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Testosterone and sexual function in men

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ABSTRACT

Testosterone (T) is deeply involved in every step of the male sexual response. However, the occurrence of sexual disorders cannot be automatically related to a decline in T levels. In fact, this relationship is complicated by organic, relational and psychological factors, which can independently impair sexual function. For example, it is recognized that erectile dysfunction (ED) can result from vascular damage as well as from low levels of T. T therapy (TTh) can improve sexual function but meta-analyses show that it improves erectile function only in men with ED and overt hypogonadism. Similarly, impaired sexual desire can result from a wide range of organic, relational and psychological factors, although it is recognized as one of the most specific symptoms of hypogonadism. Accordingly, low desire is improved by TTh in men with overt hypogonadism. The association between low T levels and delayed ejaculation has not been well studied and needs further confirmation, as does the role of TTh in such cases. Meta-analyses have found that TTh can improve orgasmic function in hypogonadal men. Clinicians should bear in mind that sexual dysfunctions have multifactorial causes and hypogonadism represents only one of these. Only hypogonadal men are likely to improve their sexual symptoms when treated with TTh. The assessment of serum T levels is mandatory before patients are prescribed TTh, as are the assessment and possible treatment of other concomitant conditions.

1. Introduction

Male hypogonadism (HG) is a clinical entity due to any condition impairing testis action, i.e. the production of sex steroids (androgens) and spermatozoa. HG can be either congenital or acquired and it can be related to any alteration in the central control of testicular function (central, secondary or hypogonadotropic HG) or to primary damage to the testis itself (primary or hypergonadotropic HG). In addition, an HG-like syndrome can also be due to any impairment in androgen activity, for example through increased levels of sex hormone binding globulin (SHBG), a protein that binds tightly to testosterone (T), thereby limiting its biological effects. The classification of HG according to the site of the impairment is clinically useful because it helps to determine choice of therapy [1]. However, it does not provide any information about the clinical features, which develop irrespective of the localization of the damage. A classification based on the time of onset of HG is more useful in this respect. In fact, when the damage leading to HG starts to exert deleterious effects on the hypothalamus-pituitary-testicular (HPT) axis during male fetal life, the resulting phenotype is characterized by specific symptoms, often dramatic, such as feminized or ambiguous genitalia, cryptorchidism or hypospadias. The clinical features are still specific when HG develops during childhood or adolescence, resulting in delayed or absent pubertal development. After completion of puberty, T is required to maintain male secondary characteristics, including sexual behavior. However, the clinical features of T deficiency in adult men are not as specific as they are in the earlier phases of life. Several symptoms and signs have been associated with low T levels in adults [2]. However, none of these can be considered specific because they widely overlap with aspects of normal ageing or with the clinical features of several chronic diseases (T tends to decline with senescence and is often low in chronic illnesses). In fact, it is not clear whether the complaints reported by ageing men or ill subjects depends, at least in part, on T decline or if low T represents only a marker of poor health, developing alongside, rather than before, the other clinical manifestations.

The difficulty in defining the pathophysiological effects of male HG has important practical consequences. According to current guidelines [3,4], the diagnosis of HG in adulthood requires the presence of low T levels and the presence of at least one symptom of androgen deficiency. This implies that physicians must ascribe a symptom to low T levels

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each time they diagnose HG in adults. The wide overlap between androgen deficiency symptoms and the symptoms of several other common conditions can lead to both underdiagnosis and overdiagnosis of HG. Moreover, the lack of appropriate therapy can result in the persistence of symptoms and signs, with adverse consequences on quality of life, physical or mental health.

Sexual complaints are the most specific symptoms of HG and their presence can be considered a minimum criterion for diagnosing HG in adult men with low T levels [2–6]. The aim of the present narrative review is to summarize the available evidence linking T with sexual function in men.

2. Methods

An extensive search of PubMed was conducted up to 31 January 2018 using the following terms: ((“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 (“physiology”[Subheading] OR “physiology”[All Fields] OR “function”[All Fields] OR “physiology”[MeSH Terms] OR “function”[All Fields])), limiting the results to studies of men (filters: humans and male) and published in English. The retrieved papers were scrutinized for evidence on the relationship between endogenous T and sexual function and the effect of T therapy (TTh) on sexual symptoms.

3. Testosterone and sexual function

In men, T can be considered to drive sexual behavior because it enhances several key steps of the entire male sexual response (see below). Based on this assumption, finding a deterioration of sexual function in men with HG would not be surprising. However, this relationship is not straightforward, because it is affected by several other factors in the determination of sexual dysfunction. Fig. 1 shows total and free T levels (TT and FT, respectively) in men reporting mild, moderate or severe symptoms of three conditions, erectile dysfunction (ED), impaired morning erections and low sexual desire, in a population of 4890 men seeking medical care for sexual dysfunction at the University of Florence [5]. According to these results, men with the most severe symptoms are characterized by lower T levels than those without or with a milder form of the symptom, independent of age. Whereas both TT and FT are significantly lower in men with severely reduced morning erections or sexual desire, only a trend towards significance can be observed for severe ED. Moreover, a similar non-significant trend is observed also for the reduction of TT in men with a mildly decreased sexual desire, whereas the difference achieves statistical significance when a moderate reduction in sexual desire is considered. Overall, these results suggest that the three sexual disorders, previously demonstrated to be those most directly related to low T in the general European population [6], do not entirely depend entirely on androgen deficiency and a multifactorial pathogenesis should be advocated. Nonetheless, undoubtedly, androgen deficiency has a role in their development, and it is likely to be the most important pathogenic component when a severe sexual dysfunction is reported.

3.1. Testosterone and erectile dysfunction

Penile erection relies on the integrity and functioning of the vasculature of the corpora cavernosa. T has an important role in regulating penile integrity and functioning. It is known that T is involved in the development of the human penis during fetal life [7] and in its growth during the first months of life (mini-puberty) [8] as well as during puberty [9]. Conversely, T levels are not correlated with penile length during adulthood. However, T is still greatly involved in penile function in adults. In fact, the mechanisms on which the erectile process is based are deeply affected by T. Nitric oxide (NO) is the key mediator for erectile function. NO is synthesized by the enzyme NO synthase (NOS), which is produced by endothelial cells (eNOS) and non-adrenergic/non-cholinergic (NANC) nerves (nNOS). Once produced, NO diffuses into penile smooth muscle cells, where it stimulates the formation of cyclic guanylate monophosphate (cGMP), which in turn promotes their relaxation. Both eNOS and nNOS have been shown to be up-regulated by T in animal models [10,11]. In addition, T down-regulates the activity of RhoA-ROCK (Ras homolog gene family member A-Rho-associated, coiled coil containing protein kinase) pathway [12], which is involved in the sensitization to calcium of penile smooth muscle cells, allowing

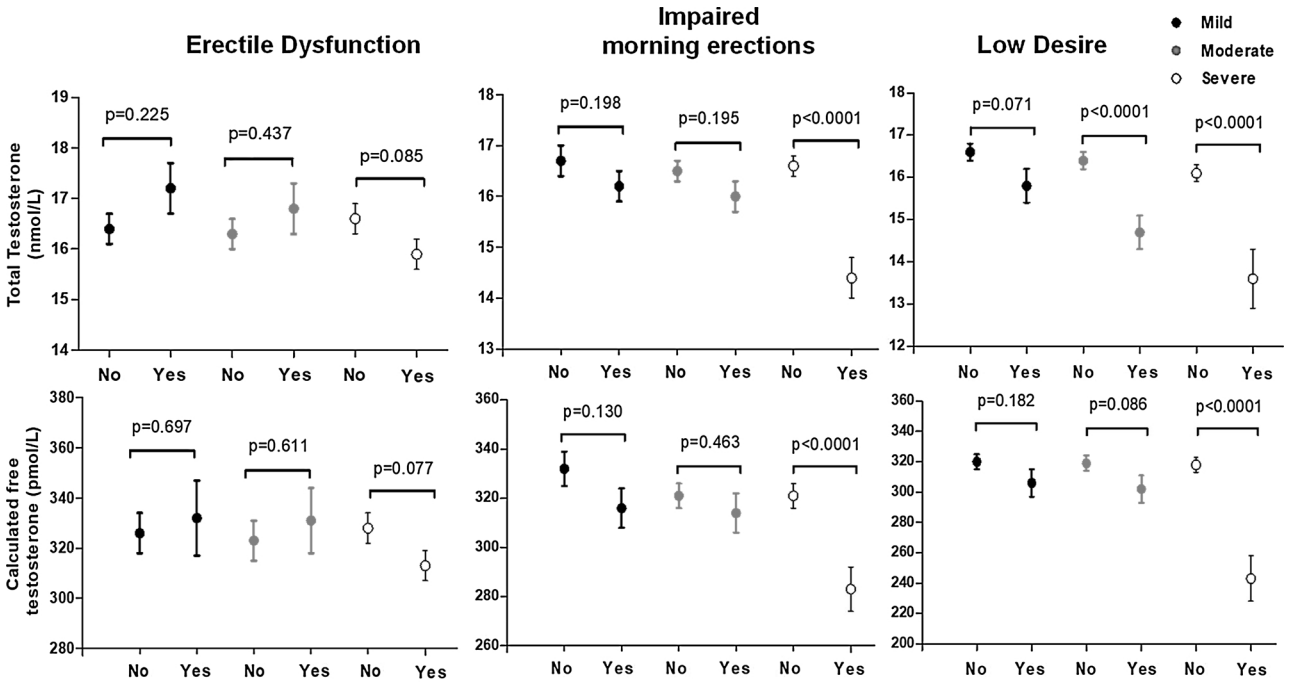

Fig. 1. Age-adjusted differences in total and calculated free testosterone between subjects with or without erectile dysfunction, impaired morning erections or low desire categorized as mild, moderate or severe. Data are expressed as mean ± standard error. The figure is adapted from [5] with permission.

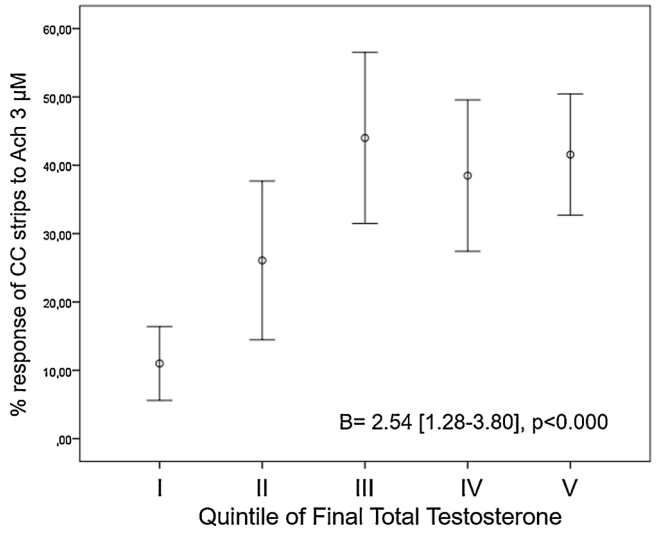

Fig. 2. Relationship between testosterone levels and percentage of relaxation of corpora cavernosa strips incubated with the maximum dose of acetylcholine (Ach = 3 µM). Data are expressed as means with 95% confidence intervals and obtained from 182 rabbits fed with a regular diet or with a high-fat diet, which induced metabolic impairments similar to the features of metabolic syndrome [11].

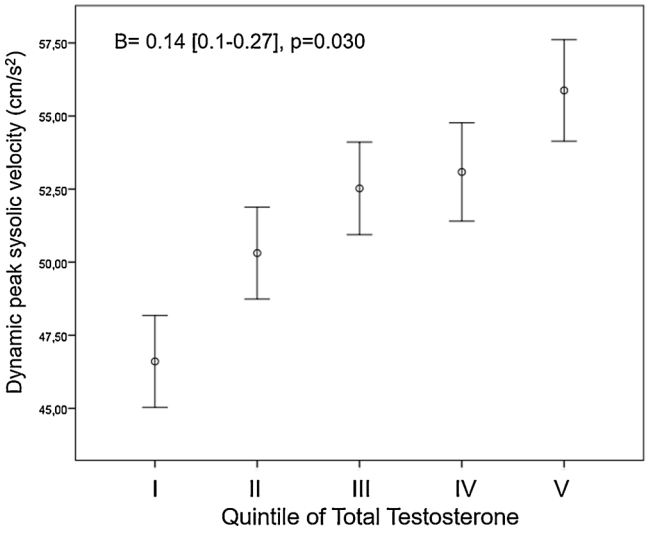

Fig. 3. Relationship between testosterone and peak systolic velocity as derived by penile color Doppler ultrasound after intracavernosal injection of 10 µg of prostaglandin E_1. The inset reports the age- and metabolic syndrome-adjusted relationship. Data are expressed as means and 95% confidence intervals and are obtained from a population of 2752 men seeking medical care for sexual dysfunction at the University of Florence, Italy.

for prolonged relaxation. However, also type-5 phosphodiesterase (PDE5), which underlies the molecular mechanism that leads to the conclusion of an erection, is positively regulated by T [11–13]. Consistent with the pivotal role of T in the erectile process, in animal models of castration-induced hypogonadism, stimulated intracavernous pressure was significantly impaired [14,15].

Besides the effects of an absolute absence of T on erectile function, milder forms of hypogonadism, such as those characterizing metabolic syndrome (MetS), seem to exert adverse effects. In an animal model of MetS, rabbits fed a high-fat diet (HFD) develop a number of clinical features of the MetS phenotype, including a decline in T levels [11]. Compared with rabbits fed a regular diet, HFD rabbits are characterized by a decreased relaxation of the corpora cavernosa upon incubation with acetylcholine (Ach) [11]. In addition, as shown in Fig. 2, the degree of corpora cavernosa relaxation with a maximum dose of Ach (3 µM) in control and HFD rabbits is positively associated with endogenous T levels.

In men, the evidence on the relationship between low T and ED is conflicting. Data from the Massachusetts Male Aging Study (MMAS), which involved 1700 community-dwelling men, failed to show an independent significant association between the prevalence of ED and levels of TT or bioavailable T [16]. Similar results were obtained in a later study (the European Male Ageing Study; EMAS) on more than 3300 middle-aged and elderly men from the general European population, which showed that ED does not display an overall linear relationship with total T levels and only a weak association is found with FT levels [17]. However, when evaluating the same relationship only in men with low TT levels (< 8 nmol/L), it became significant and stronger [6,17]. This suggests that ED should be regarded as a symptom of hypogonadism only when T levels are clearly subnormal, whereas different etiologies and risk factors should be considered in men with ED and with borderline T levels. In particular, ED is known to be a risk factor for cardiovascular (CV) disease (CVD) [18,19]. Accordingly, ED has been included among the CVD risk factors in the QRISK3 algorithm recently validated in England for the estimation of 10-year CVD risk [20]. Hence, in men with ED, CV comorbidities and risk factors should be investigated.

Penile color Doppler ultrasound (PCDU) is a well-recognized instrument for the identification and quantification of penile artery insufficiency [21]. It has been demonstrated that the impairment of penile blood flow as detected by PCDU can predict the incidence of major adverse CV events [22,23]. However, besides CVD, penile blood flow also depends on T levels. Fig. 3 shows the relationship between peak systolic velocity on PCDU after intracavernosal injection of 10 µg of prostaglandin E_1 and endogenous T levels, in a population of 2752 men seeking medical care for sexual dysfunction (B = 0.45 [0.34–0.57], p < 0.0001). The association is maintained even after adjusting for age and MetS (B = 0.14 [0.1–0.27], p = .030), thus highlighting that T modulates penile blood flow independently of ageing and MetS, two conditions known to be associated with both T decline and CVD. The androgen dependence of peak systolic velocity in humans parallels the aforementioned observations of rabbit models (Fig. 2) and supports a physiological role for T in facilitating erectile function.

Further evidence of the important role of T in erectile function is provided by the results from randomized clinical trials (RCTs). At the beginning of 2016, the results from the Testosterone Trials – a set of seven RCTs specifically designed to assess the risks and benefits of T therapy (TTh) for older men – became available. The evaluation of sexual improvement in more than 700 men aged 65 years or more with serum TT below 9.5 nmol/L randomly assigned to receive T gel 50 mg daily or placebo for 12 months demonstrated that TTh is able to improve ED in men with late-onset HG [24]. In addition, this significant – although moderate – improvement in erectile function was shown to be independent of potentially moderating factors, including age, body mass index (BMI), diabetes mellitus, and alcohol intake [25], thus suggesting that TTh can be a therapeutic option for the vast majority of elderly men with HG complaining of ED.

Brock and colleagues recently demonstrated an improvement of erectile function with TTh in a younger population. In a sample of 715 men older than 18 years (mean age 55.3 ± 11.0 years) with TT < 10.4 nmol/L and at least one symptom of androgen deficiency, receiving T gel 60 mg daily or placebo for 12 weeks [26], TTh was associated with a significantly greater improvement in erectile function – as assessed by the International Index of Erectile Function (IIEF-15) – particularly in younger men and in those achieving serum TT within the normal range. In addition, among those receiving TTh, obesity was a predictor of less improvement in ED [27]. In line with these results are

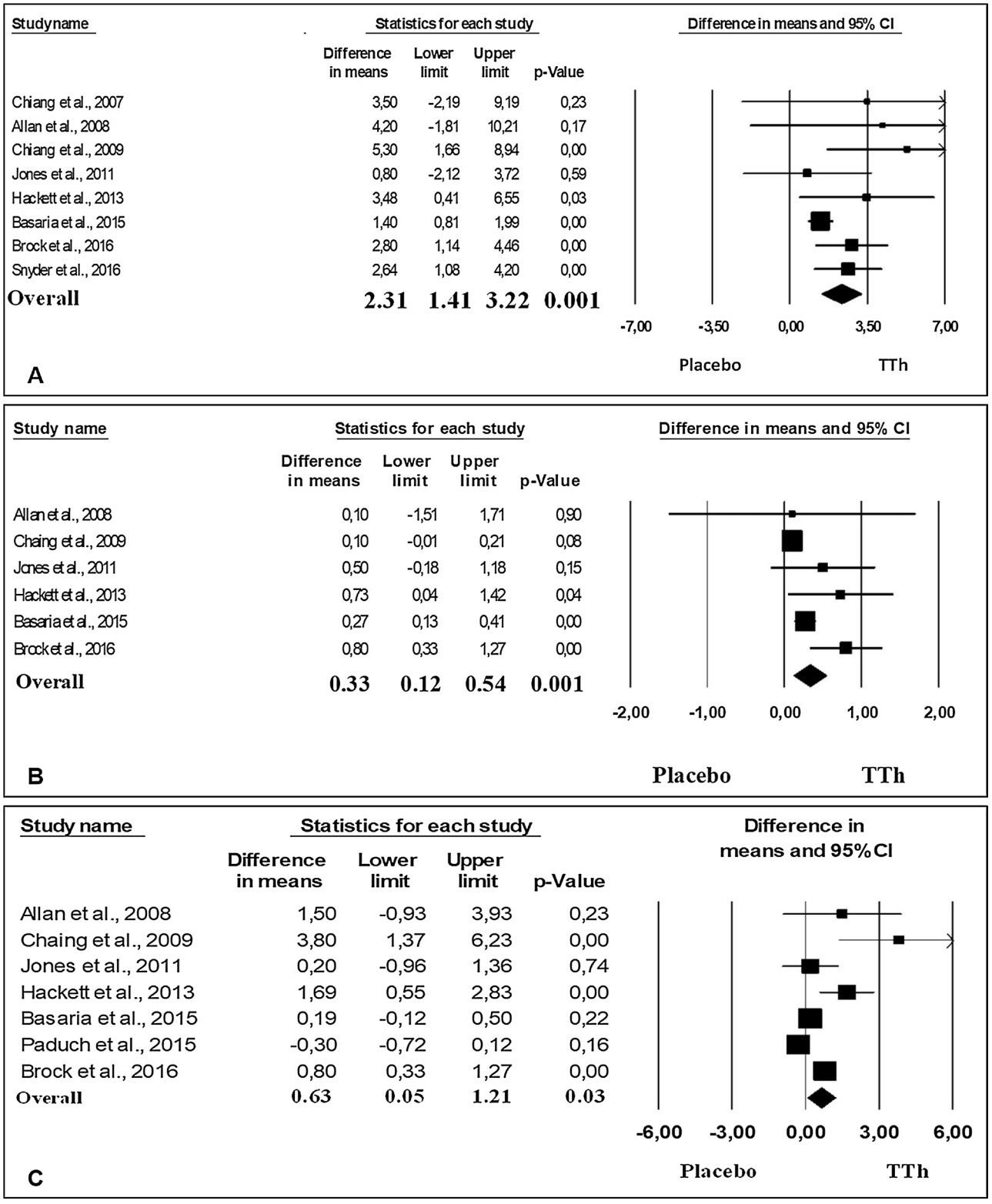

Fig. 4. Mean (with 95% confidence interval; CI) of testosterone treatment (TTh) versus placebo on International Index of Erectile Function (IIEF) subdomains as derived from random models including erectile function domain (A), sexual desire (B), and orgasm (C). Figures are adapted from [28] with permission.

findings from a recent meta-analysis [28], gathering data from all the available RCTs, which evaluated the effect of TTh on sexual function, as assessed by the IIEF-15. Results of the meta-analysis confirm the efficacy of TTh in improving erectile function in HG men (Fig. 4, Panel A), with weaker improvements with increasing BMI and increasing prevalence of diabetes mellitus [28]. Besides metabolic conditions, non-organic factors can also blunt the effectiveness of TTh on erectile function, as shown by the BLAST study, which found that the positive effect is limited to non-depressed men [29].

3.2. Testosterone and sexual desire

Sexual desire is the motivational state that may prompt individuals to seek out and engage in sexual activity [30]. Cognitive, sensory and emotional stimuli perceived as sexually meaningful can stimulate the brain and arouse sexual desire, which is the first step of the entire sexual response in both males and females. The brain area involved in the processing of sexual stimuli responsible for sexual desire are the medio-basal hypothalamus and limbic system, where the androgen receptor (AR) is expressed [31]. Although the exact neurophysiological mechanisms regulating sexual desire are still largely unknown, data from animal models suggest that T plays an important role. Mice with testicular feminization (Tfm) due to mutations in AR as well as AR knockout (ARKO) mice have impaired sexual behavior [32,33]. Sexual behavior is compromised also in castrated rats, whereas restoring androgen levels has been demonstrated to be effective in re-establishing sexual behavior, despite high doses being required [34]. Part of the effect of T on sexual desire may be mediated by estradiol, a T metabolite locally derived from the activity of the enzyme aromatase. The role of estradiol in mediating the effect of T on the brain structures involved in sexual desire is proven by restoration of sexual behavior in aromatase knockout mice [35] by the administration of estradiol [36]. Furthermore, the relevance of estradiol in sexual desire has been confirmed in a study on healthy men with experimentally induced HG, where TTh was able to restore sexual desire, but this effect was prevented in subjects receiving TTh together with anastrozole [37].

The multifactorial origin of the impairment in sexual desire in humans makes the study of the relationship between T and libido complicated. Accordingly, epidemiological studies have provided conflicting results. The Olmsted County study, which involved a population of 414 men, did not find a relationship between total T and sexual desire [38], whereas only a weak association was reported by the MMAS [39]. In contrast, the Concord Health and Aging in Men Projects (CHAMP), a prospective population-based study involving 1226 elderly men from three local government areas surrounding Sydney, Australia, found a significant relationship between a decline in T over 2 years of follow-up and a decrease in sexual interest [40]. In the EMAS study, a decrease in sexual thoughts was found to be one of the symptoms most specific to low T levels in a cross-sectional evaluation [6]; moreover, a prospective analysis confirmed that the development of secondary HG is associated with the occurrence or worsening of low libido [41]. Although the EMAS found low sexual desire to be a specific symptom of HG, the clustering of three sexual symptoms (ED, decreased morning erections and low sexual desire) strengthened the specificity [6]. This has been confirmed in a population of almost 5000 men consulting for sexual dysfunction, where decreased sexual desire alone unsatisfactorily discriminated men with normal or low T, whereas the concomitant presence of decreased morning erection improved the accuracy [5]. Overall, these results confirm the role of T in regulating sexual desire, although they underline that this is not the only factor involved. In fact, other hormonal (prolactin), psychiatric, relational or pharmacologic conditions may induce a decrease in sexual desire [30].

Trials comparing the effects of TTh with those of placebo on several aspects of sexual function in men with late-onset HG have demonstrated a significant increase in sexual desire in the TTh study arm [24]. The previously described RCT by Brock and colleagues [26] – specifically aimed at assessing the improvement in sexual desire in men with low T levels and low libido – found a significant improvement associated with TTh, which was observed after four weeks and maintained until the end of the trial (12 weeks). Fig. 4 (Panel B) shows the results of the meta-analysis of those RCTs which evaluated sexual desire through the IIEF-15 questionnaire [28]. This meta-analysis [28], similar to a previous one not restricted to studies using the IIEF-15 [42], essentially confirms that sexual desire is significantly improved by TTh as long as it is administered to men with low serum T levels, although exactly how low is unclear. The BLAST study, a 30-week RCT involving almost 200 diabetic men with TT below 12 nmol/L and/or FT below 250 pmol/L, randomized to receive placebo or 1000 mg of injectable T undecanoate, found that only men with baseline TT < 8 nmol/L or FT < 180 pmol/L experienced an improvement in sexual desire when treated with TTh [43]. Conversely, men in the TTh arm with only mildly reduced levels of T at baseline reported the same level of sexual desire over the duration of the study, and achieved a statistically significant difference from the placebo arm only due to a worsening in the latter rather than due to an improvement in their own right [43]. However, when categorizing the results of the aforementioned meta-analyses [28,42] according to baseline T levels, the effect of TTh on libido was not different in men with mildly or severely reduced T.

3.3. Testosterone and ejaculatory dysfunction

Most of the available evidence for the physiological involvement of T in the ejaculatory process derives from animal models [44]. In animals, AR is expressed in several areas of the brain involved in the ejaculatory reflex, including the medial preoptic area, bed nucleus of the stria terminalis, median amygdala and posterior thalamus [45]. Moreover, spinal nuclei involved in the control of ejaculation, such as the nucleus of the bulbocavernosus nerve, are androgen-dependent [46], as are the muscles of the pelvic floor (bulbocavernosus, ischiocavernosus and levator ani muscle) [47], which are the final effectors of the reflex. Besides the pelvic floor contraction, the contractility status of the structures involved in the emission phase of the ejaculation (essentially the entire male genital tract) affects the occurrence and timing of ejaculation. This is controlled at least in part by the NO-PDE5 system, which, similarly to what is observed within the CC, is regulated by T [48].

In humans, evidence of the relationship between T and ejaculation are scanty. In a population of almost 3000 men (mean age 51.3 ± 13.1 years) seeking medical care for sexual dysfunction at the University of Florence, an increase in the self-reported ejaculatory latency period during penetrative intercourse was associated with a stepwise reduction in serum levels of T [44]. However, a population-based study of 1429 men from Finland (mean age 26.9 ± 4.7 years) failed to demonstrate a relationship between salivary T levels and self-reported ejaculatory latency time [49]. Similarly, in a population of almost 1000 men with delayed ejaculation, T was not associated with ejaculatory latency time [50]. RCTs have mainly considered orgasm as the outcome, and so tend not to provide data purely related to ejaculation. Fig. 4 (Panel C) shows a *meta*-analysis of the placebo-controlled RCTs which assessed the effect of TTh on orgasm as measured by the IIEF-15 questionnaire [28]. According to this and a previous meta-analysis [42], TTh is associated with a significantly greater improvement in orgasm compared with placebo. Moreover, the improvement was greater as baseline T decreased [28,42]. One placebo-controlled RCT specifically evaluated ejaculation together with its specific components, including frequency and force of ejaculation, and semen volume [51]. The RCT, which involved 715 men older than 18 years with TT below 10.4 nmol/L treated for 12 weeks with placebo or 60 mg of axillary T gel 2%, found a significant improvement in all the aforementioned areas of ejaculatory function associated with TTh (but not for an item termed 'bother', which decreased similarly in the TTh and placebo arms) [51].

4. Conclusions

T is deeply involved in the physiology of the entire male sexual response. Sexual dysfunctions represent the most specific of the putative clinical features of hypogonadism [5,6] and, according to the guidelines [3,4], they allow the diagnosis of hypogonadism to be made in men with low T. However, a wide range of factors other than low T can disrupt sexual response at one or more levels, thus resulting in sexual dysfunction, including ED, low sexual desire and ejaculatory

disorder. Although RCTs demonstrate that TTh can improve sexual function, mounting evidence shows that the improvement may be expected only when the symptoms are associated with low T levels, particularly when T is overtly reduced. Hence, clinicians should test each patient with sexual dysfunction for serum T and prescribe TTh only for those with hypogonadism. In addition, clinicians might bear in mind that sexual symptoms, although specific to low T, could be secondary to other conditions, which should be identified and possibly treated in conjunction with TTh in order to obtain the best therapeutic results.

Contributors

Giulia Rastrelli conceived the outline of the article, collected and interpreted the original data, and drafted the manuscript.

Giovanni Corona revised the article for scientific content.

Mario Maggi conceived the outline of the article, collected and interpreted the original data, and revised the article for scientific content.

All authors saw and approved the final version.

Conflict of interest

The authors declare that they have no conflict of interest.

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