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REVIEW ARTICLE

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Controversial aspects of testosterone in the regulation of sexual function in late-onset hypogonadism

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[Correction added on 2 June 2020, after first online publication: 'different meta-analyses' was typeset wrongly on the Materials and Methods in the abstract and it has now been removed from this version.]

Abstract

Background: Testosterone (T) plays a pivotal role in coordinating a series of psychological, cognitive and physical events that might (or might not) culminate in male sexual activity. In fact, T deficiency is associated, in a statistically significant way, with several sexual dysfunctions including erectile dysfunction (ED), reduction of spontaneous erection and hypoactive sexual desire (HSD). Although these associations are statistically significant, there is debate if they are also clinically meaningful. In addition, sexual dysfunctions are present also in several metabolic conditions - such as type 2 diabetes mellitus and obesity - that often associate with low T. In particular, this is the case of ED, but not of HSD, that, therefore, should be considered a more genuine correlate of T deficiency in adulthood and aging (late-onset hypogonadism, LOH).

Objectives: The aim of this review is to scrutinize evidence from our and other studies on sexual effects of T replacement therapy (TRT) in LOH.

Materials and methods: We will use preclinical and clinical data coming from our and other laboratories and meta-analyses.

Results: Intervention studies in clinical trials involving subjects with LOH, and their meta-analyses, indicate that TRT is able to ameliorate HSD, spontaneous erection and ED. However, the relative improvement of ED by TRT is marginal [2-3 points of International Index of Erectile Function-erectile function domain (IIEF-EFD)] and significantly smoothed in subjects with the aforementioned metabolic conditions. In LOH, positive effects of TRT on other domains of sexual activity, such as orgasm and sexual satisfaction, are also apparent in the different meta-analyses.

Discussion and conclusions: Hence, TRT is a reasonable treatment for restoring sexual drive in LOH, with some additional positive effects also on erection (spontaneous and sexual-related) and on orgasm. In contrast, preclinical and clinical studies indicate that T administration to eugonadal subjects does not improve male sexual activity.

KEYWORDS

erection, late-onset hypogonadism, sexual desire, testosterone, therapy

1 | INTRODUCTION

The Roman poet Marcus Valerius Martialis (c. 38 and 41 AD-c. 102 and 104 AD) wrote in one of his epigrams "Cur tantum eunuchos habeat tua Caelia, quaeris, Pannyche? Volt futui Caelia, nec parere" (Martial Epigrams 6 67). The American poet William Procter Matthews III translated this epigram into English: "Your Celia keeps company with eunuchs:/Pannychus, do you find this odd?/It's the child she hopes to be spared, Pannychus, not the rod" (https://briefpoems.wordpress.com/2016/06/11/bedside-lamps-brief-poems-by-martial/). This is tantamount to say that in subjects without testes, as in eunuchs, fertility is impossible but sexuality could be preserved. The topic of eunuch sexuality, under a historical perspective, has been extensively covered in a review by Aucoin & Wassersung.[1] The authors conclude that eunuchs, from different cultural backgrounds, were both sexually active and objects of men's and women's active sexual desire. For instance, this was the case for concubines in a harem, at least in pre-modern polygamous societies.[1] Modern research has substantiated the notion that severe testosterone (T) deficiency is associated with a preserved erection. In a double-blind, placebo-controlled study, explicit erotic movies stimulated full erections in severely hypogonadal patients.[2] Interestingly, these erections were longer lasting than in control individuals.[2] However, spontaneous erections, as objectively measured by nocturnal penile tumescence, were quantitatively reduced in hypogonadal subjects and restored by T replacement therapy (TRT).[2] Do these findings indicate that T is not essential for male sexuality?

2 | AIM AND METHODS

The aim of this narrative review was to analyze evidence suggesting a role for T in the different aspects of male sexuality focusing on penile erection, sexual motivation (libido), and orgasm in late-onset hypogonadism (LOH). LOH is a male syndromic condition of the advancing age, characterized by low levels of T associated with clinical symptoms.[3] We will use preclinical and clinical evidences coming from our and other laboratories and, when possible, data from available meta-analyses. Meta-analyses are considered the highest level of evidence for evaluating interventions in health care. A meta-analysis is aimed at combining the results of multiple scientific studies; this aggregation of information leads to a greater statistical power and more robust point estimate than those derived from each individual studies.

3 | TESTOSTERONE AND MALE SEXUALITY

During fetal life, T, along with its active metabolite dihydrotestosterone (DHT), plays a pivotal role in dictating and shaping male external and internal genitalia, which, through the actions of the same androgens, are further developed during puberty, until the achievement of the mature, adult phenotype. Disturbances of T secretion or action during fetal life can lead to severe defects in masculinization up to a completely feminine appearance, as in the case of complete androgen receptor (AR) insensitivity (very early-onset hypogonadism).[4] When T deficiency is orchestrating its effect during the pubertal transition, as in Klinefelter syndrome, a eunuchoid phenotype often results (early-onset hypogonadism). In contrast, when T deficiency appears during adulthood, the phenotype is only slightly affected or not affected at all (late onset hypogonadism, LOH). As stated before, LOH is a syndromic condition of the aging male characterized by low levels of T associated with clinical symptoms.[3] However, symptoms characteristic of LOH are relatively mild and vague and often overlapping with those of the natural male aging process and of its possible associated morbidities. Symptoms of LOH are often clustered under three distinct domains: psychological (eg, feeling sad or blue, depressed mood, decreased energy, and self-confidence), physical (eg, decreased muscle strength and physical performances), and sexual (eg, reduced sexual desire and spontaneous or sexual-related erections). Almost 10 years ago, it was clarified that in a large sample (n = 3369) of the European general population (EMAS study) only the three aforementioned sexual symptoms show a syndromic association with low total and free T in both the training and validation sets.[5] Hence, it was proposed that the simultaneous presence of reduced sexual desire and impaired spontaneous and sexual-related erections, along with a decreased total (<11 nmol/L) and calculated free T (<220 pmol/L), are necessary to define LOH. According to this definition, 2.1% of the European general population older than 40 years meets the aforementioned criteria. The biochemical thresholds to define the syndrome were derived using locally estimated scatterplot smoothing (LOESS) curve analysis, fitting the likelihood of each symptom versus decreasing concentrations of androgens, after adjusting for confounders. Although statistically significant, all the associations were relatively weak, underscoring the point that the same sexual symptom can be generated in overall eugonadal individuals by other morbidities. Later on, EMAS results were confirmed in a study involving a large cohort of subjects complaining of sexual symptoms and, therefore, consulting for them at the local sanitary service. In this "bothered" population, total T and calculated free T (cfT) show a weak, but significant, association with a composite index of sexual dysfunction that included severely reduced sexual desire and spontaneous erection, at thresholds very similar to those reported by Wu et al 2010.[6] In fact, the assessment of the Youden index showed that the best thresholds for detecting men with androgen deficiency-related symptoms were 10.4 nmol/L for total T and 225 pmol/L for cfT.[6] However, association does not mean causation. In fact, it is possible that lessened sexual activity, for any reason, could decrease testicular secretion of T. The first example was reported half a century ago. An island resident observed an increase in beard growth on the day preceding, and during, his occasional visits to his mainland lover, suggesting that coitus (and related desire) was associated with an increase

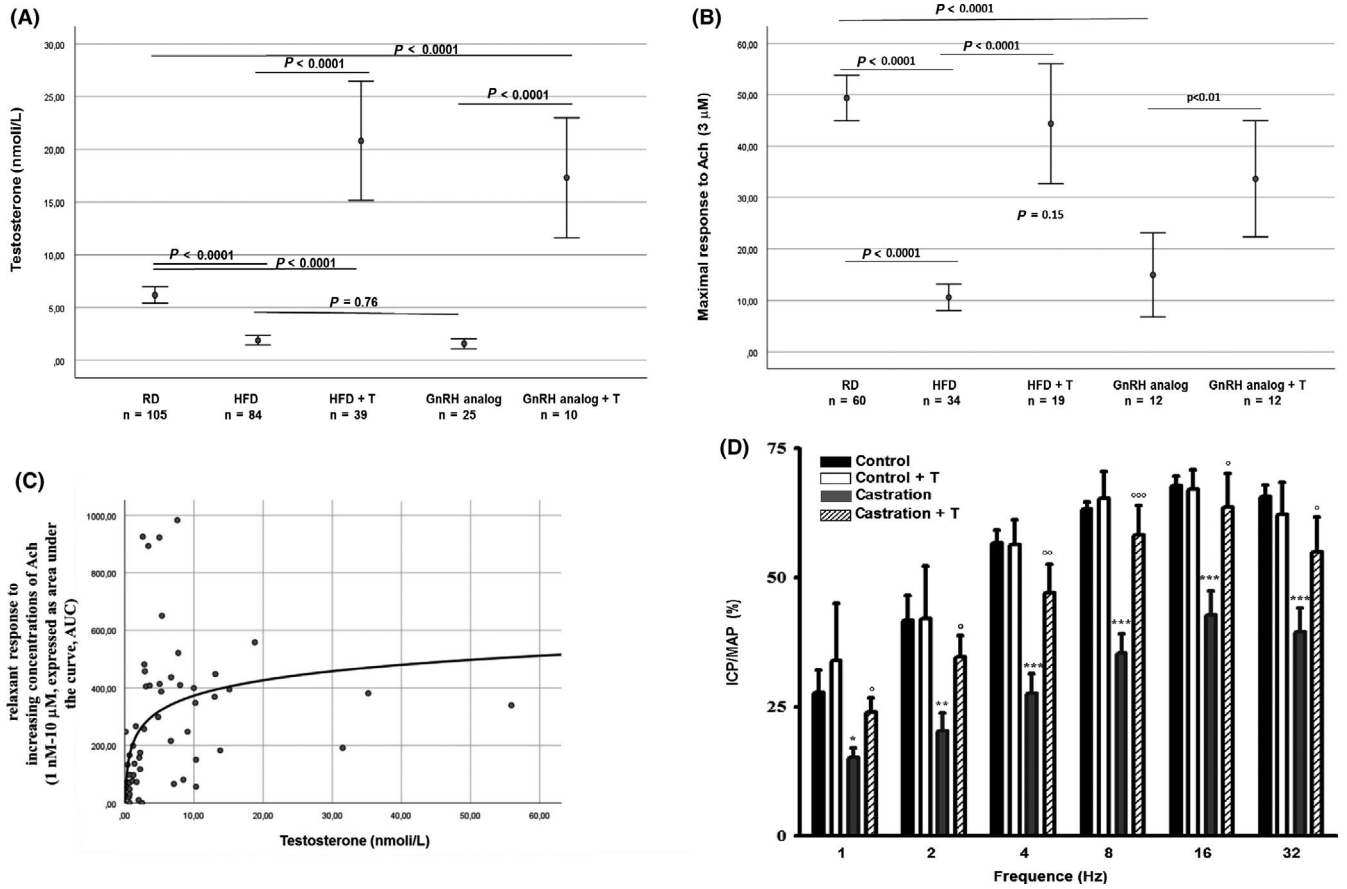

FIGURE 1 Effect of testosterone (T) on penile erection. Panel (A) Testosterone plasma levels in control rabbits (regular diet, RD), rabbits fed a high fat diet (HFD), and rabbits chronically treated with a GnRH analog (triptorelin, GnRH analog) Effects of treatment with a pharmacological dose of T to either HFD (HFD + T) or GnRH analog (GnRH analog + T) rabbits are also shown. Panel (B) Responsiveness to Acetylcholine (Ach) in isolated penile strips in the experimental groups of Panel (A). Panel (C) Relationship between the relaxant response to increasing concentrations of Ach (expressed as area under the curve) and increasing concentration of circulating T in a subgroup (n = 63) of the aforementioned rabbits. All data are partially derived from previously published studies in rabbit.[17-19,24] Panel (D) Frequency-dependent erectile response in basal condition and after treatment with T in adult control and castrated rats. Erection was elicited by electrical stimulation (2.5 V, 5 ms, 30 s) of the rat cavernous nerve at varying stimulation frequency (1, 2, 4, 8, 16, 32 Hz). Erectile function was quantified by calculating max intracavernosal pressure/mean arterial pressure (ICP/MAP) × 100 ratio for each stimulation, in at least 5 animals/experimental group. Values as expressed as mean ± SEM. Data are partially derived from a previous study in rat[25]

in androgen-dependent events.[7] Thirty years later, Jannini et al found that any effective treatment for erectile dysfunction (ED) increased otherwise borderline low T levels.[8] The T rise they found was independent from the kind of therapies employed, but strictly related to the relative improvement in ED.[8] Evidence for an opposite direction of the relationship between low T and sexual dysfunction comes from the longitudinal extension of the EMAS study. It was reported that the development of both primary and secondary hypogonadism predicts the occurrence or worsening of sexual symptoms at follow-up.[9,10] However, even in subjects that remain eugonadal at follow-up, both studies reported the occurrence or worsening of sexual symptoms.[9,10] This suggests that T is one, but not the only, determinant of sexual dysfunction in the general European population. To evaluate the comorbidity burden of sexual symptoms compatible with T deficiency in subjects consulting for sexual dysfunction, we used a validated aggregate comorbidity measure, termed "chronic disease score" (CDS), which reflects the weighted number of medications used by the patients. We found that several symptoms and signs, potentially associated with LOH, could be due to chronic illnesses, occasionally present in subjects with sexual dysfunction.[11]

As stated before, symptomatic T deficiency in adulthood (ie, LOH) is a relatively common event in the general population (2.1%). Interestingly, its prevalence is increased by a factor of ten in subjects complaining of sexual dysfunction, among whom LOH prevalence was estimated to be more than 20% of individuals.[12] Of those, one in six has primary hypogonadism, while the rest of the hypogonadal sample shows low T with inappropriate low gonadotropins (secondary hypogonadism). In half of the population with primary hypogonadism, it was possible to define a congenital or acquired damage to the testis, while, in secondary hypogonadism, the large majority (90%) does not show any evident reason for hypothalamic-pituitary-testis (HPT) deficiency.[12] The latter forms are now classified as "functional hypogonadism," a condition

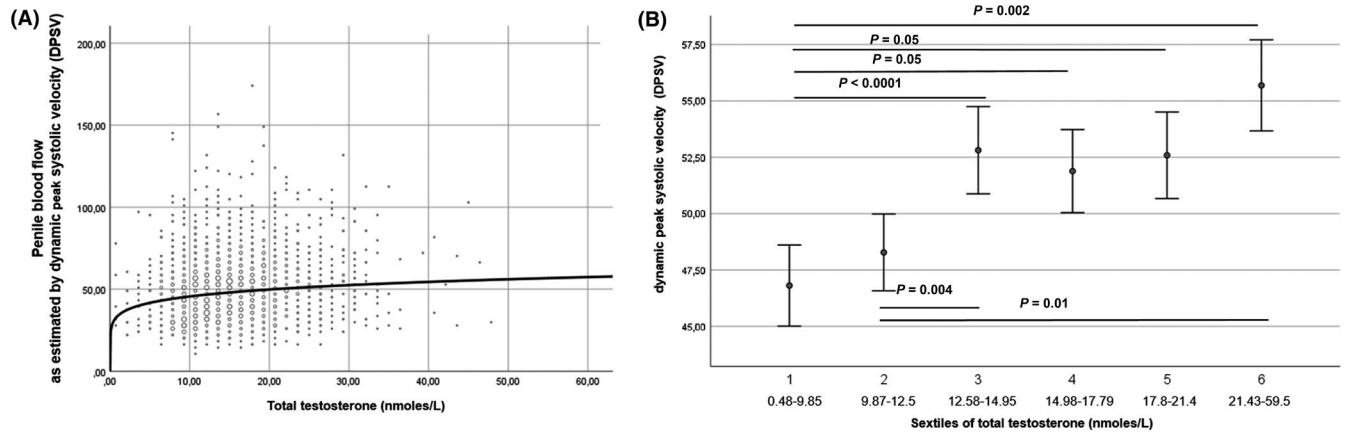

FIGURE 2 Relationship between endogenous testosterone (T) levels and penile blood flow. Panel (A) Relationship between endogenous T levels and penile blood flow, as estimated by dynamic peak systolic velocity (DPSV) at penile color Doppler ultrasound. The best fitting model is a non-linear regression, which grows exponentially from the hypogonadal range and plateaus in the eugonadal one. Panel (B). Relationship between increasing sextiles of plasmatic T levels (nmoles/L) and DPSV in a cohort of 2531 ED subjects

where the T deficit can be overcome, as it is potentially reversible, which is to be differentiated from "organic hypogonadism," where there is a proven, irreversible, HPT pathology either structural, destructive or congenital in nature.[13,14] According to this categorization of functional versus organic hypogonadism, 85% of subjects consulting for sexual dysfunction with T deficiency has functional hypogonadism, which is associated with either obesity or metabolic syndrome (MetS) or type 2 diabetes (T2DM) in the large majority of cases.[12] The most recent Endocrine Society guidelines suggest that, in functional hypogonadism, treating the underlying condition, possibly with lifestyle measures, is the first option of therapy, with no need for T treatment.[14] For example, in obesity-associated secondary hypogonadism losing weight and doing physical exercise should be the first-line intervention. It is important to recognize that both these strategies are associated with a consistent rise in T levels and in an improvement of sexual symptoms.[15] In particular, doing regular, aerobic physical exercise is associated with a four-point increase in IIEF-EFD,[16] which is almost equal to the effect of PDE5 inhibitors.

4 | TESTOSTERONE AND ERECTION IN LOH

4.1 | Preclinical data

In experimental animals, the effect of T deprivation on penile erection can be studied in preclinical models of primary (eg, castration) or secondary hypogonadism, either organic (eg, chronic administration of GnRH analog) or functional (high fat diet-induced MetS). Figure 1A shows testosterone levels in control rabbits (regular diet, RD), and rabbits fed a high fat diet (HFD) and rabbits chronically treated with a GnRH analog (triptorelin, GnRH analog).[17] Both HFD and GnRH analog induced a similar level of hypogonadism ($P < .0001$ vs RD). Effects of treatment with a pharmacological dose of T to either HFD (HFD + T) or GnRH analog (GnRH analog + T) rabbits are also shown. Interestingly, in rabbit penis, expression of the androgen receptor (AR) is highly associated with genes involved in corpora cavernosa relaxation, involving both cGMP-dependent (eg, nitric oxide, NO)[18] and AMP-dependent (eg, adenosine) pathways.[19] According to the aforementioned studies, AR expression was closely linked to NO formation (eNOS, nNOS, DDAH1), signaling (GCsa1, GCsb1, PKG1) and degradation (PDE5). In addition, it was associated with the major relaxing receptors for adenosine through the cAMP pathway (ADORA2a, ADORA2b) and NO formation (ADORA1), as it is with genes involved in adenosine metabolism (ADA, AMPD2). Genetic manipulation of NO formation (eNOS, nNOS)[20-22] or adenosine action (ADORA2b)[19] or degradation (ADA)[19] has clearly shown the crucial relevance of these pathways in penile erection.

Acetylcholine (Ach) is the primary neurotransmitter of the parasympathetic nervous system. It contributes to the physiological process of erection by inhibiting noradrenaline (NA) release by sympathetic nerves and by stimulating NO formation and release by endothelial cells of the cavernous vessels. NO activation of guanylate cyclase-mediated cGMP production, and of its downstream cGMP-dependent protein kinase G type 1 (PKG1), leads to smooth muscle relaxation, which can be counteracted by cGMP metabolism through phosphodiesterase type 5 (PDE5).[23] All these processes, including cGMP formation and breakdown (PDE5), are significantly associated with AR expression within the penis.[18,24] Considering that Ach responsiveness recapitulates a large series of events (ie, from NO formation to smooth muscle relaxation), it is interesting to know whether altering T levels could influence the response to Ach in isolated penile strips in the experimental groups of Figure 1A. Figure 1B shows experimental results. Both GnRH analog and HFD-induced HG dramatically decrease responsiveness to the maximal dose of Ach (3 μM). Although T supplementation completely restores Ach responsiveness, it does not increase the response above the control (RD) level, even if the plasmatic levels of T were higher in these groups than in the control rabbits (see Figure 1A). This is graphically

represented in Figure 1C, which reports the area under the curve to Ach responsiveness as a function of increasing concentration of circulating T in a subgroup (n = 63) of the aforementioned rabbits. The best fitting model of the experimental data is a logarithmic relationship (P = .002), with a clear decrease in steepness as long as physiological concentrations of T are reached. Similar results were obtained by our group in a rat model of primary HG (surgical castration), by studying the erectile response after in vivo electrical stimulation (ES) of the cavernous nerve, at increasing frequency.[25] Figure 1D shows, in both control and HG, the frequency-dependent increase in penile blood flow upon ES, which was depressed in castrated rats.[25] T replacement normalizes the response, but a similar administration of T to otherwise eugonadal rats does not further increase the response to ES.[25] Responsiveness to other neurotransmitters, involved in regulating the erectile process, is also positively affected by in vivo T administration in HFD-induced HG. In fact, we previously showed that T administration increased the relaxation of CC strips to adenosine in the presence of metformin.[19]

In an animal model of primary or secondary HG, the aforementioned data indicate a favorable effect of T treatment on penile erection. However, the same data clearly indicate a null effect of T administration in eugonadal animals, suggesting that T is not an aphrodisiac medication but just a hormonal substitution for T-deficient subjects.

4.2 | Clinical data

Clinical data essentially support preclinical results. In fact, in a large series of subjects with ED (n = 2531), there was a significant relationship between endogenous T levels and penile blood flow, as estimated by dynamic peak systolic velocity (DPSV) at penile color Doppler ultrasound (PCDU, P = .001, after adjusting for age and Chronic Disease Score (CDS see above). Figure 2A shows, as a bubble plot, the relationship. The best fitting model is a non-linear regression power model (F = 56.9 P < .0001), which grows exponentially from the hypogonadal range and plateaus in the eugonadal one. We therefore divided the ED population in T sextiles and verified the relationship between T and DPSV at ANCOVA, introducing as covariates possible cofounding factors, such as age and comorbidities (CDS). Figure 2B shows that the lowest two sextiles of T levels (<12.5 nmol/L) are different from the other ones, while, for T values higher than 12.5 nmol/L, there is no further increase of DPSV as a function of total T. Figure 3A shows the relationship between increasing T levels (sextiles) and reported decreased spontaneous erection (SIEDY score) in the same cohort of ED subjects.[26] After adjusting for confounders such as age and comorbidities (CDS score), the lowest sextile of T level (<10 nmoles/L) was associated with a significant reduction of spontaneous erection, while no other differences were observed for higher values of T. Similar results were observed for reduced sexual desire (SIEDY score, Figure 3B and see below). Several observational trials demonstrated that even responsiveness to PDE5i was T-dependent and, therefore, that T deficiency may impair the erectile response to PDE5i, especially in the aging male.[27] Hence, results obtained in ED patients are similar to those reported in animal models, in Figure 1. They overall suggest that T is associated with decreased penile blood flow and erection only in the hypogonadal range. Aversa et al almost 20 years ago provided the first demonstration of an association between T levels and penile blood flow.[28] However, association does not mean causation. Hence, only results from placebo-controlled intervention studies might shed light on the real value of T administration in ED patients with hypogonadism.

4.3 | Meta-analyses of randomized controlled trials

Nine meta-analyses evaluating the effect of TRT on several sexual outcomes in randomized controlled trials (RCTs) have been published thus far.[9,10,29-35] Among them, specific standardized mean outcomes were not clearly documented in two[9,29] and one[33] was based on mean differences derived from the IIEF questionnaire. In order to present more comparable data, we decided to focus the present analysis only on studies reporting sexual function outcomes using the standardized mean difference as effect size.

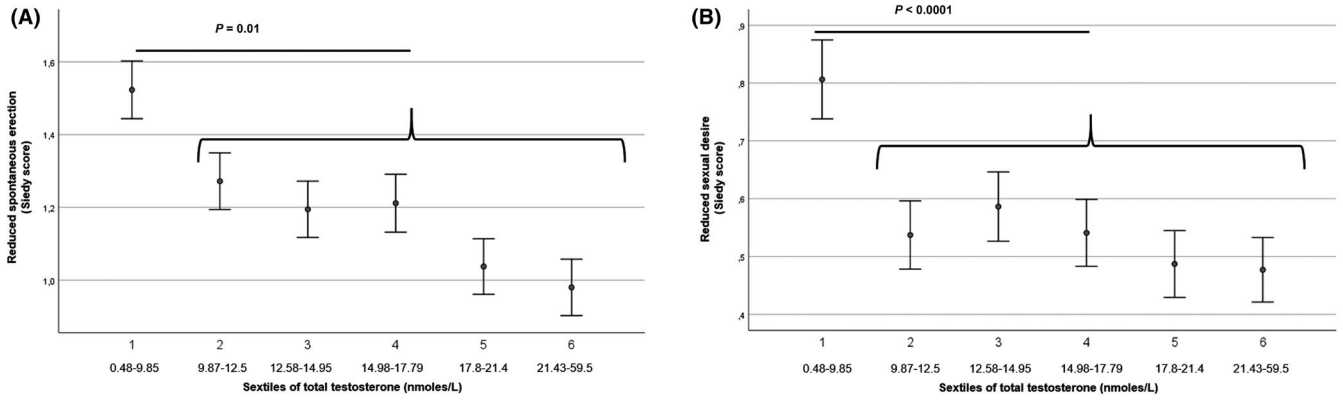

FIGURE 3 Relationship between testosterone (T) levels and erection. Relationships between increasing sextiles of plasmatic T levels (nmoles/L) and perceived reduction of spontaneous erection or reduction of sexual desire (SIEDY score, panel A and B, respectively) in a cohort of 2531 ED subjects

TABLE 1 Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy and several sexual parameters

Inclusion criteria	Isidori *et al* (2005)		Bolona *et al* (2007)		Corona *et al* (2014)		Elliot *et al* (2017)		Algeffari *et al* (2018)		Ponce *et al* (2018)	
Number of trials included	17		17		29		17		4		4	
Number of patients analyzed	657		862		1930		3165		587 with T2DM		1179	
Hypogonadism definition used (TT)	10 nmol/L		10.4 nmol/L		12 nmol/L		12 nmol/L		10 nmol/L		10 nmol/L	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
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		X
Orgasmic function		X		X	X			X		X		X
Sexual satisfaction	X			X	X			X	X		X	

Abbreviation: TT, total testosterone.

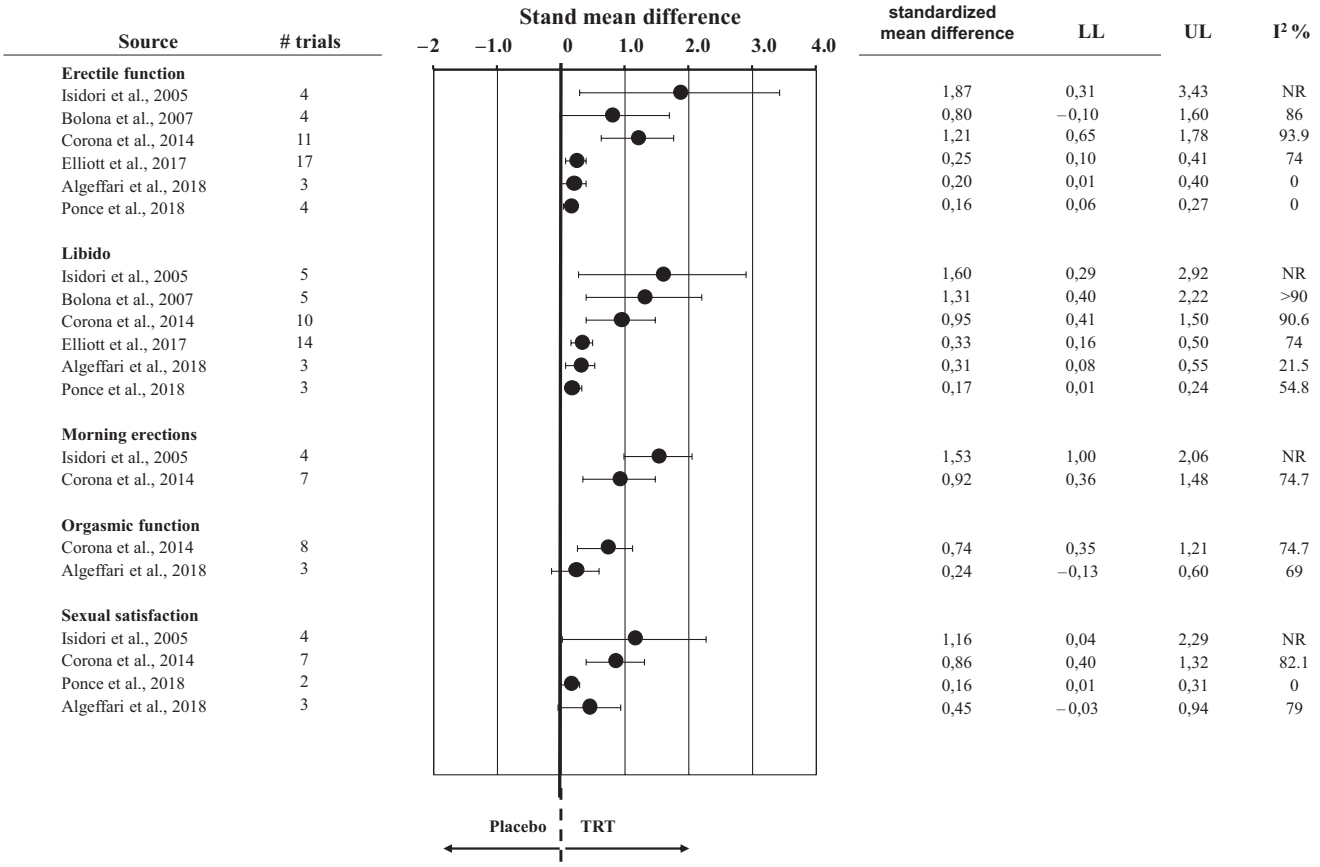

FIGURE 4 Summary of the results obtained by the available meta-analysis on the efficacy of testosterone replacement therapy (TRT) on sexual symptoms. Abbreviations: Diff = difference, LL = lower limit, UL = upper limit. I^2 describes the percentage of variation across studies

The included trials range from 4 to 29, and the number of subjects considered from 587 to 3,165 (Table 1). Algeffari et al[35] restricted their analysis to subjects with type 2 diabetes (TDM2), whereas all the other meta-analyses scrutinized data regarding the overall general population. Figure 4 reports, as a forest plot, results of the different meta-analyses on the efficacy of T therapy

in the RCTs considered. The meta-analyses scrutinized here differ by year of publication, number of patients enrolled, characteristics of the population studied (only hypogonadal or mixed population, T2DM), and definition of hypogonadism (testosterone cutoffs, symptoms). Table 1 summarizes these points. A positive effect of TRT on erectile function was detected in all the meta-analyses except one.[31] In the Boloña survey,[31] in fact, only a small, but not statistically significant effect on erection was found, although the effect became fully significant when the analysis was restricted to young subjects. According to Sawilowsky,[36] the effect size of TRT on erection ranges from small to very large, most probably due to the selection criteria and to the characteristics of the trials enrolled (see Table 1). The only meta-analysis[33] which considered trials reporting as the main outcome a universally recognized and validated instrument, that is, the International Index of Erectile Function (IIEF)-erectile function domain (IIEF-EFD), demonstrates an overall modest effect of TRT (2-3 points IIEF-EFD). The effect is present only considering hypogonadal subjects and is modulated positively by the severity of hypogonadism and negatively by the presence of comorbidities, such as diabetes or obesity. It is interesting to note that this positive effect is definitively lower than the one obtained with any PDE5 inhibitor (at least 5 points IIEF-EFD) and, according to Rosen,[37] TRT, if used alone, would be sufficient to treat only milder forms of ED.

In conclusion, preclinical and clinical data indicate that T exerts a positive effect on erection; however, with several caveats: (a) TRT is effective on erection only in HG (and not in eugonadism), (b) the effect of TRT on erection is overall modest and (c) its magnitude is attenuated in subjects with metabolic derangements, as often happens in subjects with LOH.

5 | TESTOSTERONE AND OTHER ASPECTS OF MALE SEXUALITY IN LOH

5.1 | Testosterone and sexual desire in LOH

Sexual desire is the motivational state that may prompt individuals to seek out and engage in sexual activity, an obligatory act for species perpetuation and an enjoyable aspect of human life.[38] In the DSM-IV-TR and DSM-5, male hypoactive sexual desire disorder (MHSDD) is defined as a disorder characterized by persistently or recurrently deficient (or absent) sexual/erotic thoughts or fantasies and desire for sexual activity. These symptoms should persist for a minimum of six months, and they must cause clinically significant distress. MHSDD is categorized according to its severity and subtyped into lifelong versus acquired and generalized versus situational.[39] In addition, the dysfunction should not be accounted for by another psychiatric disorder (except another sexual dysfunction) and must not be due exclusively to the physiological effects of a substance or a general medical condition. In fact, several medical or psychiatric conditions can lead to MHSDD. For example, T has been regarded as the main hormonal fuel of sexual desire and its deficiency can lead to symptoms often overlapping with MHSDD. Although the relationship between low T and reduced sexual desire is apparent in almost all clinical and epidemiological studies, including longitudinal ones,[40] other hormonal alterations increase the odds for low desire more robustly than low T. For instance, hyperprolactinemia increases the risk for hypoactive sexual desire (HSD) by a factor of ten, while low T only doubles the risk.[38,41] We recently introduced a distinction between primary reduced libido (ie, not associated with known pathological conditions causing loss of libido) and secondary reduced libido (ie, associated with known medical conditions such as hypogonadism, severe hyperprolactinemia, and any past or actual psychopathology and/or psychoactive medication[41]). In a large series (n = 3714) of male patients consulting an andrology clinic for sexual dysfunction, HSD (as measured by SIEDY question # 14[26]) was present in 36% of consultations, being isolated in 5% of subjects and associated with other sexual dysfunctions in the remaining cases. In fact, HSD is present in 38%, 28% and 50% of those reporting ED, premature ejaculation (PE) and delayed ejaculation (DE), respectively. In this cohort, subjects with hypogonadism, psychopathology and hyperprolactinemia reported reduced libido in 40%, 48% and 84% of cases, respectively.[41] Hence, almost one in two subjects showing low T (total T < 12 nmol/L) reported reduced libido.[41]

Although low T is only one of the factors associated with reduced libido[38] (see also Figure 3B), this symptom is rather specific to the condition of LOH. In fact, by using Chronic Disease Score (CDS), a widely accepted measure of comorbidities, we found that several LOH correlates-—such as reduced penile blood flow, severe ED, reduced spontaneous erection, and related psychological burden—are relatively unspecific for LOH because they could be ascribed either to low T or to age-associated morbidities.[11] However, this is not the case for HSD.[11] In fact, in a logistic adjusted model, low desire was positively associated with low T, but it was negatively associated with high CDS. In other words, subjects with LOH could have ED and HSD, while subjects with comorbidities more often complain of ED with a preserved or even increased sexual desire.[11] Hence, hypoactive sexual desire is a genuine symptom of LOH.

If HSD is a genuine symptom of LOH, treating LOH with TRT should improve the condition. Figure 4 shows, as a forest plot, results derived from different meta-analyses investigating this point. In all the meta-analyses scrutinized,[10,30-32,34,35] there was a statistically significant improvement of low desire upon treatment with T, although with a large variation in the effect size (Figure 4). When the analysis was categorized according to baseline T level,[32] it was found that the positive effect of T treatment was not apparent in studies enrolling eugonadal subjects, being present only in those enrolling hypogonadal patients (ie, total T < 12 nmol/L). In a meta-regression analysis of the same data, it was also found that the degree of HSD improvement was directly related to the severity of T deficiency.[32] The positive effect of T treatment on libido was confirmed also when only RCTs using an IIEF-specific subdomain were selected.[33]

In conclusion, HSD is a genuine symptom of LOH, even though several other intrapsychic, relational and hormonal factors can lead

to HSD. When HSD is associated with low T (ie, T < 12 nmol/L), TRT can significantly improve it in a manner that is proportional to the severity of hypogonadism. In contrast, TRT is not indicated for use in eugonadal men, because it is apparently ineffective.

5.2 | Testosterone and orgasmic function in LOH

Preclinical studies suggest that T controls orgasmic function at several levels, including the central nervous system, the spinal cord, the muscles of the pelvic floor (bulbo-cavernosus, ischio-cavernosus, and levator-ani muscle), and the ejaculatory ducts (see for review[42,43]). As a result, high T potentially favors orgasm and ejaculation, whereas low T levels may be associated with a delayed ejaculation. Although a cross-sectional study on a large series of subjects consulting for sexual dysfunction essentially supports this notion,[43] other studies were contradictory.[44,45] A recent study suggests that men with lifelong premature ejaculation (PE) have suffered from a higher androgenization during fetal life because they show an increased anogenital distance, a surrogate marker of in utero androgen priming.[46]

Considering these contradictory findings, results from intervention studies with TRT would be very important in shedding light on this topic. In a recent meta-analysis involving a total of 587 men with T2DM from 6 RCT, no effect of TRT on orgasmic function was found,[35] while in another one enrolling 677 patients from 10 studies on an unselected population, a small but significant improvement was reported[32] (see Figure 4). A meta-regression analysis of those results indicates that the improvement was greater as a function of baseline severity of T deficiency.[32] Later on, a significant improvement in orgasmic function was confirmed by selecting RCTs using the IIEF subdomain to measure the orgasmic parameter.[33] More importantly, it was confirmed by a large, placebo-controlled trial, performed on more than 700 patients treated for 12 weeks with a transdermal gel and evaluated by using a specific questionnaire (MSHQ-EjD-SF) to score ejaculatory dysfunction.[47]

In conclusion, TRT might improve orgasmic function with an effect that is more evident in subjects with severe hypogonadism. Whether TRT could be helpful in treating delayed ejaculation is still a matter of debate.

6 | FINAL CONCLUSIONS

T exerts an important role in shaping the male phenotype. However, its role decreases, in an exponential manner, as a function of male age, as it is essential in fetal life, extremely relevant during pubertal transition and ancillary later on. In fact, the LOH cross-sectional, longitudinal and intervention studies discussed above substantiate a statistically significant relevance of T in supporting adult male sexual life, whereas other potential roles of T in adulthood—such as in improving bone turnover, body composition and metabolism, erythropoiesis, wellbeing, and mood—are still under debate and are not the topic of this review. Concerning the effects of T in adult male sexual life, the evidence summarized here indicates that hypogonadism decreases and TRT increases, in a statistically significant way, spontaneous and sexual-related erections as well as sexual desire, as also stated before in previous recommendations of the International Consultation of Sexual Medicine.[48] Saying that these effects are statistically significant does not automatically mean that they are clinically meaningful. As an example, TRT ameliorates erectile dysfunction by 2-3 points of IIEF-EFD that is at least one-half of the effect of any PDE5i. In other words, TRT per se is effective in treating only a mild ED, but infective in more severe forms of the same disorder. This small effect is even attenuated in subjects with metabolic derangements, as in obesity and T2DM, most probably because the cardiovascular and neurological problems associated with these conditions bury the positive effect of TRT. Interestingly, subjects with obesity or T2DM represent the large majority of those with LOH. These observations are in line with the aforementioned paradox of preserved erectile function in castrated individuals.

Effects of TRT on sexual desire are, in our opinion, more clinically meaningful for several reasons. First, more than 20% of subjects consulting for sexual dysfunction in our andrology service have low T (<12 nmol/L). Of those, nearly one-half has reduced sexual desire. Considering that there are no specific treatments for reduced sexual desire, apart from removing the underlying condition, TRT is a clinically meaningful option in hypogonadal subjects for improving libido. The more severe the T deficiency, the more evident the effect of TRT. In contrast, the effect is almost null in eugonadal individuals. Positive effects of TRT could be envisaged also for improving orgasmic function, although the latter point is still a matter of debate. The clinical implication of these findings in LOH (that is often associated to other comorbidities) could be that T alone might restore sexual desire in LOH individuals without clinically meaningful effect on erection. Hence, the associations with other medications, such as PDE5i, are important caveat. Otherwise, a T2DM patient with hypogonadism treated only with T might experience an increase in sexual drive without the possibility to do it, that might result even frustrating. On the other side, treating these patients with PDE5i only might restore the possibility to have erections, but without the necessary desire to use them.

In conclusion, TRT is a reasonable treatment for restoring sexual drive in LOH, with some additional positive effects also on erection (spontaneous and sexual-related) and on orgasm.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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