reduced T levels enhance responsiveness to α-adrenergic agonists, resulting in increased sympathetic cavernosal smooth muscle tone.[33–35]

Figure 2 represents the relationship between circulating T and the maximal acetylcholine responsiveness in a large series of rabbits (n = 100) fed a regular or a high-fat diet, which induced a metabolic impairment similar to the features of metabolic syndrome, including hypogonadotropic hypogonadism and erectile dysfunction. Data from rabbits fed a high-fat diet supplemented with T are also represented. The best-fitting model is a logarithmic relationship (calculated $R^2 = 0.237$, $P < .0001$). Considering that acetylcholine responsiveness recapitulates the entire erectile process, including the ability to produce and to respond to NO, the logarithmic relationship demonstrates a clear T dependency of the penile relaxation within a T range in the hypogonadal range (total T < 10 nmol/L). Conversely, at higher T levels, this relationship is greatly reduced or even eliminated.

Human Studies

According to animal models, T controls the entire erectile process, including its initiation (ie, NO production) and its conclusion (PDE5 activity). Considering this dual, apparently opposite, effect of T on NO (cGMP generation) and PDE5 (cGMP metabolism) and its appearance only in the hypogonadal range, it is expected that clinical results will be conflicting. In fact, they are conflicting, at least in epidemiologic studies.

The Massachusetts Male Aging Study failed to find a significant association between prevalence of ED and total T (TT) or bioavailable T.[37] Similarly, in the European Male Aging Study study only a weak association between ED and free T was observed.[38] However, using a spline regression analysis, the same authors showed a significant relationship between total T and ED at total T concentrations ≤8 nmol/L, whereas the relationship shows a plateau for higher T levels.[38] Similarly, baseline data of TTrials showed only a small but statistically significant association between ED and both TT and FT.[27] Overall these data suggest that ED should be considered as a distinctive symptom of hypogonadism only when T is clearly subnormal, whereas different other factors including cardiovascular,[39,40] relational[41,42] and intrapsychic[43,44] determinants can better contribute to the pathogenesis of ED in men with borderline T levels. Figure 1, panels B and C, obtained in the aforementioned sample of patients seeking medical care at our Unit for sexual dysfunction, essentially confirm these observations. In particular, Figure 1, panel B shows the relationship between total T levels and the ability to obtain an erection sufficient for penetration. After the adjustment for age, no significant association was documented when the whole population was considered (not shown). However, when the data were analyzed as a function of T quartiles, the association was confirmed only in the lowest T quartile (ie, hypogonadal status; total T < 11.2 nmol/L). Figure 1, panel C,

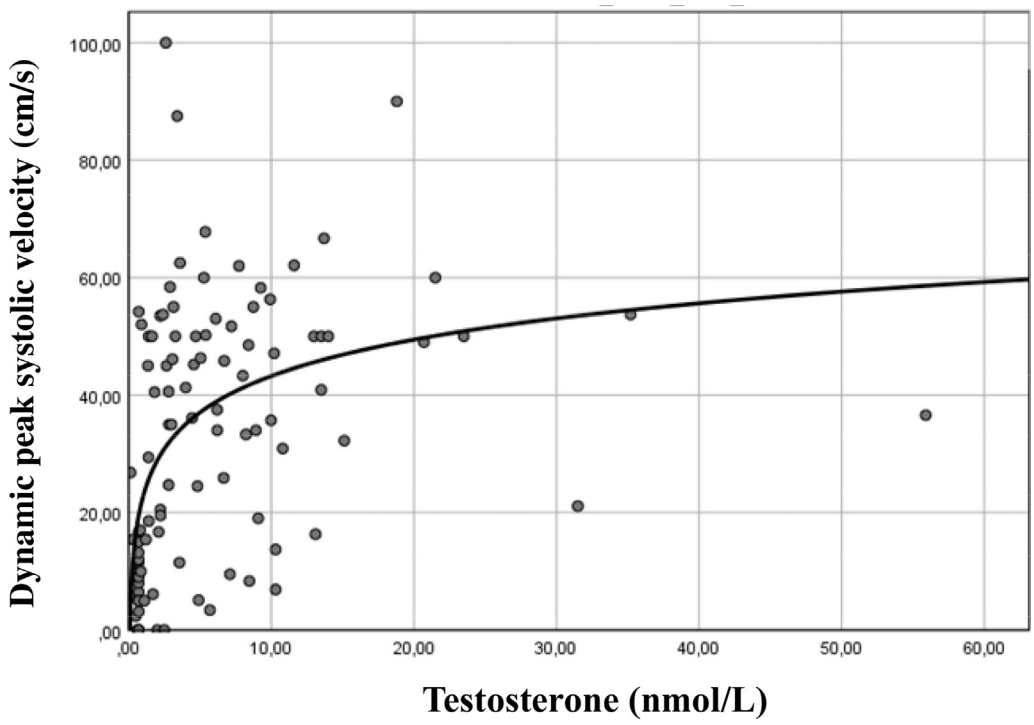

Figure 2. Relationship between total testosterone and dynamic penile blood flow.

shows the relationship between T levels and the dynamic peak systolic velocity at penile Doppler ultrasound scanning. Results are very similar to those from animal studies, as depicted in Figure 2. In fact, the best-fitting regression line shows that the relationship between T and penile blood flow is almost linear in the presence of a biochemical hypogonadism (total T $<$ 10 nmol/L), but almost absent in the eugonadal range. Hence, experimental and clinical (epidemiologic) evidence indicates that T has a modest, positive effect only in hypogonadal men. Intervention studies essentially support this view (see below).[33–35]

Ejaculation

Most of the available evidence concerning the physiological involvement of T in the ejaculatory process derives from animal models, whereas the data on men are scanty.[9,35]

Animal Studies

As reported above, ARs are expressed in several areas of the brain, including the medial preoptic area, bed nucleus of the stria terminalis, median amygdala, and posterior thalamus, which are also involved in the control of the ejaculatory reflex.[9,35] At this level, T can negatively influence serotonin turnover.[9] In addition, other evidence has shown that T can modulate ejaculatory reflex acting also at the spinal and peripheral level. Spinal nucleus of the bulbo-cavernosus nerve, as well as muscles of the pelvic floor (bulbo-cavernosus, ischio-cavernosus and levator-ani muscle), are positively modulated by androgens.[9,35] Finally, the integrated NO–PDE5 pathway is expressed even in the male genitalia tract, because it is one of the most important factors involved in its contractility under T control.[9]

Human Studies

Only a few reports have investigated the role of androgens in regulating ejaculatory reflex. In a large sample (3,000 men) of subjects seeking medical care for sexual dysfunction at our Unit, an inverse association between the reported ejaculatory timing during penetrative intercourse and T levels was observed.[9] The latter data were, here, confirmed in a larger sample (n = 4,659) of patients seeking medical care at our Unit for sexual dysfunction (Figure 1, panel C). This association was not confirmed in a sample of 1,429 dwelling men from Finland (mean age 26.9 ± 4.7 years)[45] and in a survey of ≤1,000 men with delayed ejaculation.[46] In addition, more recent data, obtained in 271 outpatients (mean age 26.6 ± 1.9 years) consulting for evidence-based lifelong premature ejaculatory, documented a significant negative association between polyglutamine (cytosine adenine guanine)-repeats in the N-terminal transactivation domain of AR and ejaculatory timing, suggesting that genetic factors can modulate the association between T levels and ejaculatory control.[47]

TRT OUTCOMES IN PATIENTS WITH SEXUAL DYSFUNCTION

Available Testosterone Preparations

Nowadays, several T formulations are available for TRT. The analysis of the specific characteristics of T preparations is beyond the aim of this article, and the most important pharmacodynamic and pharmacokinetic data are summarized in Table 1 and revised elsewhere.[48–51] Although direct comparisons among different T products are lacking, long-acting injectable T undecanoate (TU) and T gels represent the most frequently prescribed and most manageable

Table 1. Available testosterone preparations for the treatment of adulthood hypogonadism

Formulation	Trade names	Chemical structure	Half-life	Standard dosage
Oral				
Testosterone undecanoate	Andriol Andriol Testocaps	17-α-hydroxyl-ester	4 h	120–240 mg 2–3 times/d
Mesterolone	Proviron	1α-methyl-4,5α-dihydrotestosterone	12 h	50–100 mg 2–3 times/d
Parental				
Testosterone enanthate	Testoviron Depot Delatestryl Testoenant	17-α-hydroxyl-ester	4–5 d	250 mg every 2–3 wk
Testosterone cypionathe	Delatestril	17-α-hydroxyl-ester	8 d	200 mg every 2–3 wk
Testosterone propionate	Testovis	17-α-hydroxyl-ester	20 h	100 mg every 2 d
Testosterone undecanoate in castor oil	Nebido Aveed (US)	17-α-hydroxyl-ester	34 d	1000 mg every 10–14 wk 750 mg every 10 wk
Surgical implants	Testopel Testoimplant	Native testosterone	—	4–6 implants, 200 mg, lasting up to 6 mo
Transdermal				
Testosterone patches	Not scrotal: Androderm Andropatch Testopatch	Native testosterone	10 h	50–100 mg/d
Testosterone gel 1–2%	1% gel: 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 US)	Native testosterone	6 h	50–100 mg/d
Underarm testosterone (testosterone solution 2%)	Axiron	Native testosterone	NA	60–120 mg/d
Dihydrotestosterone	Andractim	Native dihydrotestosterone	NA	5 or 10 g/d
Transmucosal				
Testosterone buccal	Striant	Native testosterone	12 h	30 mg/twice daily
Testosterone nasal	Natesto	Native testosterone	10–100 min	11 mg 3 times/d

NA = not available.

T preparations.[52,53] Conversely, oral TU is no longer considered a valid therapeutic option because of its unpredictable absorption.[48–51] In addition, the older T injectable formulations lead to wide plasma T fluctuations, increasing the risk of dangerous side effects, such as polycythemia.[54] T pellet implant represents another effective option, but its application is quite invasive, making this option unattractive for many patients.[48–52] Finally, trasmucosal or nasal formulations are still associated with local side effects or the necessity of multiple administration doses, reducing their attractiveness.[48–52]

TRT Sexual Outcomes

As reported in the previous sections, T profoundly regulates all aspects of sexual function and, in particular, erectile

Table 2. Characteristics of the observational/registry studies evaluating the effect of testosterone replacement therapy on several sexual function parameters

Study	No. of patients	Study name	Follow-up (mo)	T preparation	Mean age (y)	Sexual function parameters			
						Libido	Erectile function	TRT + PDE5i	Ejaculation
Zitzmann et al[55]	1,438	IPASS	9–12	Long-acting injectable TU	49.2	↑	↑	↑	NA
Khera et al[56]	849	TRiUS	12	T gel 1%	51.2	↑	↑	NA	↑
Rosen et al[57]	750	RHYME	36	Mixed	59.1	↑	↑	↑	NA
Rastrelli et al[58]	1,954	SIAMS-NOI	12	Mixed	50.9	↑	↑	NA	↑
Permpongkosol et al[59]	428	Prospective registry	60	Long-acting injectable TU	65.6	↑	↑	NA	↑
Almehmadi et al[60]	261	Prospective registry	96	Long-acting injectable TU	58	NA	↑	NA	NA

IPASS = International, Post-Authorisation Surveillance Study Study; NA = not available; PDE5i = PDE5 inhibitor; RHYME = Registry of Hypogonadism in Men; SIAMO-NOI = Società Italiana di Andrologia e Medicina della sessualità-Osservatorio Nazionale Outcome Ipogonadismo; T = testosterone; TRiUS = Testim Registry in the United States; TRT = T replacement therapy; TU = testosterone undecanoate.

function and libido.[33–35] Hence, a large body of evidence has documented the positive effects of TRT on sexual function in hypogonadal men. Conversely, neutral or negative data have been observed when T is administered in eugonadal men.

In the following section, a critical analysis of the available data supporting a role for TRT in men with sexual dysfunction will be provided. Data obtained from either observational register studies or from meta-analyses including randomized placebo-controlled trials (RCT) will be analyzed. In addition, when available, specific subanalysis categorizing outcomes according to the different T preparations will be scrutinized.

Observational Register Studies

Few large observational register studies have evaluated the impact of TRT on sexual symptoms (Table 2). The International, multicenter, Post-Authorisation study is a large survey performed on long-acting injectable TU conducted at 155 centers in 23 countries in Europe, Asia, Latin America, and Australia.[55] Overall, 1,438 hypogonadal men (mean age 49.2 ± 13.9 years) received 6,333 injections, with a follow-up of up to 12 months. TRT resulted in significant improvement of sexual desire and erectile function, along with amelioration of overall quality of life. In addition, the subjects who declared a concomitant use of PDE5 inhibitors during the course study reported an overall significant improvement of the outcomes during the combined therapy.[55] Conversely, no information on the effects of TRT on ejaculatory outcomes was reported.[55]

The Testim Registry in the United States is a multicenter registry of hypogonadal men treated with a testosterone 1% topical gel and followed up for 12 months.[56] The study included 849 hypogonadal men (mean age 51.2 ± 11.9 years) and shows that TRT resulted in an improvement of all the domains of sexual function investigated, including libido, erectile function, and ejaculation.[56] The Registry of Hypogonadism in Men is a prospective, multinational patient registry including untreated men with diagnosed hypogonadism. The analysis of 999 subjects (mean age 59.1 ± 10.5 years), 750 of whom received at least 1 T prescription during 3 years of follow-up.[57] Over untreated subjects, patients who received TRT showed an overall improvement of sexual desire and erectile function, but, similar to what was reported in the International, multicenter, Post-Authorisation study, no data on ejaculatory function were provided.[57] The Società Italina di Andrologia e Medicina della sessualità-Osservatorio Nazionale Outcome Ipogonadismo is an Italian disease registry with a collection of longitudinal data of hypogonadal men attending 15 highly specialized Italian Endocrinology/Andrology centers.[58] Overall, 432 subjects (mean age 50.9 ± 14.9 years) were followed up for a 12-month period. Among them, 55 did not start TRT during follow-up for different reasons.[58] At the end of the study, TRT was associated with an improvement of all International Index of Erectile Function (IIEF)-15 subdomains, including orgasmic function.

Some other registers, with even longer follow-up, essentially confirmed the above findings. Quite recently, Permpongkosol et al[59] reported data on 428 men treated with the long-acting TU up to 8 years, showing a constant and progressive improvement in all IIEF-15 subdomains and in the Aging Male Symptoms score. Similar results were reported in another long-lasting register, including 261 patients (mean age 58 years) treated with the long-acting injectable TU for up to 5 years.[60]

Lessons from TTrials

Despite their strengths, observational studies present important limitations, including selection, information, and confounding biases. In addition, usually limited information regarding the level of T before and during testosterone therapy (TTh) are available. Accordingly, physicians often prefer to treat

Table 3. Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy and several sexual parameters

Inclusion criteria	Isidori et al[65]		Bolona et al[66]		Corona et al[67]		Elliot et al[71]		Ponce et al[72]	
Number of trials included	17		17		29		17		4	
Number of patients analyzed	657		862		1,930		3,165		1,179	
Hypogonadism definition used (TT)	10 nmol/L		10.4 nmol/L		12 nmol/L		12 nmol/L		10 nmol/L	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Outcomes according to T preparation		X		X	X			X	X	
Sexual parameter analyzed										
Erectile function	X		X	X	X		X		X	
Libido	X		X	X	X		X		X	
Morning erections	X			X	X			X		X
Orgasmic function		X		X	X			X		X
Sexual satisfaction	X			X	X			X	X	

T = testosterone; TT = total testosterone.

healthier individuals, and healthier individuals more often request treatment for their hypogonadism-related problems. RCTs are often considered as the highest level of evidence for evaluating interventions in health care.

In men, T levels progressively decline as a function of age. Associated morbidities and in particular obesity and metabolic diseases can further accelerate this process.[61] The role of TRT in aging men is conflicting.[62] In 2003, the Institute of Medicine of the National academy of Sciences in the United States emphasized the limited information on the beneficial role of TRT in aging men.[62] The testosterone trials were designed and founded as a coordinated set of 7 trials to better understand the role of TRT in elderly men. In these trials, 788 hypogonadal men (TT $<$ 2.75 ng/mL) $>$65 years of age (mean age 72 years) were enrolled in a 12-month placebo-controlled study with T gel 1% used as an active treatment.[62] TRT improved most aspects of sexual function, and the final effect was proportional to the increase in T levels. As expected, the observed improvement was higher for the frequency of sexual activity and libido than erectile function.[62] These findings are not surprising and in line with the high prevalence of vascular damage of the penile bed observed in aging men.[63,64] On the other hand this would imply that, for older people, hard erections are not an essential requisite to remain sexually active.[44]

Meta-Analyses

Along with RCTs, meta-analyses are often considered as the highest level of evidence for evaluating interventions in health care. In addition, these statistical instruments are particularly useful to address questions for which multiple data sources are conflicting.

Up to now, 8 systematic meta-analyses evaluating the effect of TTh on several sexual outcomes have been published,[11,65–71] some of them showing limitations. For example, specific standardized mean outcomes were not clearly documented in 2 of them.[68,69] In addition, our last meta-analysis [11] was based on a limited number of studies, selecting those producing a mean score on the IIEF questionnaire. Hence, to present more comparable data, we decided to focus our present analysis only on the studies reporting sexual function outcomes as effect size. According to Cohen,[72] a small treatment-effect size is considered to be $\leq$0.2, a medium effect size to be $\leq$0.5, and a large effect size to be $\leq$0.8. The trials included ranges from 4 to 29 and the number of subjects considered from 657 to 3,165 (Table 3). Erectile function and libido outcomes were documented in all the meta-analyses considered, whereas the effect of TTh on morning erections and sexual satisfaction were reported by 2 [65,67] and 3 studies,[65,67,71] respectively. Finally, orgasmic function outcome was investigated only in 1 study (see also Table 3). [67] In addition, the threshold of 10 nmol/L of total T, for the definition of hypogonadism at enrollment, was considered by 3 studies,[65,66,71] whereas 3 meta-analyses considered 12 nmol/L (Table 3).[67,71] When the analysis was limited to only hypogonadal patients, TRT resulted in a significant improvement of all the sexual parameters evaluated (Figure 3). Conversely, when data obtained in studies enrolling eugonadal patients were considered, no effect on erectile function and libido was observed (not shown).[51] According to Cohen,[72] TRT resulted in a mild to moderate effect in the vast majority of the available meta-analyses. These effects were essentially confirmed by our recent meta-analysis performed using only those studies with the IIEF score used as the main outcome.[11] In addition, the same study documented that the effects were lower in men with a higher prevalence of organic conditions, underlining possible vascular damage such as obesity and diabetes, and higher in subjects with more severe hypogonadism.[11] Accordingly, the BLAST Study, a 30-week randomized placebo-controlled RCT evaluating the effects of long-acting injectable TU in 199 hypogonadal men identified from 7 primary care type 2 diabetes registers, clearly showed that benefit in sexual symptoms after treatment was evident principally in patients with TT levels $\leq$8 nmol/L.[73] Similar results were observed in other RTCs.[74,75] In

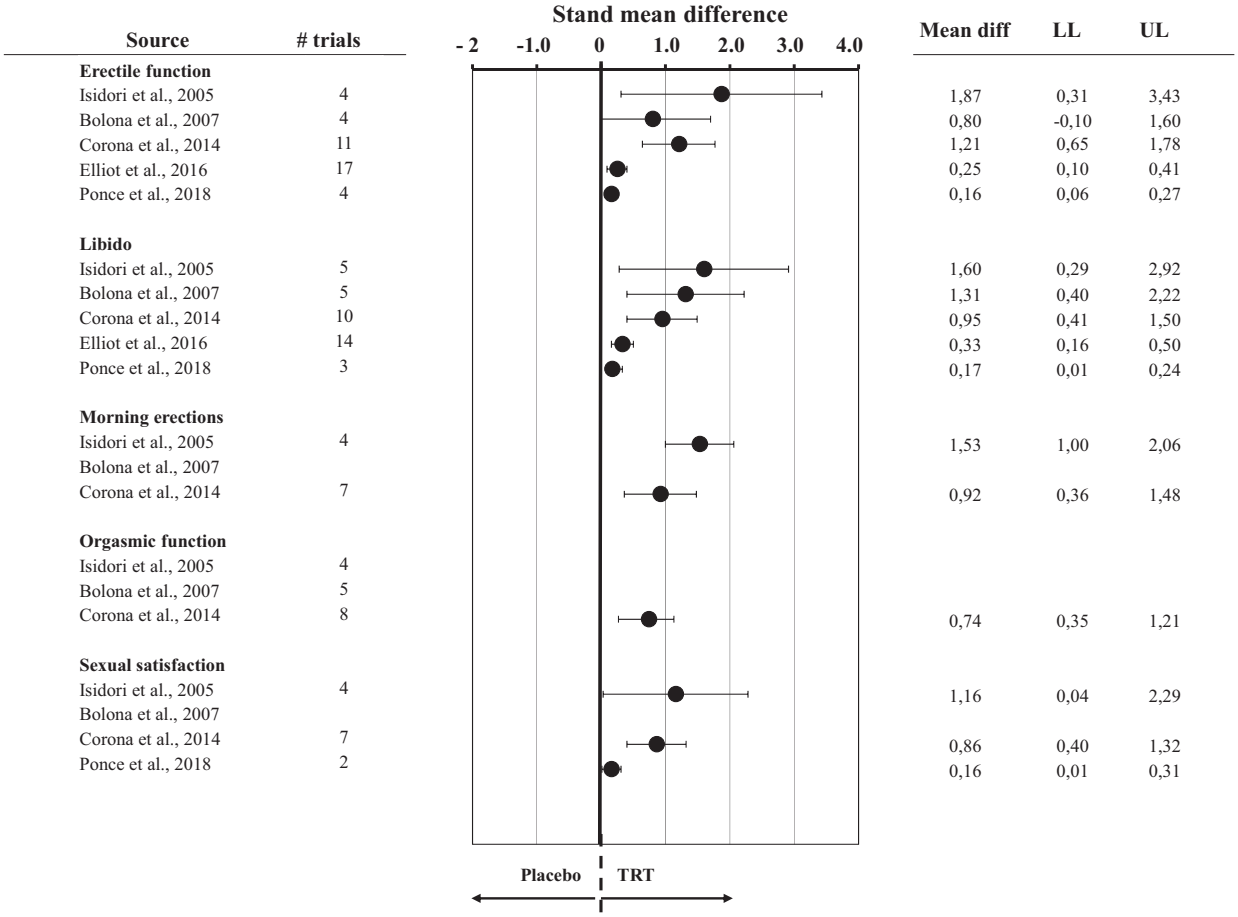

Figure 3. Summary of the results obtained by the available meta-analysis on the efficacy of testosterone replacement therapy (TRT) on sexual symptoms. Abbreviations: Diff = difference; LL = lower limit; UL = upper limit.

addition, it is important to clarify that depression is frequently associated with diabetes, and this relationship can further complicate ED in these patients.[40,76,77]

Only our study has investigated the possible effect of TRT according to the use of different T preparations. When studies enrolling only eugonadal patients were excluded, oral preparations did not show a positive effect when compared with placebo on erectile function, whereas only a small effect on libido was detected (Table 4). Conversely, no difference in the positive efficacy of both transdermal and parental testosterone preparations was documented (Table 4). Insufficient data were available to evaluate possible differences among specific transdermal and parenteral preparations. In particular, no comparison between the older, short-term, injectable testosterone formulations and the newer, long-acting, injectable TU was possible.

Table 4. Effect size (with 95% CI) on erectile function and libido across randomized controlled trials evaluating the effect of TRT vs placebo

Type of testosterone preparation	Outcome
Erectile function	
Oral	1.77 [−0.19; 3.73]
Transdermal	0.31 [0.04; 0.59]
Parental	0.46 [0.18; 0.74]
Libido	
Oral	1.41 [0.14; 2.68]
Transdermal	0.32 [0.14; 0.51]
Parental	0.81 [0.31; 1.32]

TRT = testosterone replacement therapy.
Adapted from reference.[50]

Finally, only 1 meta-analysis[67] investigated the possible effect of the combined therapy with TRT and PDE5 inhibitors. The data confirmed possible advantages using the combined therapy when placebo- and non-placebo—controlled trials were considered. Conversely, when the analysis was restricted to only placebo-controlled RCTs, the significant effect was lost. However, it is important to recognize that only limited numbers of trials were available at that time and that many of them enrolled a mixed population of eugonadal/hypogonadal subjects.[11] In particular, 3 of 5[78–80] of the included RCTs enrolled mixed eugonadal/hypogonadal samples. In addition, in the large Spitzer trial,[81] although only hypogonadal subjects were enrolled, patients underwent a sildenafil-alone run-in period before TRT, at the end of which T increased up to the normal range (≤12.0 nmol/L). In line with this

observation, some evidence has documented that sexual inertia is associated with functional hypogonadotropic hypogonadism, which can be restored with the improvement of sexual activity.[82–84]

CONCLUSIONS

Overall, available data indicate that T represents an important modulator of all the steps involved in the regulation of the male sexual response cycle. This association is attenuated in the epidemiologic studies because, besides hormones, other factors including organic, relational and intrapsychic determinants can modulate androgens' role. Evidence arising from interventional studies confirms a possible role of TRT in ameliorating several aspects of sexual functioning including libido, erectile function and overall sexual satisfaction. Conversely, data on the role of TRT in improving orgasmic function are more conflicting and analyzed only in a limited number of RCTs. It is important to recognize that, whatever outcome is considered, the effects of TRT are clearly evident only in the presence of hypogonadal status (ie, total T $<$ 12 nmol/L), whereas the positive effects of TRT are no longer confirmed for higher T levels. In addition, TRT alone can be effective in restoring only milder forms of ED, whereas the combined therapy with other drugs is required when more severe vascular damage is present.

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