Testosterone and Sexual Function

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Introduction

There is much evidence supporting the concept that testosterone (T) represents the fuel of male sexual function [1–7]. Accordingly, data from the European Male Aging Study (EMAS), a population-based survey which included more than 3400 subjects across eight European centers showed that among the different symptoms, sexual dysfunction represents the most important determinant for medical consultation and the most specific symptom associated with low T [8]. In particular, it was recognized that a triad of sexual symptoms (low libido and reduced spontaneous and sex-related erections) is the only syndromic association with decreased T levels [8]. In that large European survey, the simultaneous presence of the three sexual symptoms (hypoactive sexual desire, erectile dysfunction [ED], and perceived reduced sleep-related erections) combined with a total T level of less than 11 nmol/L and a FT level of less than 220 pmol/L were therefore considered the minimum criteria for the diagnosis of late onset hypogonadism (LOH; [8]). In line with these data, by comparing the prevalence of endocrine abnormalities in two different cohorts from the general (Florentine spin-off of the EMAS cohort; $n = 202$) and the symptomatic populations of Florence (a series of $n = 3847$ patients attending our clinic for sexual dysfunction), we recently reported that subjects seeking medical care for sexual dysfunction represent a population enriched with LOH [9]. In the same symptomatic population, even more recently we confirmed that the simultaneous presence of reduced morning erections and desire is the cluster of symptoms that, along with

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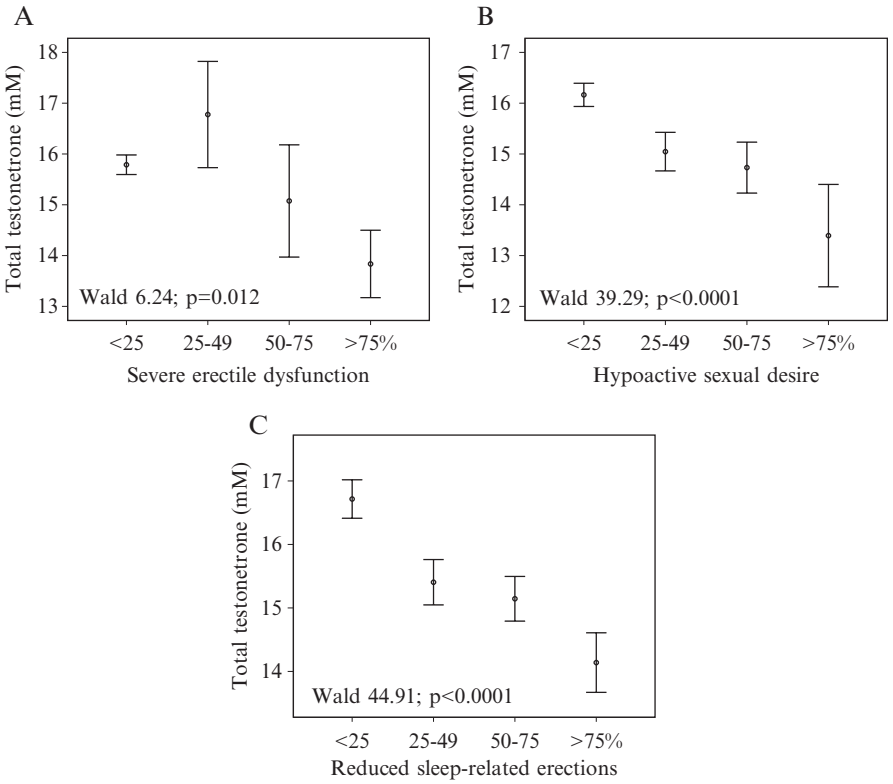

Fig. 14.1 Age-adjusted relationship between total testosterone and severe erectile dysfunction (**a**), hypoactive sexual desire (**b**), and sleep-related erections (**c**). Data were derived from a consecutive series of 4793 subjects (mean age = 51.1 ± 13.3 years) seeking medical care at our unit for sexual dysfunction

total T < 10.4 nmol/L or cfT < 225 pmol/L, defines LOH in a specific, evidence-based manner [10]. The addition of a third symptom, ED, further improved the accuracy [10]. Accordingly, Fig. 14.1 shows the stepwise inverse relationship between T levels and the aforementioned sexual complaints as detected in a large ($n = 4793$ mean age = 51.1 ± 13.3 years) sample of our cohort of patients.

Despite this evidence, however, some data indicate that sexual activity per se can influence T levels. In other words, sexual inertia related to erectile ED can impair T production.

In the following sections preclinical and clinical data supporting the role of T in regulating male sexual function will be analyzed in detail.

Testosterone Regulation of Male Sexual Response

Testosterone plays a crucial role in regulating male sexual response by acting on several levels.

Central Control

Androgen receptors (AR) are expressed in several distinct areas of the human brain, including the temporal, preoptic, hypothalamus, amygdala, midbrain, frontal, and prefrontal areas and cingulated gyrus (Brodman area 24, BA24; [5, 11–13]). Interestingly, the BA24 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 [14] and functional magnetic resonance imaging ([15]; see for review [16]). The role of T in BA24 is further supported by the observation that T supplementation to symptomatic hypogonadal men increases blood perfusion (as assessed by single-photon emission-computed tomography) in this area as well as in midbrain and superior frontal gyrus (BA8; [17]). Another androgen-sensitive brain area is represented by BA37 (middle occipital gyrus) which is involved in the processing of novel visual stimuli [16, 18].

Spinal Control

T acts at the spinal cord level controlling ejaculation reflex [19]. The spinal nucleus of the bulbocavernosus muscle (SNB) is androgen-dependent [20]. Circulating androgens in adult rats can profoundly alter the expression of gastrin-releasing peptide in the lower spinal cord [21] that, by innervating the SNB, mediates the ejaculatory reflex [19]. Interestingly, bulbocavernosus muscle, like other muscles of the pelvic floor involved in the ejaculatory ejection of the seminal bolus (ischiocavernosus and levator ani muscle), is specifically androgen-dependent. In fact, hypertrophic action on the levator ani is a good predictor of effective anabolic androgens [19].

Peripheral Control

Experimental studies in animals and human cell cultures indicate that T directly or indirectly controls several mechanisms underlying erection and detumescence. In particular, T controls the commitment of penile cells to a smooth muscle phenotype favoring the functional and structural integrity necessary for penile erection [2]. Accordingly, androgen deprivation is associated with the accumulation of fat containing cells (fibroblasts or preadipocyte-like cells), especially in the subtunical region of the corpus cavernosum [2].

In addition, T controls numerous enzymatic activities within the corpora cavernosa (CC; Fig. 14.2). The role of T in regulating nitric oxide (NO) formation (acting on endothelial-NO and/or neuronal-NO synthases) has been demonstrated in numerous animal models ([22–25]; see for review ref. [2]; Fig. 14.2, panel B). Furthermore, T also negatively regulates the activity of the Ras homolog gene family member A/Rho-associated kinase (RhoA/ROCK) pathway, overall decreasing calcium sensitivity within penile smooth muscle cells ([26]; Fig. 14.2; panel A).

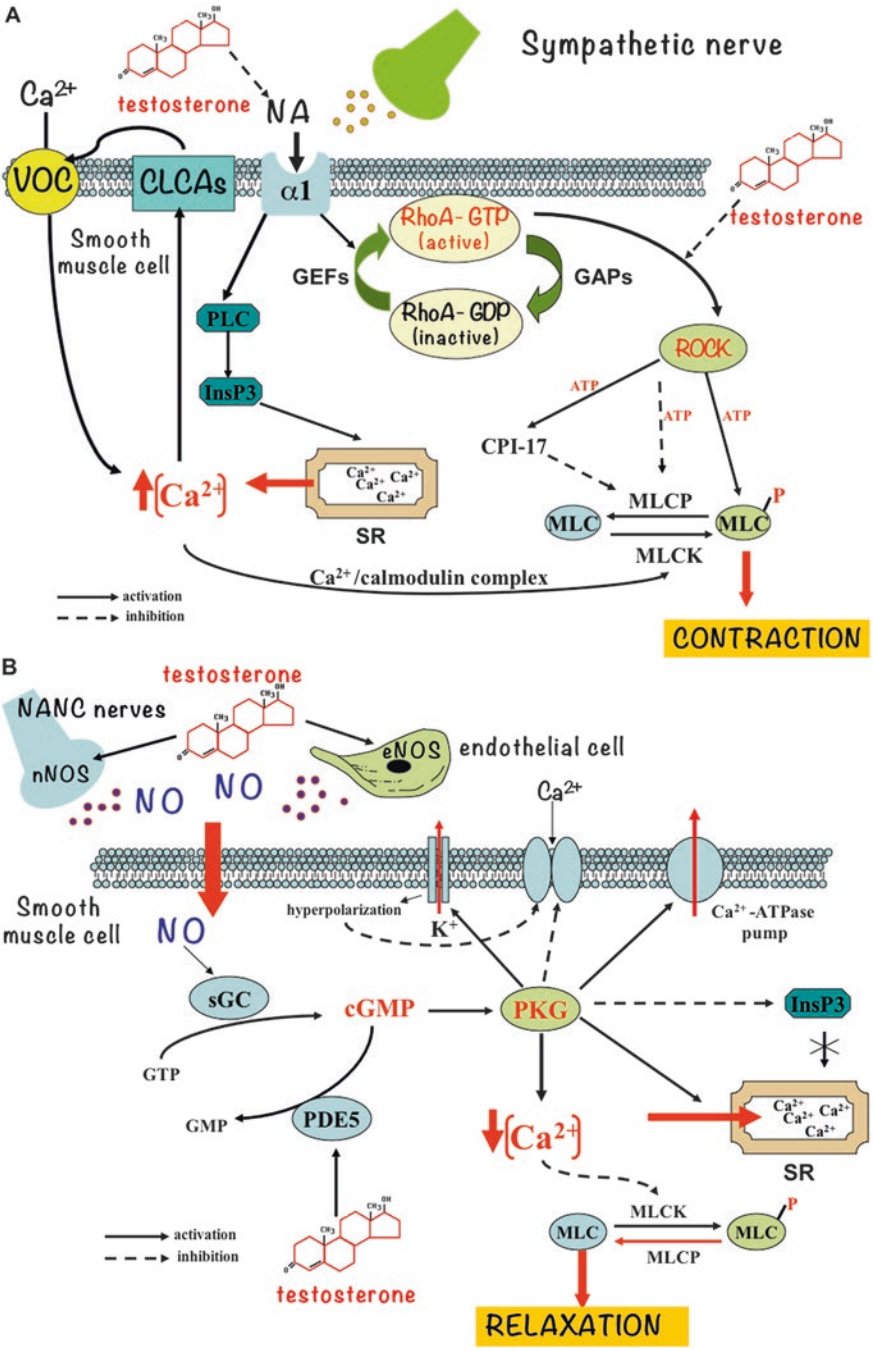

Fig. 14.2 Schematic representation of the biochemical events leading to penile flaccidity (*upper panel*) or erection (*lower panel*) along with the proposed events regulated by **testosterone**. Panel **a**. Noradrenaline (NA) binding to <1 receptors generates inositol 1,4,5-trisphosphate (InsP3), which, by increasing intracellular calcium (Ca^{2+}) levels, activates Ca^{2+}-sensitive chloride channels (CLCAs) resulting in membrane depolarization, with the diffusion of the stimulus to the neighboring cells and the opening of voltage-operated channels (VOC). The increased Ca^{2+} flow promotes,

Finally, T positively controls the expression and the activation of phosphodiesterase type V (PDE5; Fig. 14.2, panel B; [22–25]; see for review ref. [2]).

Another recognized mechanism of androgen action is the regulation of α1-adrenergic responsiveness of smooth muscle cells (Fig. 14.2, Panel A; see for review ref. [2]). Consistent findings point toward T as having an effect on the postganglionic parasympathetic neurons, or even further upstream, within the autonomic nervous system [2]. Accordingly, androgens appear necessary to support adequate neuronal stimulation to the corpora cavernosa, maintaining structural integrity in tissue as seen after denervation following prostate surgery in men [2].

Hypogonadism and Male Sexual Dysfunction

Sexual Desire

There is evidence documenting that hypogonadism represents a possible cause of reduced libido in men [27]. Accordingly, by performing the largest meta-analysis published so far scrutinizing the role of T replacement therapy (TTh) on several aspects of male sexual function we confirm that TTh can improve sexual desire in hypogonadal (T < 12 nM) subjects at baseline [3]. Conversely, the positive effect of TTh was not confirmed in those studies considering only eugonadal patients (T levels below 12 nM) at enrollment (Table 14.1). In line with these data, meta-regression analysis performed in the whole sample showed a trend toward an inverse relationship between baseline mean T levels and the amount of effect on the libido component, which reached statistical significance when studies enrolling eugonadal or mixed eugonadal/hypogonadal subjects at baseline were excluded from the analysis [3].

Despite this evidence the contribution of T in the age-related decline of male sexual desire in the general population is conflicting [28]. However, incidence of secondary hypogonadism in a 4.3-year follow-up observational EMAS cohort was associated with new/worsening of low libido, along with ED and infrequent spontaneous erections [29] confirming the association between androgens and sexual desire in humans.

Fig. 14.2 (continued) through calmodulin, activation of myosin light chain (MLC) kinase and cell contraction. Cell contraction is also obtained by altering the Ca^{2+} sensitivity through a NA-induced activation of a second pathway, RhoA/ROCK, which through a series of kinase activation increases the sensitivity of MLC to Ca^{2+}. **Testosterone** is intended to negatively regulate the latter event. Panel **b**. Nitric oxide (NO) is generated by NO synthases in either nonadrenergic-noncholinergic (NANC) neurons (nNOS) or endothelial cells (eNOS). Both steps are positively regulated by **testosterone**. NO diffuses into smooth muscle cells and activates a soluble guanylate cyclase (sGC), which in turn transforms GTP into cGMP. CGMP activates protein kinase G (PKG), which, through the indicated pathways, finally decreases intracellular Ca^{2+} levels, leading to relaxation. Phosphodiesterase type V (PDE5) metabolizes cGMP into GMP, thereby limiting its effects. The latter event is positively control by **testosterone**. SMC = smooth muscle cells; CC = corpora cavernosa

Table 14.1 Effect size (with 95% confidence interval [CI]) in several sexual parameters across randomized controlled trials evaluating the effect of testosterone substitution vs. placebo

Sexual parameter	Outcome
Erectile function component	
Overall erectile function component[a]	0.82 [0.47;1.17]*
Overall sexual-related function component[b]	0.75 [0.37;0.1.12]**
Sleep-related erections	0.87 [0.47;1.27]**
Libido component	
Overall libido component	0.81 [0.47;1.17]**
Orgasm component	
Overall orgasmic component	0.68 [0.34;1.02]**
Other sexual parameters	
Frequency of intercourse	0.75 [0.33;1.16]**
Overall sexual satisfaction	0.80 [0.41;1.20]**
Overall sexual function	0.67 [0.22;1.12]**

[a]Including coital and non-coital erections
[b]Only coital erections considered
*$p<0.001$, **$p<0.0001$
Adapted from ref. [3]

It is important to recognize that although T plays a crucial role in regulating male sexual desire, its contribution is similar to that played by other intra-psychic and relational factors, as well as medical conditions [27]. For instance, a depressed mood or hyperprolactinemia have a greater deleterious effect on sexual drive than hypogonadism per se [27].

Erectile Function

Because T positively controls both the enzymatic steps necessary for initiation (positive effect on NOS and negative on RhoA/ROCK) and the end (positive effect on PDE5) of the erectile process, its net effect on erection is rather modest. Accordingly, Rhoden et al. [30], in a large consecutive series of almost 1000 elderly subjects with or without ED, failed to find an association between T and the International Index of Erectile Function (IIEF-5). Hence, erections are indeed still possible in hypogonadal conditions, where a decreased 3′,5′-cyclic guanosine monophosphate (cGMP) formation, resulting from impaired NO production, is most probably counterbalanced by reduced PDE5 activity and cGMP hydrolysis. Accordingly, it has been reported that eunuchs who were castrated after puberty were still capable of maintaining erections [31]. For that reason, it was a custom in ancient Rome for women to use more potent eunuchs for pleasure without the risk of procreation [31].

The main physiological action of T is therefore to timely adjust the erectile process as a function of sexual desire, therefore finalizing erections with sex [11, 28].

In line with the aforementioned evidence, data derived from studies evaluating the effect of TTh on patients with ED have yielded mixed results [2, 3, 32, 33]. Some of those trials had only a few men enrolled, and their inability to show an

effect may reflect limited study precision. Similarly, previous meta-analyses on this topic have produced conflicting results. Jain et al. [34] included only five randomized placebo-controlled studies. Boloña et al. [35] found a small yet significant effect of TTh on erectile function in men with low-to-normal T levels, and a greater effect in the subgroup of younger subjects. In addition, the same authors reported a small but significant effect of TTh on satisfaction with erectile function in those men with sexual dysfunction and a Total testosterone level >10 nM [35]. Conversely, the effect on the same parameter in hypogonadal men (TT < 10 nM) was moderate, not significant and inconsistent, and there was no significant effect on overall sexual satisfaction whatever the TT level was at baseline. Finally, Tserstvadze et al. [36], did not document any effect on erections of testosterone supplementation alone or in combination with PDE5i. However, it is important to note that Tserstvadze et al. [36] analyzed only nine randomized controlled trials (RCTs) enrolling mixed eugonadal/hypogonadal subjects, which may have resulted in a possible inclusion bias. In fact, our meta-analysis [3] in line with Isidori et al. [37] documented a positive effect of TTh on both sexual-related and spontaneous erections as well as sleep-related erections when only studies enrolling hypogonadal (TT < 12 nM) men at enrollment were analyzed (see also Table 14.1). Accordingly meta-regression analysis showed an inverse relationship between baseline T levels and final outcome [3]. In addition, our data clarified that the effect of TTh on ED was less apparent in diabetic subjects. The effect of TTh alone on erectile function is lower in the presence of penile vascular diseases. Accordingly, it is well known that diabetes [38–41] and even the pre-diabetic condition [42, 43] can determine penile atherosclerosis and impair penile neurogenic control, through several mechanisms, many of which are testosterone-independent [44].

In complicated cases of ED hypogonadal men, the association between TTh and PDE5i is thus mandatory [2, 3]. Additionally, because T regulates PDE5 expression, several studies have also suggested that hypogonadism represents a risk factor for reduced PDE5i effect [2, 3, 45, 46]. All these observations emphasize the concept that hypogonadism must be ruled out and, if present, adequately treated, before prescribing any PDE5i. Our meta-analysis, however, did not allow us to adequately clarify this point. In fact, although a positive effect of TTh and PDE5i combined therapy has been observed in uncontrolled studies, the results were not confirmed when only RCTs were considered. However, it should be recognized that 3 out of 5 [47–49] of the aforementioned RCTs enrolled mixed eugonadal/hypogonadal samples. In addition, in the large Spitzer's trial [50], although only hypogonadal subjects were enrolled, T supplementation was initiated after a sildenafil alone run-in period at the end of which T increased to the normal range (about 12.0 nmol/L). Accordingly, it has previously been reported that sexual inertia is associated with functional hypogonadotropic hypogonadism and can be restored with the improvement of erectile function ([2]; see below). Hence, more studies on hypogonadal men are advised in order to better clarify the role of TTh as an add-on to PDE5i in the treatment of ED.

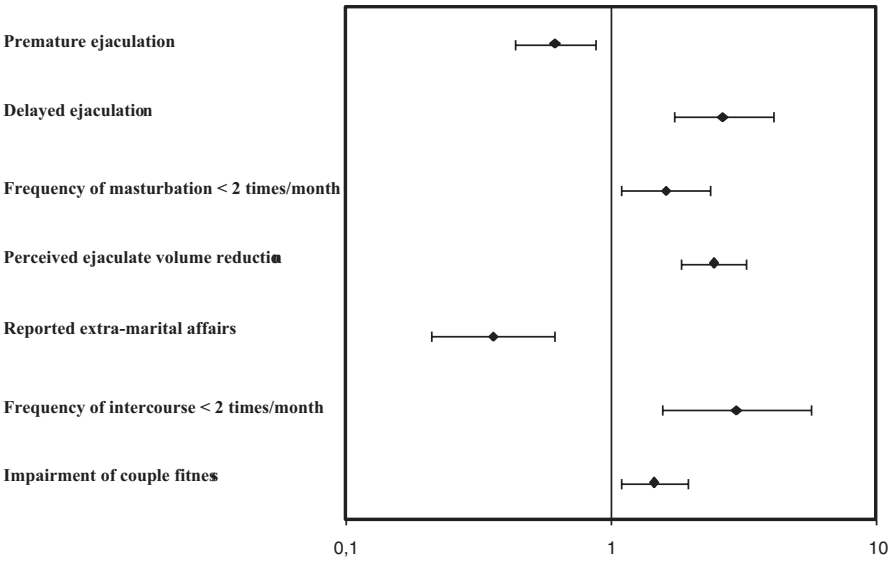

Fig. 14.3 Ageadjusted risk of hypogonadism according to European Male Aging criteria (see ref. [8]) of several sexual parameters. Impairment of couple fitness was evaluated using SIEDY Scale 2 score (see refs. [51, 52]). Data were derived from a consecutive series of 4793 subjects (mean age = 51.1 ± 13.3 years) seeking medical care at our unit for sexual dysfunction

Orgasm

In 2006, we originally reported that hypogonadism represented a risk factor for delayed ejaculation [53]. In a further study we documented that different T levels could be linked to various subsets of ejaculatory disturbances as they are higher in subjects with Premature Ejaculation (PE) and lower in those with Delayed Ejaculation (DE) ([54]; see also Fig. 14.3). Similar results were confirmed by other authors [55]. T might control ejaculatory reflex acting both at the central and peripheral levels [19]. As reported above, AR are expressed in several supra-spinal and spinal areas involved in the control of ejaculation including the medial preoptic area, the bed nucleus of the stria terminalis, the median amygdale, and the posterior thalamus as well as SNB [19]. Additionally, they can also regulate ejaculatory reflex acting at peripheral levels by modulating the integrated system NO-PDE5, involved in the contractility of the male genital tract [19]. Interestingly, our meta-analysis on the effect of TTh in placebo-controlled RCTs also documented a positive effect of T in ameliorating orgasmic function ([3]; see also Table 14.1). Furthermore, in line with what has been observed for libido and erectile function, meta-regression analysis documented an inverse relationship between baseline T levels and final outcomes [3].

Other Outcomes

T is important not only in controlling the mechanical process of penile erection but it also controls several other male sexual behaviors and attitudes. Figure 14.3 shows the age adjusted risk of hypogonadism according to EMAS criteria in a large series of subjects seeking medical care at our unit for sexual dysfunction.

Autoeroticism. The practice of stimulating oneself sexuality is indeed androgen-dependent [56]. Accordingly, Fig. 14.3 confirms that masturbation is associated with a higher risk of hypogonadism.

Perceived ejaculate volume reduction. As reported above, T is profoundly involved in the regulation of the growth and activity of male accessory glands, i.e. prostate and seminal vesicles, which contribute to more than 90 % of ejaculatory volume [19]. Accordingly, we previously reported that the severity of the perceived ejaculate volume reduction (PEVR) was inversely related to T levels [57]. In line with these data we confirmed that hypogonadism represented a risk factor for PEVR (Fig. 14.3). Hence, hypogonadism can affect ejaculate volume interfering with either the production of the ejaculate bolus or its propulsion throughout the male genitalia tract (see above).

Unfaithfulness. In line with other groups [57, 58] we confirm here that self-defined unfaithful men have a lower risk of hypogonadism ([59]; see also Fig. 14.3). It can be speculated that looking for additional partners, or the possibility of additional partners, is a competitive situation, which might be associated with higher T levels [60]. However, it is still unclear whether in mating male individuals, T is higher to allow a better sexual and reproductive fitness (affecting libido/penile erections and/or spermatogenesis) or the reverse is true: sexual activity positively affects T production (see below).

Sexual Activity and Testosterone Levels

There is evidence to suggest that sex is actually an excellent way to boost T levels. An often cited, single observation published in *Nature* almost 40 years ago [61] opened the possibility of this second scenario. An island resident observed an increase in beard growth on the day preceding, and during, his occasional visits to his mainland lover [61]. In 1992, Dabbs and Mohammed [62] evaluated salivary T concentrations in male and female members of four heterosexual couples on a total of 11 evenings before and after sexual intercourse and on 11 evenings on which there was no intercourse. They found that T levels increased on nights after sexual activity and did not on nights when there was no intercourse [62]. Accordingly, the anticipation of sex in animals increases T levels [63]. More recently, Jannini and colleagues robustly substantiated the hypothesis of an LH-mediated, sex-induced drive in T production [63–66]. In particular, they reported that the restoration of sexual activity in patients with ED ameliorated milder forms of hypogonadism.

Interestingly, they showed that the increase in T was independent from the kind of therapies used, but strictly related to the successful outcome of therapeutic intervention. Hence, they speculated that sexual inertia resets the reproductive axis to a lower activity, somehow inducing a secondary hypogonadism, characterized by a reduced LH bioactivity [66]. Our data are in line with the latter hypothesis. We previously reported that the frequency of intercourse is directly associated with T levels [67]. Accordingly, we confirm that reduced frequency of sexual intercourse is associated with a higher risk of hypogonadism (Fig. 14.3). In addition, we found that the impairment of sexual activity due to relational complaints (as assessed by a higher score in Scale 2 of Structured interview on erectile dysfunction structured interviewed) was associated with overt hypogonadism [67]. Similar results were confirmed in a larger sample of patients with sexual dysfunction (Fig. 14.3).

Conclusions

Testosterone plays a major role in regulating male sexual function. TTh is capable of improving all aspects of male sexual function and should be considered the first line treatment in ED patients with overt hypogonadism. However, TTh as a monotherapy might not be adequate in all cases because of the multifactorial nature of the pathophysiology of ED. In those cases a combination therapy with PDE5i may improve the outcome. In young uncomplicated individuals with milder forms of hypogonadism, the restoration of normal sexual function however obtained might improve T levels.

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