Sexual Medicine Reviews, 2025, **13**, 433–455
https://doi.org/10.1093/sxmrev/qeaf025
Advance access publication date 16 June 2025
Invited Review

The hormonal regulation of men's sexual desire, arousal, and penile erection: recommendations from the fifth international consultation on sexual medicine (ICSM 2024)

Giulia Rastrelli, MD, PhD[1], Leen Antonio, MD, PhD[2], Serge Carrier, MD[3], Andrea Isidori, MD[4], Mario Maggi, MD[5,*]

[1]Andrology, Women's Endocrinology and Gender Incongruence Unit – Careggi Teaching Hospital, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence 50139, Italy
[2]Laboratory of Clinical and Experimental Endocrinology, Department of Chronic Diseases and Metabolism (CHROMETA), KU Leuven, Leuven, BE-3000, Belgium
[3]Division of Urology, Department of Surgery, McGill University Health Center, Montreal, QC, H4A 0B1, Canada
[4]Department of Experimental Medicine, Sapienza University of Rome, Rome 00161, Italy
[5]Endocrinology Unit – Careggi Teaching Hospital, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence 50139, Italy
*Corresponding author: Endocrinology Unit – Careggi Teaching Hospital, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence 50139, Italy. Email: mario.maggi@unifi.it

Abstract

Introduction: The sexual response, including sexual desire and arousal/penile erection in men, is affected by several hormones and neurotransmitters.
Objectives: To give resources to understand the usefulness to assess different hormones when considering a man with hypoactive sexual desire or erectile dysfunction and to provide evidence-based recommendations for clinical practice. A level of evidence grading system was used to provide strong, moderate, or conditional recommendations.
Methods: An extensive revision of the scientific literature was performed by the subcommittee of the International Consultation of Sexual Medicine. The results were first extensively discussed by the sub-committee members and presented publicly for further discussion with other experts. The roles of hypothalamic (kisspeptin, α-melanocyte-stimulating hormone), pituitary (prolactin, oxytocin [OT], and growth hormone), thyroid, adrenal (dehydroepiandrosterone, glucocorticoids, and mineralocorticoids) and sex hormones were considered.
Results: Testosterone has a primary role in controlling and coordinating male sexual desire and arousal, acting at multiple levels. Accordingly, meta-analysis indicates that testosterone therapy for hypogonadal individuals can improve low desire and erectile dysfunction. Hyperprolactinemia is associated with low desire which can be successfully corrected by appropriate treatments. OT, α-melanocyte-stimulating hormone, and kisspeptin are important in eliciting sexual arousal; however, the use of these peptides or their analogs, for stimulating sexual arousal is still under investigation. Evaluation and treatment of other endocrine disorders are suggested only in selected cases.
Conclusions: Endocrine abnormalities are common in patients with sexual dysfunction. The identification of some of these is mandatory (ie, testosterone, prolactin), whereas, for others, it is known that their disorders may cause sexual dysfunction without, however, being frequently recognized in subjects consulting for sexual dysfunction (ie, thyroid and growth hormones). Others may be important, but the clinical use is limited by issues with their measurement (ie, estradiol, dihydrotestosterone), whereas for some hormones or neuropeptides, the clinical usefulness for diagnostic and/or therapeutic purposes should still be established.

Keywords: testosterone; prolactin; erectile function; sexual desire; hormones.

Received: January 23, 2025. **Revised:** March 29, 2025. **Accepted:** April 15, 2025

Recommendations		
Recommendation	**Quality of Evidence**	**Strength of Recommendation**
Sexual desire and testosterone		
1. Clinicians should consider that testosterone significantly contributes to the regulation of male sexual desire	High quality of evidence	Strong recommendation
2. Clinicians should measure serum testosterone in all men complaining of reduced sexual desire	High quality of evidence	Strong recommendation
3. Clinicians should use testosterone replacement therapy to improve libido in hypogonadal (total T < 12 nmol/L) men	High quality of evidence	Strong recommendation
Sexual desire and estradiol and DHT		
4. Clinicians should consider that both AR and ER cooperate in the regulation of male sexual desire	High quality of evidence	Strong recommendation
5. Clinicians should consider not prescribing nonaromatizable androgens or aromatase inhibitors to treat low desire in hypogonadal men	Moderate quality of evidence/High quality of evidence	Moderate recommendation/Strong recommendation
Sexual desire and adrenal steroids		
6. Clinicians should consider that adrenal hormones, including DHEA, DHEAS as well as cortisol and aldosterone are not involved in the regulation of male sexual desire and therefore their routine measurements are not recommended.	High quality of evidence/Moderate quality of evidence	Strong recommendation/Moderate recommendation
7. Clinicians should consider that increased levels of cortisol may have deleterious effects on sexual desire beyond hypogonadism induced by cortisol excess	Low quality of evidence	Conditional recommendation
8. Clinicians should not routinely measure adrenal hormones in men complaining of reduced sexual desire	High quality of evidence	Strong recommendation
Sexual desire and prolactin		
9. Clinicians should consider that prolactin plays a major role in regulating male sexual desire, acting through both direct and indirect pathways	High quality of evidence/Moderate quality of evidence	Strong recommendation/Moderate recommendation
10. Clinicians should evaluate prolactin levels in all men complaining of reduced sexual desire	High quality of evidence	Strong recommendation
11. Clinicians should consider that it is unlikely that mild increases in prolactin are the cause of decreased sexual desire	Moderate quality of evidence	Moderate recommendation
12. Clinicians should treat severe hyperprolactinemia to improve sexual desire once the cause of hyperprolactinemia has been properly established	High quality of evidence	Strong recommendation
Arousal/erection and testosterone		
13. Clinicians should consider that prepubescent penile development and pubertal growth are regulated by T but not thereafter	High quality of evidence	Strong recommendation
14. Clinicians should consider that the following mediators are involved in erectile physiology and are all targeted by T: NO-cGMP pathway, RhoA-ROCK signaling, transient receptor potential channels, the adrenergic response, and cavernous SMC turnover	High quality of evidence/Moderate quality of evidence	Strong recommendation/Moderate recommendation
15. Clinicians should consider that there is strong evidence that a sustained decrease in circulating T levels is associated with decreased EF	High quality of evidence	Strong recommendation
16. Clinicians should treat hypogonadal men (total T level < 12 nmol/L) with T for improving EF because TRT is associated with significant but modest increases in self-reported EF measurements. However, clinicians should consider that this effect may be consistent only if hypogonadism is severe and the individual suffers from no other metabolic or cardiovascular comorbidities impairing EF	High quality of evidence	Strong recommendation
Arousal/erection and estrogens		
17. Clinicians may consider the role of estrogens on EF still controversial	Low quality of evidence	Conditional recommendation
18. Clinicians should not consider estrogen measurement in the assessment of EF	Low quality of evidence	Moderate recommendation
Arousal/erection and DHT		
19. Clinicians may consider the effects of DHT on EF similar to those of T	Low quality of evidence	Moderate recommendation
20. Clinicians should not consider DHT measurement in the assessment of EF	Moderate quality of evidence	Moderate recommendation
21. Clinicians should not consider using DHT and its analogues (eg, mesterolone) as an alternative to T treatment for treating EF in hypogonadal men	Moderate quality of evidence	Moderate recommendation
Arousal/erection and adrenal steroids		
22. Clinicians should consider that DHEA and DHEAS do not contribute to the regulation of EF desire, and therefore their routine measurements are not recommended	High quality of evidence	Strong recommendation
23. Clinicians may consider that glucocorticoids and mineralocorticoids may indirectly affect the preservation of EF	Moderate quality of evidence	Moderate recommendation

Continued

Recommendation	Quality of Evidence	Strength of Recommendation
Arousal/erection and prolactin		
24. Clinicians should consider that prolactin does not play a direct role in the regulation of male erectile function	Moderate quality of evidence	Strong recommendation
25. Clinicians may not routinely measure prolactin in all patients complaining of erectile dysfunction	Moderate quality of evidence	Conditional recommendation
26. Clinicians may consider that treating severe hyperprolactinemia might have positive, although rather limited, effects on arousal/erection	Moderate quality of evidence	Conditional recommendation
27. Clinicians may consider that endogenous prolactin levels at the lower end of the normal range could be associated with erectile dysfunction, although its significance is uncertain	Low quality of evidence	Conditional recommendation
Sexual desire, arousal/erection and thyroid function		
28. Clinicians should consider assessing sexual desire and erectile function in men with hypo- and hyperthyroidism	Moderate quality of evidence	Moderate recommendation
29. Clinicians should consider that treating hypo- and hyperthyroidism can improve ED, and possibly sexual desire	Low quality of evidence	Moderate recommendation
30. Clinicians should not routinely perform thyroid hormone evaluation in men presenting with sexual dysfunctions	Moderate quality of evidence	Moderate recommendation
Sexual desire, arousal/erection and growth hormone		
31. Clinicians should consider evaluating sexual desire and erectile function in men with growth hormone excess (acromegaly) and in men with growth hormone deficiency	Moderate quality of evidence	Moderate recommendation
32. Clinicians should consider that treating GH excess could lead to improved erectile function	Low quality of evidence	Moderate recommendation
33. Clinicians should not routinely perform measurements of GH and IGF-1 levels in men with sexual dysfunctions	Moderate quality of evidence	Moderate recommendation
Sexual desire, arousal/erection and oxytocin		
34. Clinicians should consider that conclusive data regarding a potential therapeutic role of oxytocin in male sexual desire and EF are lacking	Low quality of evidence	Moderate recommendation
Sexual desire, arousal/erection and α-MSH		
35. Clinicians should consider that available studies do not support using analogs of α-MSH for improving sexual desire and erectile function, due to associated adverse events	Low quality of evidence	Conditional recommendation
Sexual desire, arousal/erection and kisspeptin		
36. Clinicians should consider that acute administration of kisspeptin increased erection and desire in one trial in men with hypoactive sexual desire disorder	Moderate quality of evidence	Conditional recommendation

Introduction

Definition of normal and reduced sexual desire in the male

Sexual desire can be defined as the motivational state that may prompt individuals to seek out and engage in sexual activity. Although engagement in sexual activity is more often driven by the willingness to experience couple intimacy leading to enjoyable pleasure, from an evolutionary point of view, it is a necessary step to allow for reproduction.[1] Therefore, sexual desire is an intermediary process that propels a strategy into action. Sexual desire has several underpinned dimensions: a cognitive (thoughts, fantasy, and imagination), a neurobiological (hormones and neurotransmitters), and an affective (mood and emotional states) dimension, finally coalescing to create occasions for sexual experiences.[1] The term libido is derived from a Freudian construct of drive but is often used as a synonym of sexual desire, more often viewed as a comprehensive word indicating human mental states and their biological counterparts involved in the beginning of sexual behavior.[1] Low sexual desire and libido have been conceptualized in the Diagnostic and Statistical Manual of Mental Disorders (DSM). In the last edition (5th edition), it is defined as male hypoactive sexual desire disorder (MHSDD): a condition characterized by persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity that causes significant distress.[2] This deficiency or absence of sexual desire must occur for more than 6 months.[2] MHSSD should be independent and not a clinical sequela of a nonsexual mental disorder or a consequence of severe relationship distress or other significant stressors, and it is not attributable to the effects of a substance/medication or other medical conditions (including endocrine ones).[2] The presence of another sexual dysfunction does not rule out a diagnosis of MHSDD.[2] In other words, MHSDD should not be a mere consequence of a medical or mental disorder or their treatments, but a genuine, isolated state. In a clinical study involving 3714 subjects with sexual dysfunction, 36% of the entire cohort complained about any form of MHSDD, but only 14% of those reported isolated MHSDD. While in the vast majority, it was associated with erectile dysfunction (ED) or ejaculatory disorders. In addition, those reporting low libido, hypogonadism, hyperprolactinemia, or any psychiatric conditions or medications were present in 26%, 1.3%, and 17.7%, respectively.[1] Hence, based on that study,[1] the DSM 5 definition is satisfied only by less than 60% of the subjects reporting low desire. A more practical definition was made by a consensus statement from the Fourth International Consultation on Sexual Medicine defining MHSDD just as "persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity", without any further constraints.[3]

A European epidemiological study (the European Male Ageing Study; EMAS) revealed that, overall, only 8% of the

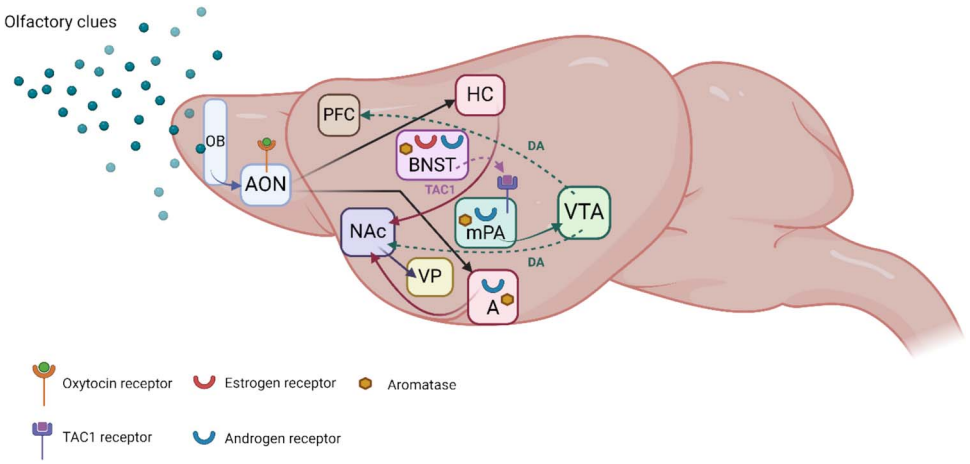

Figure 1. Neurocircuits involved in sexual desire. The figure illustrates the neuronal circuits which proved to be involved in the modulation of appetitive behaviors in studies in rats. The areas which proved positivity for the expression of aromatase, androgen and estrogen receptor are also depicted. Created in BioRender. Rastrelli, G. (2025) https://BioRender.com/vrogyib". OB, olfactory bulbs; AON, anterior olfactory nucleus; PFC, prefrontal cortex; HC, hippocampus; BNST, bed nucleus of the stria terminalis; NAc, nucleus accumbens; mPA, median preoptic area; VTA, ventral tegmental area; VP, ventral pallidum; A, amygdala.

male population aged 40-79 (n = 3369) never think about sex, with 20% reporting thinking less than once a week. The proportion of those with low desire showed a clear age dependency. Never thinking about sex was quite rare (1%) in the youngest age band and quite high (20%) in the oldest one. The frequency of sexual thinking in the EMAS cohort was unaffected by overall general health and quality of life or by organic morbidities (including low urinary tract symptoms and metabolic and cardiovascular [CV] diseases) but was significantly decreased by psychological disturbances, such as depression.[4] Similar figures come from studies in other countries.[5-8] Overall, it is possible to conclude from the aforementioned studies that one in six men shows any form of reduced sexual desire.

Pathophysiology of male sexual desire

Summary of evidence from preclinical studies

The neurobiology of sexual desire has been extensively investigated in preclinical models[9] and thereafter extrapolated to humans.[10] Figure 1 summarizes the evidence obtained by these studies. For example, studies in the rat[11] indicated that sexual chemosensory cues, through the vomeronasal organ, reach the olfactory bulb (OB), which processes olfactory information on the possible partner, and oxytocin (OT)-sensitive neurons in the anterior olfactory nucleus improve the signal-to-noise ratio of the OB signals. The amygdala, along with the hippocampus, by evaluating their relevance, assigns valence to the cues and projects to the nucleus accumbens (NAc). The ventral tegmental area (VTA) releases dopamine in the NAc and prefrontal cortex (PFC), activating the reward system. NAc activation disinhibits the ventral pallidum (VP), leading to the initiation of motor output and partner-directed behaviors.[11] A recent study in sexually naïve mice[12] strongly suggests that estrogen receptor- and TAC1-positive neurons in the bed nucleus of the stria terminalis (BNST), having aromatase (ARO) activity, after receiving chemosensory cues, project to the median preoptic area (MPA) of the hypothalamus where receptors for TAC1 are present. In the male, the aforementioned network of estrogen-sensitive, dedicated neurons in BNST has important activity in discriminating potential female mates. Thereafter, the activation of dopaminergic VTA neurons modulates reward in NAc.[12]

However, meaningful generalization of results obtained in laboratory animals to humans could not be easily made. For example, in humans, olfactory cues have a marginal or even null effect in eliciting sexual desire. Nonetheless, animal studies have helped in understanding that several neurotransmitters - including dopamine, serotonin, noradrenaline, OT, melanocortin, and endogenous opioids - were positively or negatively involved in regulating human sexual desire. However, pharmacological manipulation of these neurotransmitters has more often demonstrated their role in inducing MHSDD (eg, selective serotonin uptake inhibitors, SSRI) rather than efficiently treating it. The pharmacological treatments for MHSDD based on neurotransmitter manipulation are yet in their infancy.

Summary of evidence from clinical studies

In the last few decades, neuroimaging studies have shed light on the regions of the human brain (cortical and subcortical) involved in orchestrating human sexual behavior, including sexual desire.[10] In a meta-analysis of all functional magnetic resonance imaging (fMRI) studies, human brain areas involved in sexual desire – defined as an increase in frequency and intensity of sexual thoughts or fantasies – or love – defined as a state of intense longing for union with another - were investigated.[13] The commonly sexual desire- and love-activated areas included the insula, hypothalamus, ventral striatum, ventral tegmental area, amygdala, thalamus, hippocampus, plus limbic and cortical areas (such as the anterior cingulate, specific regions of occipital and temporal cortex, middle frontal gyrus, superior temporal and precentral gyrus, temporo-parietal junction, somatosensory cortex, and inferior parietal lobule). All these regions participate in integrating the emotional, cognitive, and motivational states characterizing the desire. At variance with sexual desire, feeling love is more associated with a distinct part of the insula and with several dopaminergic regions such as the dorsal striatum and the NAc involved in the rewards, having inherent incentive and bonding value. The authors concluded that love is more an

abstract representation of the pleasant sensorimotor experiences that characterize desire, incorporating mechanisms of reward expectancy and habit learning.[13]

Although sexual desire is the result of interpersonal, psychological, and biological factors, we will focus on biological factors and, in particular, on hormonal regulation.

Methods

The previous version of this ICSM paper[14] served as the foundation of the work. All the committee members examined the previous ICMS paper and reached an agreement on: (i) which hormones were still relevant to be included in the new version of the paper and (ii) which hormones were not included in the previous version but, from 2015 onwards, have had enough evidence to be included in the new version of the paper. All the hormones that the committee considered worthy of discussion for their role in men's sexual desire or arousal/erection were revised for new evidence. Each member of the committee, according to their expertise and preference, took care of one hormone and revised evidence for its role both in sexual desire and in arousal/erection. The committee members agreed that the search should be performed on relevant databases (Medline, Scopus, Web of Knowledge), should mainly focus on publications from 2015 onwards, and the paper should be considered if published in peer-reviewed journals. From September 2023 to January 2024, the committee held online meetings every month, in which one member per meeting presented the results of her/his search and a draft of the results section of the manuscript. These were discussed until the committee achieved an agreement on the recommendations (statements, strength, and grading of recommendations). This was made according to a modified Delphi method and the GRADE methodology.[15,16] The draft of the results was then edited, and once all the sections were complete, a draft of the entire manuscript was made. All the committee members revised the manuscript. On June 28-29, 2024, an ICSM meeting was held in Madrid, and the committee presented its recommendations. Comments and suggestions from the attendees were integrated into a final draft of the paper.

Results and discussion

The role of hormones in male sexual desire

Testosterone

Several epidemiological studies strongly suggest an association between endogenous testosterone (T) levels and sexual desire. In the EMAS cohort, a low sexual desire was associated with both calculated free T (cFT; $P < 0.0001$) and total T ($P = 0.048$).[17] In particular, a reduction of each 1 nmol/L T below 8 nmol/L was associated with a 48% (20–83%) increased risk of low desire. Hence, a threshold of 8 nmol/L was proposed for the association between low T and sexual desire. In the same study, a threshold for cFT was also found, corresponding to 220 pmol/L.[17] In a previous study—conducted in a German series of 434 consecutive male patients aged 50–86 years consulting for andrological problems—a higher threshold was proposed for explaining the association between low T and decreased libido (ie, 15 nmol/L).[18] In a more recent survey, conducted at the University of Florence, Italy, of 4890 men attending an outpatient clinic for ED, it was found that the best threshold to verify the association between reduced T and severe sexual symptoms, including low libido, was total T < 10.4 nmol/L and cfT <225 pmol/L.[19] In the baseline evaluation of the TTrials, an intervention US study enrolling 788 hypogonadal men (total T < 275 ng/dL), there was a significant association between total T or cFT and low libido, as assessed through a validated tool (DISF-SDD), which was stronger for cFT, in particular in the subgroup reporting sexual dysfunctions.[20] A weak, but non-significant, relationship with estradiol (E2) was also observed. However, in that study,[20] no specific threshold for low T in determining low desire was observed. In another Australian longitudinal study, including 1226 community-dwelling men in the final analysis, no relationship was found between sex hormones and self-reported sexual desire at baseline, but after two years of follow-up, changes in total and cFT predicted a decline in sexual desire.[21] In particular, men who declined their sexual desire over the follow-up period had a 10% decline in total T.[21] No significant associations were found for mass-spectrometry measured E2 and dihydrotestosterone (DHT) and sexual desire.[21] In a 14-year follow-up of 294 married men from the original Olmsted County study population, low sex drive (as assessed by Brief Male Sexual Function Inventory) was associated with bioavailable T, but not with total T or E2.[22] Another US longitudinal study (the Massachusetts Male Ageing Study), using a self-reported questionnaire, found an association between low total or bioavailable T and low libido. However, large changes in libido were associated with only modest differences in T levels.[23] Hence, a negative relationship between T levels and libido was observed in almost all epidemiological studies.

Low libido is often considered the most genuine correlate of low T, among other sexual dysfunction issues. In fact, while all the other aspects of male sexual functioning can be negatively affected not only by age but also by comorbidities, low sexual desire is essentially unaffected by comorbidities.[1,4,24] This is well demonstrated also by the results of the secondary analyses of the TRAVERSE study, a randomized double-blind placebo-controlled trial conducted on a population of more than 5000 men with functional hypogonadism and previous CV disease or at high risk for CV events.[25] Indeed, in this population highly burdened by CV and metabolic diseases, T treatment was associated with an improvement in sexual desire but no other sexual complaints.[26] The effect of circulating T in modulating sexual desire also in elderly men has been demonstrated in a randomized clinical trial enrolling 177 healthy men 60-80 years old with an experimentally induced hypogonadism (using goserelin acetate, a GnRH agonist) and then replaced with increasing doses of T gel or placebo.[27] In this study, sexual desire increased in men replaced with T in a dose-dependent manner.[27]

The relationship between T and sexual desire is proven not only in functional hypogonadism but also in organic one. In fact, even in a population with congenital hypergonadotropic hypogonadism (Klinefelter syndrome), low libido, but not ED, was dose-dependently associated with the severity of T deficiency, as shown by the results of a meta-analysis.[28]

A recent meta-analysis indicated that treatment with several antiandrogens, including androgen receptor (AR) antagonists, for prostate cancer resulted in a five- to six-fold increased risk of reduced libido, suggesting an important role of AR in regulating desire.[29] In rodents, a high level of AR mRNA and protein expression occurs in several portions of the central nervous system, known to play an important role in

sexual motivation, including the medial amygdala, lateral septum, BNST, and hypothalamic MPA[24] (Figure 1). Rakin et al. generated, for the first time, mice selectively lacking AR gene in the nervous system by using Cre-loxP technology, without interfering with peripheral AR functions (AR^{NesCre} males).[30] In AR^{NesCre} males, LH and T levels were higher and morphology of genitalia as well as potential fecundity was unaltered, as it was expression of ERα. Copulatory sexual behavior was deeply depressed in these mice, including mounting, intromissions, and thrusts with 33% reaching ejaculation.[30] However, neuronal[30] or global deletion of AR mRNA expression did not significantly alter the relevance of pre-copulatory olfactory clues, ie, the sexual motivation, as also summarized elsewhere.[31] In AR^{NesCre} mice, pheromonal cues emitted by receptive females are normally detected by the olfactory system and signals are transmitted to other centers including medial amygdala, bed nucleus of stria terminalis and to the hypothalamic medial preoptic area.[30,31]

XY subjects with complete androgen insensitivity syndrome (CAIS), but normal female estrogen levels, showed the same sexual arousal rating and similar brain activation as control females after exposure to male nude images.[32] However, gonadectomized subjects with CAIS showed an overall lower sexual functioning, as assessed by the female sexual function index, than healthy female controls.[33] Most of the distress might be generated by the short and blind-ending vagina that characterizes the syndrome. In a small, controlled trial, T administration was superior to standard estrogen administration in improving sexual desire despite the virtual absence of AR.[33] This suggests that, within the central nervous system, local transformation of T in bioactive metabolites, through ARO or 5α reductase, is more important than systemic administration of estrogens for improving sexual desire.[33]

Eight different meta-analyses from 2005 up to 2022 explored the relationship between T administration and sexual desire in controlled trials (Table 1), including up to 3500 subjects with or without low T.[34-41] Although all the meta-analyses reported a significant improvement in sexual desire in the T arm, the magnitude of the effect was variable (mean difference 0.17–1.6, see Table 1). In addition, in meta-analyses considering only trials enrolling subjects without hypogonadism—T > 12 nmol/L[30,34] or T > 10 nmol/L[35]—the positive effect of T treatment on sexual desire was not apparent. When low libido was quantified in trials using the IIEF domain, the percentage of improvement over the maximal effect was statistically significant but relatively modest 8.2%.[24] In conclusion, preclinical and clinical evidence suggest that AR activation is not the only determinant of male sexual desire and that androgen aromatization to estrogen may play a relevant role (see below).

Estrogens

Studies in mice demonstrated that ARO immunoreactivity is present in several brain regions regulating sexual desire, such as BNST, medial amygdala, and hypothalamic medial preoptic nucleus, where the level of ARO expression is higher in male than in female areas[42] (Figure 1). In addition, ARO expression colocalized not only with ER but also with AR,[42] suggesting a paracrine or autocrine transformation of T to estrogens more prominent in males than in females.[42] In the human male and female brain there is an abundance of ER—in particular of ERα—in discrete areas known to be involved in the emotional processing of sexual stimuli, including several regions of the hypothalamus and amygdala,[43] further suggesting a potential role for estrogen in regulating sexual desire. Finkelstein et al.,[44] in a double-blind placebo-controlled experimental model of GnRH-analogue-induced hypogonadism performed in 400 healthy young men, showed that both estrogen and T deficiency contribute to the decline of sexual desire. In that study,[44] 198 healthy men received a GnRH analog (goserelin acetate to suppress endogenous T and E2) and were randomly assigned to receive a placebo or increasing doses of T daily for 4 months. Another 202 healthy men received goserelin acetate, placebo gel or T gel, and anastrozole (to suppress the conversion of T to E2). In the groups that received T, the inhibition of estrogen synthesis through anastrozole was associated with significant decreases in sexual desire when compared to the group not receiving the ARO inhibitor. Accordingly, low libido is the most often complained side effect of ARO inhibitors when employed for treating male infertility, as demonstrated by two meta-analyses.[45,46] As further confirmation of the strong effect of ARO inhibitors on male sexual desire, a small prospective study on letrozole in male infertility reported the loss of libido in more than half of the participants.[47] In men with ARO gene mutation, who are thus hypoestrogenic, libido and sexual activity are reported normal. However, transdermal E2 increased the frequency of sexual intercourse, masturbation, and erotic fantasies in these men, suggesting that exogenous E2 can improve sexual interest in ARO-deficient individuals.[48] In line with that, in men with advanced prostate cancer, the suppressive administration of high-dose E2 was superior to surgical castration[49] or GnRH analogs[50] in maintaining some aspect of sexuality, including desire. Similar results were recently published in 271 obese subjects with functional secondary HG (total T < 10.4 nmol/L) enrolled in a multicenter, double-blind RCT. Subjects were treated weekly with 0.1, 0.3, and 1 mg of the AI leflutrozole or placebo for 24 weeks. A dose-dependent increase in total T and Gn levels was observed, with a significant decrease in estradiol even below 40 pmol/L.[51] In front of these hormonal changes, leflutrozole not only did not demonstrate any significant difference upon treatment in IIEF but also demonstrated a significant decrease in "interest in sexual activity".[51] Interestingly, reducing estrogen levels by treatment with the nonaromatizable androgen DHT in older men did not affect most of the areas of sexuality but significantly decreased sexual desire.[52] Accordingly, a recent meta-analysis of the available trials shows that the use of ARO inhibitors is associated with reduced libido.[53] Overall, the evidence suggests that E2 in the brain might participate in regulating sexual desire in men. However, epidemiological studies did not show significant relationships between circulating E2 and sexual desire in men.[17,20-22] A possible explanation is that brain estrogen levels, which affect sexual desire, are most probably formed locally from T through ARO rather than originating from circulating E2, which consequently does not accurately describe the intracerebral estrogen amount. In contrast with this view, a secondary analysis of the treatment arm of the aforementioned TTrials[20] showed that changes in circulating E2 measured by mass spectrometry correlated better than changes in total T levels with changes in sexual desire, with an apparent threshold at 22 pg/mL.[54]

Dihydrotestosterone

In the aforementioned secondary analysis of the treatment arm of the TTrials, besides E2, changes in DHT levels were

Table 1. Main results of the available meta-analyses of placebo-controlled randomized clinical trials assessing the effect of testosterone replacement therapy on sexual desire.

Trial	# trials	Trial population	# subjects (total or TRT/ comparator)	Outcome measure	Main result	Conclusion
Isidori et al. 2005[31]	17	Mixed hypogonadal and eugonadal	326/326	Standardized mean difference between TRT and placebo arm of scores of different questionnaires assessing sexual desire or self-report	• Baseline TT < 7 nmol/L: 1.44 [0.11;2.77] • Baseline TT 7-12 nmol/L: 1.42 [0.07;2.77] • Baseline TT >12 nmol/L: 0.65 [-0.02;1.32]	TRT improves sexual desire in hypogonadal men
Boloña et al. 2007[32]	14	Mixed hypogonadal and eugonadal with sexual dysfunction	862	Standardized mean difference between TRT and placebo arm of scores of different questionnaires assessing sexual desire or self-report	• Baseline low TT: 1.31 [0.40;2.22] • Baseline low-to-normal TT: 0.41 [-0.01;0.83]	TRT has moderate to large favorable effect on sexual desire
Corona et al. 2014[33]	29	Mixed hypogonadal and eugonadal	1930	Standardized mean difference between TRT and placebo arm of scores of different questionnaires assessing sexual desire or self-report	• Baseline TT < 8 nmol/L: 0.98 [0.42;1.53] • Baseline TT < 12 nmol/L: 0.97 [0.22;1.71] • Baseline TT >12 nmol/L: 0.25 [-0.24;0.74]	TRT improves sexual desire in hypogonadal men
Corona et al. 2017[35]	14	Mixed hypogonadal and eugonadal	2298	Standardized mean difference between TRT and placebo arm of sexual desire domain score at the IIEF	0.33 [0.12;0.54]	TRT improves sexual desire
Elliott et al 2017[37]	12	Hypogonadal	3167	Standardized mean difference between TRT and placebo arm of sexual desire as assessed by validated scales	0.33 [0.16;0.50]	TRT improves sexual desire in hypogonadal men
Ponce et al. 2018[36]	4	Hypogonadal	1779	Standardized mean difference between TRT and placebo arm of scores of different questionnaires assessing sexual desire	0.17 [0.01;0.34]	TRT produces a small improvement of sexual desire in hypogonadal men
Algeffari et al. 2018[34]	3	Mixed hypogonadal and eugonadal with T2DM	225/228	Standardized mean difference between TRT and placebo arm of scores of different questionnaires assessing sexual desire	0.31 [0.08;0.55]	TRT has moderate favorable effect on sexual desire
Corona et al. 2022[30]	18	Mixed hypogonadal and eugonadal	1810/1762	Mean difference between TRT and placebo arm of sexual desire domain score at the IIEF	0.82 [0.04;1.60]	TRT improves sexual desire

Abbreviations: TRT, Testosterone replacement therapy; TT, total testosterone; IIEF, International Index of Erectile Function; T2DM, type 2 diabetes mellitus.

significantly associated with changes in sexual desire.[54] Accordingly, a meta-analysis of placebo-controlled trials for benign prostate hyperplasia with 5α-reductase inhibitors (5ARI) indicated a more than 50% increased risk of MHSDD in the treatment arm, with the risk decreased as a function of shorter trial follow-up.[55]

Role of DHEA and other adrenal hormones

An age-dependent reduction of circulating dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) has been often reported, suggesting a role for these adrenal hormones in the age-dependent impairment of several biological functions, including the sexual ones.[56] Granata et al.[57] evaluated sexual function in a small prospective study involving 12 subjects with autoimmune primary adrenal insufficiency, who were studied before and after two months of adrenal hormone supplementation. They found that DHEAS circulating levels do not correlate with any of the sexual parameters studied, including sexual desire, either at baseline or in the recovery phase.[57] Granata et al.[57] also reported that subjects with adrenal insufficiency have lower scores in all

domains, including sexual desire (as measured by the IIEF), which were normalized after replacement with cortisol and aldosterone. However, the improvement of the sexual desire domain was not confirmed after the adjustment for cortisol and renin levels during the recovery phase, suggesting an indirect, if any, role of the gluco- and mineral-corticoids in regulating male sexual desire.[57] Several uncontrolled studies indicate a positive effect of DHEA administration on sexual functions, including libido.[56] Corona et al.[58] meta-analyzed the placebo-controlled RCTs evaluating the effect of DHEA administration in elderly men. They found that DHEA did not significantly improve sexual desire in aging men.[58] In another study, 21 men with MHSDD were randomized to receive either DHEA 100 mg daily or placebo for 6 weeks, without any significant effect of DHEA administration on sexual desire.[59]

The European Registry on Cushing's syndrome documented that cortisol excess was associated with a 35% and 21% reduced libido in men younger or older than 65 years, respectively.[60] However, whether cortisol plays a direct role in the regulation of male sexual desire, or the latter relationship is the result of cortisol excess-associated morbidities, including hypogonadism and mood disturbances, is unknown.[60]

Prolactin

Most evidence on the role of prolactin in the regulation of male sexual desire derives from the observation of the clinical features in men with hyperprolactinemia. Experimental evidence on the mechanisms underlying this relationship is limited. Prolactin increases acutely dopamine turnover in brain areas with a role in the regulation of sexual behavior, including the nigrostriatal and the mesolimbic tracts.[56,61] Moreover, markedly increased circulating prolactin levels can induce a switch in the firing of tuberoinfundibolar tract (TIDA) neurons from phasic to tonic, eventually promoting dopamine release.[62] This may be a feedback mechanism to limit further prolactin release and may result in reduced GnRH pulses, thus leading to hypogonadotropic hypogonadism. According to a recent review of the literature, hypogonadotropic hypogonadism is found in more than 70% of men with severe hyperprolactinemia due to prolactinomas.[63] Therefore, the relationship of prolactin excess with decreased sexual desire may be claimed as secondary to the development of hypogonadotropic hypogonadism. However, a direct effect of hyperprolactinemia in depressing sexual desire is likely. Prolactin receptors are expressed in the diencephalic incertohypothalamic dopaminergic system (IHDA). The dopaminergic neurons here emit short axons towards the medial preoptic area, the most important area for the control of motivational and consummatory aspects of sexual behavior.[56,61] In IHDA, in contrast to other areas, prolactin does not stimulate dopamine activity and may even have an inhibitory effect,[56,61,64] thus bolstering the hypothesis of a direct, negative effect of prolactin on sexual motivation. In line with this view, a clinical study on men with hyperprolactinemia,[65] reported similar baseline prevalence of, and recovery from, sexual dysfunction in men with low or normal T levels associated with increased prolactin.

Clinical studies in the general population[66] and in men seeking medical care for sexual dysfunction,[67] which assessed the relationship between circulating prolactin and sexual desire, failed to find a linear association. Among a cohort of 2146 men with sexual dysfunction, when prolactin outside the normal range was considered, values moderately exceeding the threshold (20-35 ng/mL) were still not associated with a change in sexual desire. Conversely, severely increased prolactin levels (>35 ng/mL) were associated with a more than tenfold increased probability of reporting hypoactive sexual desire.[67] Among a larger population of 3714 men consulting for sexual dysfunction, low libido was highly prevalent among men with severe hyperprolactinemia (85%) whereas only 40% and 48% of men with hypogonadism or psychopathology reported a decrease in sexual desire.[1] A recent meta-analysis reported a much lower prevalence of low libido in hyperprolactinemia (49 [32-66]%); but when only studies recruiting men with prolactin above 35 ng/mL were included, the prevalence was considerably higher (75 [57-57]%).[68]

The prevalence of severe hyperprolactinemia, which is relevant to low libido, is very low in the general population, being 0.5% in European men from the EMAS.[66] However, the prevalence of 1.4% among men seeking medical care for reduced libido[1] strengthens the concept that hyperprolactinemia is a non-negligible cause of decreased sexual desire, as much as men require medical consultation. Indeed, in a cohort of men with macroprolactinoma, which represents the most frequent cause of severely increased prolactin in men,[67,69] mass effect symptoms (ie, headache, visual field defects) were the referral symptoms in more than 90% of subjects. However, when adequately interviewed, decreased sexual desire was present in 72.7% of subjects.[70]

Dopamine agonists (bromocriptine and cabergoline) are the first-line treatment for hyperprolactinemia, particularly when derived from prolactin-secreting adenomas.[69] Cabergoline, even more than bromocriptine or quinagolide, effectively lowers prolactin levels and reduces the adenoma size.[69] In prolactin-secreting adenomas, surgery may also be considered a first-line option if the risk of invasion of the cavernous sinus is low; otherwise, it generally represents a second-line choice.[69]

According to a recent meta-analysis of three studies assessing the change in prevalence of reduced sexual desire before and after medical or surgical treatment, the probability of remission was dramatic, with a prevalence almost 60-fold lower after therapy.[68]

The role of hormones in arousal/erection

Testosterone

Summary of evidence from preclinical studies.

Androgens are the major hormonal regulators of penile development and physiology (Figure 2).[71] T primarily affects human penile development through extracellular stromal expansion.[72] Research has demonstrated correlations between postnatal penile length, growth rate, and a T surge in the first months of life (mini-puberty).[71,73] However, no such correlation has been found in adult human males. Most studies agree that androgen sensitivity and receptor expression differ with age and penile development stage. Therefore, the role of T in adult ED is uncertain.

While the erectile response to T is partially mediated by increased sexual desire, several studies have demonstrated that T directly influences cavernous smooth muscle cells (SMCs) involving nitric oxide (NO), phosphodiesterase type 5 (PDE5), Ras homolog family member A-Rho-associated, coiled-coil containing protein kinase (RhoA-ROCK), cavernosal nerve function, and the adrenergic response (Figure 2).[75]

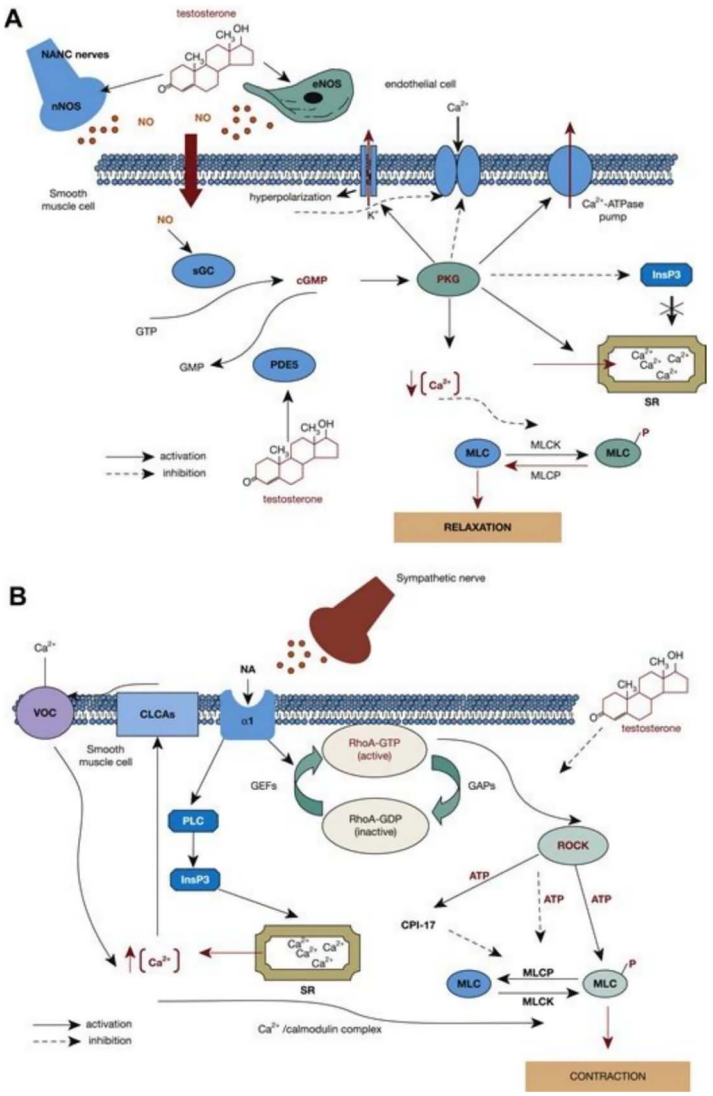

Figure 2. The role of testosterone in the penile erection mechanism. Panel A: Testosterone positively regulates the generation of NO by NOS in NANC neurons (nNOS) and endothelial cells (eNOS). NO diffuses into smooth muscle cells and activates sGC, transforming GTP into cGMP. In turn, cGMP activates PKG, which decreases intracellular Ca^{2+} levels via the pathways shown, leading to relaxation. PDE5 metabolizes cGMP into GMP to limit its effects. This, again, is positively controlled by testosterone. Panel B: NA binding to α_1-receptors generates InsP3. By increasing Ca^{2+} levels, the InsP3 then activates CLCAs, causing depolarization of the cell membrane and the opening of VOC. Increased Ca^{2+} flow promotes MLCK activation and cell contraction through calmodulin. The RhoA/ROCK pathway induces cell contractions, which, via a series of kinase activations, increases the sensitivity of MLC to Ca^{2+}. Testosterone is thought to regulate this increased sensitivity negatively. Reproduced with permission from Corona et al. 2016.[74] ATPase, adenosine triphosphatase; Ca^{2+}, intracellular calcium; CC, corpora cavernosa; cGMP, cyclic guanosine monophosphate; CLCAs, Ca^{2+}-sensitive chloride channels; eNOS, endothelial nitric oxide synthase; GAPs, Rho1-GTP activating proteins; GEFs, guanine nucleotide-exchange factors; GTP, guanosine triphosphate; InsP3, inositol 1,4,5-trisphosphate; MLC, myosin light chain; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphate; NA, noradrenaline; NANC, non-adrenergic, and non-cholinergic; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; P, phosphate; PDE5, phosphodiesterase type 5; PKG, protein kinase G; RhoA/ROCK, Ras homolog family member A-rho-associated, coiled-coil containing protein kinase; sGC, soluble guanylate cyclase; SR, sarcoplasmic reticulum; VOC, voltage-operated channels.

The NO pathway is a major target of androgens (Figure 2)[14,76]; however, animal studies have identified additional NO-independent mechanisms that require the generation of intact cyclic guanosine monophosphate (cGMP) to control veno-occlusion.[77] The RhoA-ROCK pathway[78] is among the NO-independent androgenic targets that maintain the stability of SMC contraction through calcium sensitization. Hypogonadism is known to induce ROCK1 activation,[79] which counteracts SMC relaxation. However, it does not induce ROCK2 activation, which conversely is increased by T in endothelial cells (Figure 2).[80] Recently, it has been demonstrated in rats that hypogonadism can downregulate the expression of galanin and its receptors, and, in turn, this is associated with the up regulation of ROCK1 and ROCK2.[81]

The regulation of smooth muscle myosin isoforms is also a NO-independent mechanism.[82] Impaired subtunical cell renewal has been observed in hypogonadism, contributing to veno-occlusion.[83] Several studies have found PDE5 expression to be regulated by androgens (Figure 2),[14,84,85] although there have been some conflicting findings.[86] Androgens also sustain, either directly[84,85] or indirectly,[87] the

NO-cGMP pathway.[88] However, the expression and activity of PDE5 seem more strongly inhibited by estrogens than stimulated by androgens.[88]

A recent study of human corpora cavernosa (CC) tissue strips obtained from men undergoing penile prosthesis implantation revealed that T, acutely and dose-dependently, stimulates endothelial or neuronal NO synthase (eNOS, nNOS), cGMP, and NO levels while paradoxically reducing PDE5 protein expression, confirming that T contributes to CC relaxation.[89] The latter finding, obtained in an ex-vivo acute model, collides with in vivo studies showing a positive effect of T on PDE5 expression, most likely exerted through an increase in NO activity.

The role of T on eNOS has also been attributed to the ability of T to prevent the uncoupling of eNOS into monomers occurring in castrated rats.[90] This effect of T may have the double consequence of favoring erectile function (EF), which is mainly sustained by NOS dimers, and, on the other hand, preventing the formation of superoxide radicals secondary to the uncoupling of eNOS. T can also impact the upstream regulation of eNOS. In rat CC, the expression of neurogranin and calcineurin is decreased and increased, respectively, in castrated animals, whereas T treatment is able to maintain the expression similar to controls.[91] Neurogranin has been described as a stimulating factor for eNOS expression, at least in part by downregulating calcineurin, which, conversely, is an inhibitory factor for eNOS.[91]

As shown in Figure 2, the final effect of NO on the SMC is to decrease the intracellular calcium content to induce SMC relaxation. The calcium outflow is mediated by channels, among which the transient receptor potential channels may be mentioned. In a rat model, castration can increase the expression of these channels, whereas T treatment induces their decrease,[92] and this may explain the favorable effect of T on SMC relaxation.

Another recognized androgen mechanism is the regulation of the α_1-adrenergic responsiveness of SMCs (Figure 2).[14,93] Research has consistently demonstrated that T affects postganglionic parasympathetic neurons or, further upstream, neurons within the autonomic nervous system.[94] Thus, androgens appear vital to adequate neuronal stimulation of the CC and its structural integrity, as seen after prostate surgery denervation.[83,94]

An interesting recent study found a negative correlation between testosterone levels and the severity of penile deformity among men with Peyronie's disease, indicating a possible role of T in preventing fibrosis.[95]

Summary of evidence from clinical studies.

Human studies have been highly heterogeneous, assessing EF in both spontaneous erections and those experienced in a sexual context using a range of scales such as the Sexual Encounter Profile and the IIEF.[37]

Cross-sectional surveys such as the EMAS have reported lower T levels in approximately 30% of men with ED.[17,23,52,96–99] This association has been confirmed by longitudinal studies demonstrating that a decrease (change [Δ]) in the hypogonadal range of an individual, rather than its absolute value, predicts sexual decline.[21] However, this relationship is weaker when assessed with EF rather than libido, and it seems correlational rather than causal.[21,98]

Longitudinal evaluations have failed to find, at least in the short-term follow-up, a relationship between age-related decline in T levels and a decline in EF.[21] However, when the decline in T is defined according to threshold values in terms of the development of hypogonadism, the relationship with deteriorated EF becomes evident. In fact, longitudinal data from the EMAS study found that the development of hypogonadism—either primary or secondary—over a mean follow-up of 4.3 years is associated with the development or worsening of ED.[100,101]

In young men with normal EF, androgen levels are maintained at threshold values far below those required to maintain the function of other target organs, suggesting that the dependence of EF on androgen is not strong.[102] However, this finding cannot automatically be generalized to older men with comorbidities (ie, the vast majority of men complaining of ED). It should be also underlined that both animal and human studies show that sexual activity can increase T levels; accordingly, low or low-to-normal T levels in subjects lacking sexual activity should be interpreted with caution to establish a correct cause-effect relationship.[75]

Ageing is associated with increased sex hormone binding globulin (SHBG), which can lower the bioavailability of T. From this observation, it may be inferred that free T would better predict the association between EF and androgen than total T. Although there are issues with the direct measurement of free T or its calculation using SHBG, recent evidence advocates the measurement of SHBG and the calculation of FT, as it provides more information than the measurement of total T alone. Accordingly, cFT seems to correlate better than T to EF.[103–106]

The few available RCTs addressing the role of T in ED have been extensively reviewed in several meta-analyses, with inconsistent findings related to study selection and entry criteria. Most meta-analyses have confirmed overall EF to significantly benefit from T therapy, although with a clinically modest effect size (Table 2).[34–41,97,107] On the other hand, other meta-analyses showed no significant benefit.[108,109] Regression and subgroup analyses have emphasized the possible moderating role of ageing in the responsiveness of ED to T. Overall, T replacement therapy (TRT) produced improvements in EF only in studies of hypogonadal participants (mean baseline T levels <12 nmol/L) but not in those of either eugonadal or mixed eugonadal and hypogonadal participants.

Two large multicenter trials recently conducted provided further information with conflicting results. In the Testosterone Trials (TTrials), treatment, compared to placebo, substantially increased most areas of sexual activity with a mild to moderate effect size.[110] TRT increased libido and EF, and incremental increases in total, free T, and E2 levels were associated with greater improvements in sexual activity and libido but not EF.[103]

The TRAVERSE Trial assessed changes in scores on the short IIEF-5 between baseline and after 12 and 24 months of TRT treatment or placebo in men with a great burden of CV and metabolic morbidity. In contrast with a significant improvement in hypogonadal symptoms and libido, the TRAVERSE trial did not find any improvement in EF associated with TRT.[26]

There are several possible reasons why TRT was effective on sexual activity in both studies, but a significant effect on EF was found only in the TTrial. First, the two study populations had different enrollment criteria. The TRAVERSE trial enrolled younger subjects (roughly -7 years), more obese

Table 2. Main results of the available meta-analyses of placebo-controlled randomized clinical trials assessing the effect of testosterone replacement therapy on erectile function.

Trial	# trials	Trial population	# subjects (total or TRT/comparator)	Outcome measure	Main result	Conclusion
Isidori et al. 2005[31]	17	Mixed hypogonadal and eugonadal	326/326	Standardized mean difference between TRT and placebo arm of scores of different questionnaires assessing EF or self-report	• Baseline TT < 7 nmol/L: 1.28 [0.37;2.19] • Baseline TT 7-12 nmol/L: 1.73 [0.53;2.94] • Baseline TT >12 nmol/L: 0.22 [-0.18;0.61]	TRT improves EF in hypogonadal men
Boloña et al. 2007[32]	14	Mixed hypogonadal and eugonadal with sexual dysfunction	862	Standardized mean difference between TRT and placebo arm of scores of different questionnaires assessing EF or self-report	• Baseline low TT: 0.80 [-0.10;1.60] • Baseline low-to-normal TT: 0.34 [0.03;0.65]	TRT has minimal to small favorable effect on EF
Tsertsvadze et al. 2009[92]	15	Hypogonadal with erectile dysfunction	NR	Standardized mean difference between TRT and placebo arm of different scores of the IIEF or self-report	NR	insufficient evidence to determine TRT efficacy on EF due to low quality and heterogeneity of RCTs
Corona et al. 2014[33]	29	Mixed hypogonadal and eugonadal	1930	Standardized mean difference between TRT and placebo arm of scores of different questionnaires assessing EF or self-report	• Baseline TT < 8 nmol/L: 1.23 [0.56;1.90] • Baseline TT < 12 nmol/L: 1.25 [0.51;1.99] • Baseline TT >12 nmol/L: 0.19 [-0.19;0.58]	TRT improves EF in hypogonadal men
Corona et al. 2017[35]	14	Mixed hypogonadal and eugonadal	2298	Standardized mean difference between TRT and placebo arm of EF domain score at the IIEF	0.41 [0.21;0.60]	TRT improves EF
Elliott et al 2017[37]	17	Hypogonadal	3165	Standardized mean difference between TRT and placebo arm of EF as assessed by validated scales	0.25 [0.10;0.41]	TRT improves EF in hypogonadal men
Ponce et al. 2018[36]	4	Hypogonadal	1779	Standardized mean difference between TRT and placebo arm of scores of different questionnaires assessing EF	0.16 [0.06;0.27]	TRT produces a small improvement of EF in hypogonadal men
Algeffari et al. 2018[34]	3	Mixed hypogonadal and eugonadal with T2DM	225/228	Standardized mean difference between TRT and placebo arm of scores of different questionnaires assessing EF	0.20 [0.01;0.40]	TRT has small favorable effect on EF
Corona et al. 2022[30]	18	Mixed hypogonadal and eugonadal	1810/1762	Standardized mean difference between TRT and placebo arm of EF domain score at the IIEF	0.40 [0.24;0.56]	TRT provides modest improvement of EF
Taniguchi et al. 2022[102]	6	Late onset hypogonadal	1458	Mean difference between TRT and placebo arm of EF domain score at the IIEF	1.86 [1.01;2.72]	TRT improves EF in men with late onset hypogonadism

Abbreviations: TRT, Testosterone replacement therapy; EF, erectile function; TT, total testosterone; IIEF, International Index of Erectile Function; T2DM, type 2 diabetes mellitus; NR, not reported.

(+5 points of body mass index; BMI), with a four times higher frequency of previous CV events, twice the prevalence of type 2 diabetes mellitus (T2DM), and thrice the prevalence of current smokers. It might be that the effect of T on EF is well apparent in hypogonadal men, whereas in those with T2DM[39] or at high CV risk,[26] the beneficial effects are attenuated. This is supported by the meta-analysis of RCTs, which shows that trials with a higher prevalence of T2DM reported limited results for TRT on EF. However, the T4DM trial found the effects of T on EF in men with early diabetes or prediabetes to be like those in the general population (2 IIEF points),[104,111–115] suggesting that the loss of efficacy of TRT on EF in diabetic men may be a function of the duration of T2DM with the consequent accumulation of arterial and neuropathic damage. A second reason could be that in the TTrial, participants were required to be sexually active, while in the TRAVERSE, this was not mandatory (they were only requested to have low libido), and 10% of the enrolled population was sexually inactive.

Another possible explanation for the differences among the trials may be that T loses efficacy above threshold levels. An experimental study of block-and-replace treatment found it to

have no effect on libido or EF unless testosterone levels had fallen below <100 ng/dL for at least 16 weeks.[27]

In this respect, although both studies have similar baseline T levels (230 vs 220 ng/ml), the post-treatment values achieved by TRT were significantly different, with a mean target value of 500 ng/ml in the TTrial as compared to a 350 ng/ml in the TRAVERSE. One could argue that a lower change in circulating T levels is sufficient to improve sexual activity (in both trials, a positive effect was found), whereas EF improvement requires a greater increase in T.

Another relevant variable is the time course of T effects (ie, the length of treatment necessary to achieve the maximum result). Several studies have found T to produce effects on libido, ejaculation, and sexual activity within 2 to 3 weeks, while the effects on EF can require up to 6 or even 12 months.[102,111–115] In this respect, the TRAVERSE trial was the most extended trial assessing the effect of TRT on sexual function and showed that the beneficial effects obtained at 12 months were maintained at 24 months. Nevertheless, a significant loss of participants at follow-up (up to 69% at month 12 and 90% at 24 months compared to baseline at randomization) could jeopardize the significance of some of the findings.

Along with the threshold response and time course, concomitant therapies related to the different comorbidities and ages of the population could explain the divergent results between trials. The rate of PDE5 inhibitors (PDE5i) in the two trials was 8.7% and 9.8%, respectively, in the TTrial and TRAVERSE trials. In this respect, observational studies, but not RCTs, suggest that TRT increases responsiveness to PDE5i.[116,117]

Finally, the scientific community has now largely accepted the concept of "compensated" or "subclinical" hypogonadism as an entity deserving attention. When T decreases from a previously higher level, the increase in luteinizing hormone (LH) can be used as a confirmatory biomarker for insufficient androgenization.[118–120] Recent guidelines suggest including LH and cFT in subgroups of patients more likely to benefit from treatment, independently of total T values.[94,121]

Estrogens

Research on E2 has produced mixed results, with some studies showing no effect,[122] some finding it beneficial, and others finding it harmful. Some, but not all, studies of selective estrogen deficiency have found E2 necessary for the maintenance of male sexual function.[123,124] In a clinical trial of DHT, the administration of which causes E2 suppression, EF was maintained, but sexual desire was slightly reduced.[52] The EMAS showed a correlation between E2 and psychological symptoms of male ageing but not with EF domains,[123] confirming previous findings.[22] Retrospective population studies found higher E2 levels associated with erectile dysfunction[125] but low E2 with delayed ejaculation. An RCT found aromatization to play only a minor role in the maintenance of sexual function in healthy men, to some extent dependent upon ageing and obesity.[52] A longitudinal study found an association between estrone and ED onset during a 2-year follow-up.[21] As the measurement of estrogen in men using immunoassays produces somewhat unreliable results, their use as biomarkers will be possible only when more adequate detection systems become available.

In an experimental model of metabolic syndrome, a correlation has been found between hyperestrogenism and worsening EF.[88] At the same time, a real-life survey has found hyperestrogenism to correlate with lower IIEF-EF scores.[126] Similarly, IIEF-EF is negatively correlated with the estradiol-to-testosterone ratio in men with Klinefelter syndrome.[127]

Conversely, trials of ARO inhibitors and clomiphene found these treatments to have no beneficial or detrimental effects on EF.[128,129] This has been recently confirmed in an RCT comparing leflutrozole to placebo provided for 24 weeks to 271 obese subjects with late-onset hypogonadism.[51]

Dihydrotestosterone

DHT is the most potent androgen involved in the development of genital tissue. No major discrepancies were found between the *in vitro* effects of T and DHT on EF. However, there has recently been renewed interest in the role of DHT due to patient complaints of symptoms of sexual dysfunction after exposure to 5ARIs.[130] Studies point toward a drug-related, rather than DHT-mediated, explanation for this. In animal models, 5ARIs have shown associations with structural and functional alterations in penile tissue, contributing to penile fibrosis. In addition, exposure to 5ARIs alters gene expression in the human penile foreskin.[131] However, differences in circulating hormonal levels seem not to be involved, as they were not grossly modulated. This effect appears to be exerted primarily through the modulation of cholinergic and adrenergic sensitivity, with no apparent changes in PDE5.[132] A recent study revealed a possible association between defective DHT in the presence of normal T and some male ageing symptoms, but not with changes in IIEF.[133] Trials with hypogonadal participants treated with DHT alone or T plus 5ARIs found the two treatments to have similar effects on major EF domains.[134,135]

DHEA and other adrenal hormones in ED

Previous research has suggested that an age-dependent decrease in DHEAS may play a role in the pathogenesis of ED.[56,136] The EMAS study found DHEAS to be the only hormone out of 17, including T and E2, that was negatively correlated with ED.[137] Basar et al.[138] found levels of DHEAS and free T to be significantly lower in men with sexual dysfunction, as determined by their IIEF score. However, more recent research found no association between DHEA (and its DHEAS) and ED. A large placebo-controlled RCT with an observational period of up to 2 years evaluated the effects of DHEA in older men and women. The study failed to find any physiologically relevant beneficial effects of DHEA on ED.[139] Similarly, Morales et al.[140] found no significant difference in the sexual performance outcomes, as assessed by the IIEF, Androgen Deficiency in the Aging Male questionnaire, Aging Male Symptom Scale, and Global Assessment Questionnaire, of men treated with a placebo and those treated with DHEA (50 mg twice daily). Similarly, a meta-analysis of DHEA treatment in older men found DHEA supplementation to produce no significant improvements in overall IIEF-15 scores or EF domain total scores.[58]

In recent years, there has been growing research interest in the effects of stress hormones on EF. In an animal model of psychological stress (rat restraint stress) that decreased gonadotropins and increased serum corticosterone levels, decreases in p-Akt, nNOS, eNOS, cGMP, and the penile smooth muscle to collagen ratio were paralleled by increased PDE5α and oxidative stress.[141]

The European Registry on Cushing's Syndrome found excessive cortisol to lead to a 35% reduction in libido in men younger than 65 years and a 21% reduction in those over 65.[142] A recent RCT in patients with adrenal insufficiency found a significant sexual dysfunction burden (ED reported in up to 58% of men). However, no relationship was detected between the IIEF-EF score and sex steroid levels, disease duration, and body surface-adjusted dose of glucocorticoids.[143] Conversely, EF correlated with Addison's quality of life score. Granata et al.[57] found treatment with glucocorticoids and mineralocorticoids to independently improve scores on the EF domain of the IIEF in men with adrenal insufficiency.

Prolactin

The role of prolactin on penile erection is debatable. Animal models show that increased prolactin induces vasoconstriction in several arterial districts[144] and causes hypertension and cardiac dysfunction[145] by decreasing NO production. It may be speculated that a similar effect occurring in the penile district could favor erectile dysfunction in hyperprolactinemic men. However, there are no studies in humans to support this hypothesis.

Evidence from clinical studies provides conflicting results related to the relationship between prolactin and ED. In more than 2000 men consulting for sexual dysfunction,[67] severely increased prolactin levels (>35 ng/mL) were not associated with different prevalence of ED as compared with men with normal or moderately increased serum prolactin. Impairment in morning erections was significantly more frequent among severely hyperprolactinemic men; however, the adjustment for confounders, including low total T, did not confirm this association.[67] Conversely, a smaller study on 135 men with ED found a negative relationship between prolactin levels and Rigiscan parameters.[146] In particular, after the adjustment for confounders, including total T, the rigidity at the penile base was lower as circulating prolactin levels increased, whereas no relationship was found for the rigidity at the penile tip.[146] According to a recent meta-analysis of 15 observational studies,[68] ED was present on average in 57% of subjects with hyperprolactinemia, with higher prevalence in studies reporting higher mean prolactin or lower mean T. On the other hand, the prevalence of hyperprolactinemia, however defined, among subjects with ED was low, ranging from 1 to 3%. Despite being quite rare, hyperprolactinemia in ED as derived by this meta-analysis is two- to six-fold higher than that observed in the general population,[66] thus supporting a relationship. In a study performed on 58 men with macroprolactinoma and hypogonadotropic hypogonadism who received cabergoline to normalize serum prolactin,[147] 20% did not recover from hypogonadotropic hypogonadism, and 100% of these reported no improvement in sexual dysfunction, whereas men that recovered from hypogonadism reported improved sexual symptoms in more than 90% of cases. Comparable results were reported in a smaller previous study with a similar design.[148] Overall, these data may suggest that excessive prolactin levels are involved in the pathogenesis of ED, although it seems that the effect is mediated by low T rather than direct. Accordingly, the improvement in EF occurring after medical or surgical treatment of hyperprolactinemia is rather limited, ranging from 3 to 13% according to a recent meta-analysis.[68]

An opposite effect of prolactin on erectile function is also documented. In a population of 2531 men consulting for ED, prolactin levels below 5 ng/mL were associated with impaired penile blood flows, thus suggesting an arteriogenic component for ED.[149] In line with this finding, lower prolactin levels have been associated with the retrospective perception of deterioration in EF and morning erections in more than 3000 European men from the general population.[66] In both studies, lower prolactin levels were also associated with metabolic syndrome, particularly with increased glycaemia, triglycerides, and waist circumference.[66,149] A recent meta-analysis confirms the adverse metabolic correlates of lower prolactin levels, showing higher fasting glucose, triglycerides, total and low-density lipoprotein (LDL) cholesterol, and lower high-density lipoprotein (HDL) cholesterol but not different BMI.[150] These metabolic alterations may justify an arterial impairment resulting in ED. Consistently, in men from the general population, lower prolactin has been associated with a higher probability of having T2DM[151] and the risk of developing left ventricular hypertrophy.[152] The latter association was confirmed also in the diabetic population.[153]

The mechanisms underlying the link between hypoprolactinemia, ED, and metabolic alterations are a matter of speculation. Prolactin may represent a circulating marker of neurotransmission within the brain. In particular, it could result from increased dopaminergic and/or decreased serotonergic signaling. The latter is supported by the evidence of a blunted prolactin peak after an intravenous citalopram challenge in men with metabolic syndrome or increased intima-media thickness.[154,155]

Other hormones involved in the pathophysiology of male sexual desire and arousal/erection

Thyroid hormones

Thyroid hormones, primarily thyroxine (T4) and triiodothyronine (T3), regulate metabolism and play a crucial role in various physiological processes, including growth, metabolism, and energy balance.

Thyroid hormone receptors have been found in rat and human CC, endothelial, and SMC.[156] In rabbits, hyperthyroidism reduced neurogenic and endothelium-dependent relaxation of SMC in the CC, indicating an impairment of NO-dependent relaxation of the CC.[157] Hypothyroidism induced by propyl thiouracil (PTU) in rats resulted in a significant decline of T and thyroid hormones, as well as low erectile response. Erectile responses could partially be restored by treatment with either levothyroxine or T, while erectile responses completely returned with combined hormonal treatment. PTU-induced hypothyroidism also affected endothelial and nitrergic relaxation and contraction of the corporal SMC.[158]

An association between thyroid dysfunction, low sexual desire, and ED became apparent from small studies in men with hypo- and hyperthyroidism that showed that both hypo- and hyperthyroidism were frequently associated with low sexual desire and ED.[159–162] Carani et al.[160] evaluated sexual function in 48 adult men (34 with hyperthyroidism and 14 with hypothyroidism). More men with hypothyroidism were reported to have hypoactive sexual desire when compared to men with hyperthyroidism (64% versus 18%). Normalizing thyroid hormone levels improved libido and EF in both groups.[160] In another study, men with overt hypothyroidism (n = 12) had lower scores on all domains of IIEF-15 compared to euthyroid controls (n = 12), including sexual desire and EF, which improved after treatment with levothyroxine. Men with subclinical hypothyroidism (n = 12) only reported lower

scores for EF, which improved with treatment.[163] A study from Taiwan described a higher risk of having a previous diagnosis of hyperthyroidism in men who were recently diagnosed with ED.[164] A recent study of 40 men with subclinical hypothyroidism and ED also showed an improvement in EF with levothyroxine treatment.[165]

However, studies that screened thyroid function in men presenting with ED showed that thyroid dysfunction is not common. Corona et al.[166] investigated the association between thyroid function and sexual function in two large cohorts: 3369 community-dwelling men from the EMAS and 3203 men seeking medical care for sexual dysfunction. They observed an inverse relationship between thyroid-stimulating hormone (TSH) levels and ED. In patients consulting for sexual dysfunction, men with moderate or severe hypoactive sexual desire had higher TSH levels, but this association was no longer significant after adjusting for confounders.[166] No association between primary hypothyroidism and sexual desire or ED was observed in the EMAS cohort. The prevalence of overt hyperthyroidism in patients presenting with sexual dysfunction was low (0.2%) and 3.4% of men presenting with ED had any form of hyperthyroidism.[166] In addition, Maseroli et al. showed that the prevalence of thyroid disorders in patients seeking medical care for ED is low (<1%) and not different from the general population of the same geographic area.[167] A Mendelian randomization study from the UK Biobank found no evidence of a causal relationship between thyroid function and sexual function, although genetically predicted thyroid function showed associations with sex hormones.[168] These results suggest that individuals with thyroid dysfunction are at risk of having ED, but routine thyroid function assessment is not recommended for all patients with ED.

Growth hormone – IGF1

Growth hormone (GH) is synthesized and secreted by somatotrophic cells in the anterior pituitary, under the positive control of GH-releasing hormone and negative regulation by somatostatin. GH stimulates the liver to produce Insulin-like Growth Factor 1 (IGF-1), which mediates many of the growth-promoting and metabolic effects of GH. Experimental studies showed that recombinant GH can induce a dose-dependent relaxation of human CC strips in vitro, along with an increase in cGMP,[169,170] but the GH concentration needed to elicit a 30% relaxation was at least 3 orders of magnitude higher than GH concentration increases recorded in cavernosal blood sampling in healthy men during the tumescence phase.[171] Indeed, levels of GH in systemic and cavernosal blood samples show a significant increase during penile tumescence in healthy men. This increase could not be observed in men with organic ED.[171] In a study of 65 men scheduled for radical prostatectomy, IGF-1 levels correlated with sexual function scores.[172] However, a controlled trial showed that one month of GH injections had no effect on sexual function in a small cohort of 10 healthy older men.[173]

Lotti et al.[174] published the first study which systematically analyzed EF in 57 subjects with acromegaly. Although 42.1% of patients were identified to have organic ED, it was not related to acromegaly-related parameters, including IGF-1 levels, type of treatment, duration of the disease, or secondary hypogonadism. Acromegaly patients suffering from ED had more comorbidities, including CV risk factors, such as hypertension, and worse impairment of penile vascular flow, compared to subjects with acromegaly and without ED.[174] The largest series of patients with acromegaly in which sexual dysfunction was assessed by IIEF-15 included 94 men. 59.6% of men reported ED, described as mild in 22.3%, moderate in 12.8% and severe in 24.5%. The mean score for the sexual desire domain was 6.5, with significantly lower scores in patients older than 64 years. Disease duration did not influence IIEF-15 scores for desire.[175] A recent study evaluated sexual function by IIEF-15 in 20 men with acromegaly. 14 men (70%) had impaired sexual desire, and 13 men (65%) reported ED, of which only 4 also had hypogonadism.[176] Furthermore, a study of 63 men with untreated acromegaly showed that 35% had ED. Patients with ED had higher random GH levels and lower NO levels. Normalization of GH with medical (n = 4) or surgical treatment (n = 23) resulted in improved EF.[177] There are no detailed studies in humans investigating the impact of medical treatment for acromegaly on sexual function. In rats, however, injection of the somatostatin analogue octreotide, which inhibits GH secretion, had a negative effect on penile erection.[178] It remains unclear if ED in acromegaly is directly related to high GH or IGF-1 levels or an indirect result of concomitant hypogonadism or CV morbidities related to the disease.

In men with growth hormone deficiency, IGF-1 levels correlated with IIEF-15 domain scores, in particular EF and sexual desire. Scores on all IIEF-15 domains were lower in untreated men compared to men who were treated with recombinant GH. 75% of untreated men reported to have ED, versus 35% of men who received treatment.[179]

Oxytocin

OT is a neuropeptide synthesized in the supraoptic and paraventricular (PVN) nuclei of the hypothalamus and released by the posterior pituitary gland. Data from animal models indicate that the oxytocinergic neural pathway plays a key role in the central control of penile erection, at the level of the PVN and of the spinal cord.[180] Central administration of OT induces penile erection in male rats by activating its own neurons, with the PVN as the most sensitive site for OT-induced penile erection.[181,182] It also facilitates copulatory behavior and shortens ejaculation latency. Selective OT receptor antagonists strongly impair copulatory behavior in animals when administered intracerebroventricularly.[181] However, systemically administered OT does not induce penile erection, as it cannot cross the blood–brain barrier.[180]

Blocking central oxytocinergic receptors eliminated non-contact erections.[180] However, no impairment of sexual function was observed in OT gene knock-out mice, indicating that OT is not essential for male sexual function.[183] Recent research confirmed that disrupting the OT gene did not affect erectile function in mice, neither when the knockout was induced at the embryonic stage nor when it was induced in adult male mice.[182] Interestingly, injection of an OT receptor agonist still induced penile erection in these OT knock-out mice, suggesting interactions with other cognate receptors, such as the V1 AVP receptors. Specific activation of oxytocinergic neurons by apomorphine-induced penile erection indicates that OT in itself is not an essential factor for EF, but that activation of oxytocinergic neurons plays an important role.[182]

OT levels increase during sexual arousal in both men and women.[184] In a study of 25 healthy men who were exposed to visual and tactile erotic stimuli, OT increased both in the systemic circulation as well as in cavernous blood with the initiation of sexual arousal, when the penis became tumescent. OT further increased in the cavernous blood from tumescence to rigidity but remained stable in the systemic circulation at that point. Upon detumescence, OT levels in the cavernous blood decreased but further increased in the systemic circulation in the post-orgasmic period.[185]

Animal data suggest that the oxytocinergic neural pathway is a potential target for treating sexual dysfunction. In a small placebo-controlled study with intranasal OT, which has the potential to cross the blood–brain barrier, a lack of treatment effect was found on several sexual parameters, including arousal.[186] In an uncontrolled study in 29 healthy heterosexual couples, the acute effects of intranasal OT on sexual drive, arousal, orgasm, and refractory aspects of sexual behavior were analyzed, together with partner interactions. OT did not induce changes in sexual arousal or penile erection, although men reported higher levels of sexual satiety after intercourse.[187] Other routes of administration or OT receptor agonists that can cross the blood–brain barrier might become potential central therapeutic targets for erectile dysfunction in the future.

Melanocortins

Melanocortins (MC) are a family of peptide hormones, including adrenocorticotrophic hormone (ACTH) and α-, β-, γ-melanocyte-stimulating hormones (MSH), derived from the cleavage of a large precursor peptide: pro-opiomelanocortin (POMC).

A global melanocortin 4 (MC4) receptor knock-out mice model induced impaired copulatory behavior and decreased motivation to engage in sexual activity in males.[188] However, when MC4 receptors were expressed specifically on SIM1-positive neurons, which are part of the leptin-melanocortin system and of which OT neurons are a subset, this reversed the changes in sexual function seen in the global knock-out model.[189] A genome-wide association study using two different cohorts found that a locus (rs17185536-T) on chromosome 6 near the SIM1 gene was associated with the risk of ED. The observed association appeared to be independent of risk factors for ED, such as BMI.[190] Another genome-wide association study identified a locus associated with ED, and further investigations suggested a functional relationship between this variant (rs57989773) and SIM1.[191] The findings from these studies support the role for SIM1 in the pathogenesis of ED.[192]

Male mice with POMC-neurons that lack both leptin and insulin receptors are obese and show reduced α-MSH production, reduced expression of MC4 receptors, and lower sexual motivation, with reduced mounting behavior. These changes were, however, not observed when only a single receptor was knocked out.[193] ACTH and α-MSH were identified as pro-erectile mediators that induced penile erection, and ejaculation in laboratory animals.[180] In experimental animal models, the interaction of α- and β-MSH with MC receptors (MCR3 and MCR4) within the hypothalamus and the limbic system led to a typical behavioral syndrome with grooming, stretching and yawning, spontaneous penile erection and ejaculation and increased sexual receptivity.[194]

The administration of ACTH 1-17 induced an increase in sexual performance when administered to men with psychogenic ED, which was not mediated by sex steroids or adrenal steroids.[195]

Several synthetic analogues of α-MSH were designed and tested in phase 1 and phase 2 trials as a treatment for ED. In double-blind placebo-controlled trials, subcutaneous injections with the potent agonist Melanotan II induced repeated penile erections in healthy men and men with psychogenic and organic ED.[196,197] When Melanotan II was administered to 20 men with psychogenic and organic ED, sexual desire was higher in men treated with Melanotan II injections compared to men treated with a placebo. Of the 10 men who reported a moderate or high level of sexual desire, nine developed a penile erection.[196] However, it has a long latency time, and drug-related adverse effects are common, such as severe nausea, yawning, and flushing.[198] Two recent case reports also described acute priapism in men using Melanotan II for sunless tanning.[199,200] Subcutaneous or intranasal administration of bremelanotide (melanocortin receptor acute agonist PT-141) improved EF in both healthy volunteers and in men with ED not responsive to sildenafil.[201,202] A randomized controlled trial in 342 men with ED who did not respond to sildenafil showed improvement in erectile function in 33.5% of patients in the bremelanotide group.[203] However, an expression of concern was published recently, questioning the reliability of these findings.[204] The reported time to onset was approximately 30 minutes, and side effects were flushing, nausea, hyperpigmentation, and a transient increase in blood pressure. Subcutaneous bremelatonide is currently FDA-approved for the treatment of hypoactive sexual desire disorder in premenopausal women.[205] A long-acting α-MSH analog developed for the treatment of obesity was tested in a small group of healthy overweight and obese men. Increases in frequency as well as duration of penile erection were reported as side effects.[206] Setmelanotide is EMA and FDA-approved for the treatment of specific forms of severe monogenic obesity, such as POMC deficiency. Spontaneous penile erections can occur as a side effect.[207]

Kisspeptin

Kisspeptin is a neuropeptide modulating the neuronal activity and pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH), thereby playing a critical role in regulating the reproductive endocrine axis.

Kisspeptin receptor knockout mice display no sexual behavior.[208] The effect of kisspeptin on sexual motivation was studied in copulation naive male rats. Administration of intranasal GnRH, leading to increased levels of testosterone, did not affect behavioral measures of sexual motivation. On the other hand, intraperitoneal kisspeptin administration increased T concentrations as well as sexual motivation. Intranasal kisspeptin also increased sexual motivation, although this treatment had no effect on T levels. This indicates that kisspeptin has an effect on regulating sexual motivation in male rats that is independent of T.[209]

Infusion of kisspeptin into the medial amygdala of male rats resulted in an increase of LH and induced multiple erections, which were blocked by pretreatment with a kisspeptin receptor antagonist. Infusion of kisspeptin into the lateral cerebroventricle however, did not induce erections, although LH levels increased to similar levels. This indicates a role for kisspeptin in EF, which is specific to the medial amygdala.[210]

In an observational study of bulls that were monitored during semen collection, kisspeptin levels were lower in bulls with incomplete penile erection.[211]

In healthy heterosexual male volunteers, the administration of kisspeptin enhanced limbic brain activity when these men were exposed to visual sexual stimuli, also in limbic structures known to be involved in arousal.[212] A double-blind, placebo-controlled RCT in 32 heterosexual men with MHSDD tested the effects of an intravenous kisspeptin-54 infusion.[213] Compared to placebo, kisspeptin significantly modulated brain activity in structures of the sexual-processing network on whole brain analysis when men were exposed to visual sexual stimuli. Behavioral measures of sexual desire and arousal also increased. Penile tumescence increased in response to sexual stimuli (up to 56% more compared to placebo).[214] Although more data are needed, kisspeptin treatment could potentially be a pharmacological target to treat men with low sexual desire; however, it should be considered that continuous stimulation of the GPR54 receptor is able to cause severe hypogonadotropic hypogonadism.[215] Therefore, a possible chronic treatment may not be possible, or a suitable timing of administration should be considered.

Conclusions

Several hormones are involved in modulating or regulating sexual behavior in men. Therefore, it is not surprising that endocrine abnormalities are common in patients with sexual dysfunction. Epidemiological and interventional trials confirm the pivotal role of T in inducing and maintaining sexual desire and erection. Also, the role of increased prolactin levels in reducing male sexual desire is convincing. For other hormones, data are weaker, scanty, or conflictual. For hypothalamic neurohormones, such as OT, αMSH, and kisspeptin, there is room for further research due to preliminary data on their possible therapeutic use. However, the current pilot studies lead to inconsistent data on their efficacy or disappointing side effects. Therefore, so far, evidence-based recommendations may be provided for the assessment of some but not all the hormones that are here discussed as possible modulators of male sexual function.

Author contributions

GR: Validation, Formal analysis, Investigation, Data Curation, Writing—Original Draft, Writing—Review & Editing, Visualization; LA: Formal analysis, Investigation, Data Curation, Writing—Original Draft; SC: Methodology, Validation; AI: Methodology, Formal analysis, Investigation, Data Curation, Writing—Original Draft; MM: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing—Original Draft, Supervision.

Funding

None.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Corona G, Rastrelli G, Ricca V, et al. Risk factors associated with primary and secondary reduced libido in male patients with sexual dysfunction. *J Sex Med*. 2013;**10**(4):1074–1089. https://doi.org/10.1111/jsm.12043
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th Ed., Text Rev.)* 10.1176/appi.books.9780890425787. Editor American Psychiatric Association Publishing; 2022.
3. McCabe MP, Sharlip ID, Atalla E, et al. Definitions of sexual dysfunctions in women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. *J Sex Med*. 2016;**13**(2):135–143. https://doi.org/10.1016/j.jsxm.2015.12.019
4. Corona G, Lee DM, Forti G, et al. Age-related changes in general and sexual health in middle-aged and older men: results from the European male ageing study (EMAS). *J Sex Med*. 2010;**7**(4_Part_1):1362–1380. https://doi.org/10.1111/j.1743-6109.2009.01601.x
5. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA*. 1999;**281**(6):537–544. https://doi.org/10.1001/jama.281.6.537
6. Holden CA, McLachlan RI, Pitts M, et al. Men in Australia telephone survey (MATeS): a national survey of the reproductive health and concerns of middle-aged and older Australian men. *Lancet*. 2005;**366**(9481):218–224. https://doi.org/10.1016/S0140-6736(05)66911-5
7. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *N Engl J Med*. 2007;**357**(8):762–774. https://doi.org/10.1056/NEJMoa067423
8. Mitchell KR, Mercer CH, Ploubidis GB, et al. Sexual function in Britain: findings from the third National Survey of sexual attitudes and lifestyles (Natsal-3). *Lancet*. 2013;**382**(9907):1817–1829. https://doi.org/10.1016/S0140-6736(13)62366-1
9. Ågmo A, Turi AL, Ellingsen E, Kaspersen H. Preclinical models of sexual desire: conceptual and behavioral analyses. *Pharmacol Biochem Behav*. 2004;**78**(3):379–404. https://doi.org/10.1016/j.pbb.2004.04.013
10. Calabrò RS, Cacciola A, Bruschetta D, et al. Neuroanatomy and function of human sexual behavior: a neglected or unknown issue? *Brain Behav*. 2019;**9**(12):e01389. https://doi.org/10.1002/brb3.1389
11. Walum H, Young LJ. The neural mechanisms and circuitry of the pair bond. *Nat Rev Neurosci*. 2018;**19**(11):643–654. https://doi.org/10.1038/s41583-018-0072-6
12. Bayless DW, Davis C, Ha O, et al. A neural circuit for male sexual behavior and reward. *Cell*. 2023;**186**(18):3862–3881.e28. https://doi.org/10.1016/j.cell.2023.07.021
13. Cacioppo S, Bianchi-Demicheli F, Frum C, Pfaus JG, Lewis JW. The common neural bases between sexual desire and love: a multilevel kernel density fMRI analysis. *J Sex Med*. 2012;**9**(4):1048–1054. https://doi.org/10.1111/j.1743-6109.2012.02651.x
14. Corona G, Isidori AM, Aversa A, Burnett AL, Maggi M. Endocrinologic control of Men's sexual desire and arousal/erection. *J Sex Med*. 2016;**13**(3):317–337. https://doi.org/10.1016/j.jsxm.2016.01.007
15. Rychert A, Dziurda DR, Koperny M, et al. Systems for grading the strength of recommendations in clinical practice guidelines in oncology. *Nowotwory Journal of Oncology*. 2021;**71**(6):407–416. https://doi.org/10.5603/NJO.2021.0074
16. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;**64**(4):383–394. https://doi.org/10.1016/j.jclinepi.2010.04.026
17. Wu FCW, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med*. 2010;**363**(2):123–135. https://doi.org/10.1056/NEJMoa0911101
18. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *J Clin Endocrinol Metab*. 2006;**91**(11):4335–4343. https://doi.org/10.1210/jc.2006-0401

19. Rastrelli G, Corona G, Tarocchi M, Mannucci E, Maggi M. How to define hypogonadism? Results from a population of men consulting for sexual dysfunction. *J Endocrinol Investig*. 2016;**39**(4):473–484. https://doi.org/10.1007/s40618-015-0425-1
20. Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. Association of sex hormones with sexual function, vitality, and physical function of symptomatic older men with low testosterone levels at baseline in the testosterone trials. *J Clin Endocrinol Metab*. 2015;**100**(3):1146–1155. https://doi.org/10.1210/jc.2014-3818
21. Hsu B, Cumming RG, Blyth FM, et al. The longitudinal relationship of sexual function and androgen status in older men: the concord health and ageing in men project. *J Clin Endocrinol Metab*. 2015;**100**(4):1350–1358. https://doi.org/10.1210/jc.2014-4104
22. Gades NM, Jacobson DJ, McGree ME, et al. The associations between serum sex hormones, erectile function, and sex drive: the Olmsted County study of urinary symptoms and health status among men. *J Sex Med*. 2008;**5**(9):2209–2220. https://doi.org/10.1111/j.1743-6109.2008.00924.x
23. Travison TG, Morley JE, Araujo AB, O'Donnell AB, McKinlay JB. The relationship between libido and testosterone levels in aging men. *J Clin Endocrinol Metab*. 2006;**91**(7):2509–2513. https://doi.org/10.1210/jc.2005-2508
24. Corona G, Maggi M. The role of testosterone in male sexual function. *Rev Endocr Metab Disord*. 2022;**23**(6):1159–1172. https://doi.org/10.1007/s11154-022-09748-3
25. Lincoff AM, Bhasin S, Flevaris P, et al. Cardiovascular safety of testosterone-replacement therapy. *N Engl J Med*. 2023;**389**(2):107–117. https://doi.org/10.1056/NEJMoa2215025
26. Pencina KM, Travison TG, Cunningham GR, et al. Effect of testosterone replacement therapy on sexual function and Hypogonadal symptoms in men with hypogonadism. *J Clin Endocrinol Metab*. 2024;**109**(2):569–580. https://doi.org/10.1210/clinem/dgad484
27. Finkelstein JS, Lee H, Burnett-Bowie SAM, et al. Dose-response relationships between gonadal steroids and bone, body composition, and sexual function in aging men. *J Clin Endocrinol Metab*. 2020;**105**(8):2779–2788. https://doi.org/10.1210/clinem/dgaa318
28. Barbonetti A, D'Andrea S, Vena W, et al. Erectile dysfunction and decreased libido in Klinefelter syndrome: a prevalence meta-analysis and meta-regression study. *J Sex Med*. 2021;**18**(6):1053–1064. https://doi.org/10.1016/j.jsxm.2021.03.078
29. Corona G, Filippi S, Comelio P, et al. Sexual function in men undergoing androgen deprivation therapy. *Int J Impot Res*. 2021;**33**(4):439–447. https://doi.org/10.1038/s41443-021-00418-7
30. Raskin K, De Gendt K, Duittoz A, et al. Conditional inactivation of androgen receptor gene in the nervous system: effects on male behavioral and neuroendocrine responses. *J Neurosci*. 2009;**29**(14):4461–4470. https://doi.org/10.1523/JNEUROSCI.0296-09.2009
31. Mhaouty-Kodja S. Role of the androgen receptor in the central nervous system. *Mol Cell Endocrinol*. 2018;**465**:103–112. https://doi.org/10.1016/j.mce.2017.08.001
32. Hamann S, Stevens J, Vick JH, et al. Brain responses to sexual images in 46,XY women with complete androgen insensitivity syndrome are female-typical. *Horm Behav*. 2014;**66**(5):724–730. https://doi.org/10.1016/j.yhbeh.2014.09.013
33. Birnbaum W, Marshall L, Werner R, et al. Oestrogen versus androgen in hormone-replacement therapy for complete androgen insensitivity syndrome: a multicentre, randomised, double-dummy, double-blind crossover trial. *Lancet Diabetes Endocrinol*. 2018;**6**(10):771–780. https://doi.org/10.1016/S2213-8587(18)30197-9
34. Corona G, Rastrelli G, Vignozzi L, Maggi M. Androgens and male sexual function. *Best Pract Res Clin Endocrinol Metab*. 2022;**36**(4):101615. https://doi.org/10.1016/j.beem.2022.101615
35. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol*. 2005;**63**(4):381–394. https://doi.org/10.1111/j.1365-2265.2005.02350.x
36. Boloña ER, Uraga MV, Haddad RM, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc*. 2007;**82**(1):20–28. https://doi.org/10.1016/S0025-6196(11)60963-4
37. Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: a meta-analysis study. *J Sex Med*. 2014;**11**(6):1577–1592. https://doi.org/10.1111/jsm.12536
38. Algeffari M, Jayasena CN, MacKeith P, Thapar A, Dhillo WS, Oliver N. Testosterone therapy for sexual dysfunction in men with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabet Med*. 2018;**35**(2):195–202. https://doi.org/10.1111/dme.13553
39. Corona G, Rastrelli G, Morgentaler A, Sforza A, Mannucci E, Maggi M. Meta-analysis of results of testosterone therapy on sexual function based on international index of erectile function scores. *Eur Urol*. 2017;**72**(6):1000–1011. https://doi.org/10.1016/j.eururo.2017.03.032
40. Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, et al. The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: a systematic review and meta-analysis of randomized, placebo-controlled trials. *J Clin Endocrinol Metab*. 2018;**103**(5):1745–1754. https://doi.org/10.1210/jc.2018-00404
41. Elliott J, Kelly SE, Millar AC, et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis. *BMJ Open*. 2017;**7**(11):e015284. https://doi.org/10.1136/bmjopen-2016-015284
42. Stanić D, Dubois S, Chua HK, et al. Characterization of aromatase expression in the adult male and female mouse brain. I. Coexistence with oestrogen receptors α and β, and androgen receptors. *PLoS One*. 2014;**9**(3):e90451. https://doi.org/10.1371/journal.pone.0090451
43. Österlund MK, Gustafsson JÅ, Keller E, Hurd YL. Estrogen receptor beta (ERbeta) messenger ribonucleic acid (mRNA) expression within the human forebrain: distinct distribution pattern to ERalpha mRNA. *J Clin Endocrinol Metab*. 2000;**85**(10):3840–3846
44. Finkelstein JS, Lee H, Burnett-Bowie SAM, et al. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med*. 2013;**369**(11):1011–1022. https://doi.org/10.1056/NEJMoa1206168
45. Del Giudice F, Busetto G, De Berardinis E, et al. A systematic review and meta-analysis of clinical trials implementing aromatase inhibitors to treat male infertility. *Asian J Androl*. 2020;**22**(4):360–367. https://doi.org/10.4103/aja.aja_101_19
46. Guo B, Jiao LJ, Ling MY, Tao ZY, Guo LJ. Efficacy and safety of letrozole or anastrozole in the treatment of male infertility with low testosterone-estradiol ratio: a meta-analysis and systematic review. *Andrology*. 2022;**10**(5):894–909. https://doi.org/10.1111/andr.13185
47. Shuling L, Sie Kuei ML, Saffari SE, et al. Do men with normal testosterone-oestradiol ratios benefit from letrozole for the treatment of male infertility? *Reprod Biomed Online*. 2019;**38**(1):39–45. https://doi.org/10.1016/j.rbmo.2018.09.016
48. Rochira V, Granata ARM, Madeo B, Zirilli L, Rossi G, Carani C. Estrogens in males: what have we learned in the last 10 years? *Asian J Androl*. 2005;**7**(1):3–20. https://doi.org/10.1111/j.1745-7262.2005.00018.x
49. Wibowo E, Schellhammer P, Wassersug RJ. Role of estrogen in normal male function: clinical implications for patients with prostate cancer on androgen deprivation therapy. *J Urol*. 2011;**185**(1):17–23. https://doi.org/10.1016/j.juro.2010.08.094
50. Gilbert DC, Duong T, Kynaston HG, et al. Quality-of-life outcomes from the prostate adenocarcinoma: TransCutaneous hormones (PATCH) trial evaluating luteinising hormone-releasing hormone agonists versus transdermal oestradiol for androgen suppression in advanced prostate cancer. *BJU Int*. 2017;**119**(5):667–675. https://doi.org/10.1111/bju.13687

51. Jones TH, Dobs A, Randeva H, Moore W, Parkin JM. Leflutrozole in male obesity-associated hypogonadotropic hypogonadism: Ph 2b double-blind randomised controlled trial. *Eur J Endocrinol*. 2023;**189**(3):297–308. https://doi.org/10.1093/ejendo/lvad099
52. Sartorius GA, Ly LP, Handelsman DJ. Male sexual function can be maintained without aromatization: randomized placebo-controlled trial of dihydrotestosterone (DHT) in healthy, older men for 24 months. *J Sex Med*. 2014;**11**(10):2562–2570. https://doi.org/10.1111/jsm.12550
53. Corona G, Rastrelli G, Sparano C, Vignozzi L, Sforza A, Maggi M. Pharmacological management of testosterone deficiency in men current advances and future directions. *Expert Rev Clin Pharmacol*. 2024;**17**(8):665–681. https://doi.org/10.1080/17512433.2024.2366505
54. Stephens-Shields AJ, Snyder PJ, Ellenberg SS, Taylor L, Bhasin S. Relation of testosterone, dihydrotestosterone, and Estradiol with changes in outcomes measures in the testosterone trials. *J Clin Endocrinol Metab*. 2022;**107**(5):1257–1269. https://doi.org/10.1210/clinem/dgac028
55. Corona G, Tirabassi G, Santi D, et al. Sexual dysfunction in subjects treated with inhibitors of 5α-reductase for benign prostatic hyperplasia: a comprehensive review and meta-analysis. *Andrology*. 2017;**5**(4):671–678. https://doi.org/10.1111/andr.12353
56. Maggi M, Buvat J, Corona G, Guay A, Torres LO. Hormonal causes of male sexual dysfunctions and their management (hyperprolactinemia, thyroid disorders, GH disorders, and DHEA). *J Sex Med*. 2013;**10**(3):661–677. https://doi.org/10.1111/j.1743-6109.2012.02735.x
57. Granata A, Tirabassi G, Pugni V, et al. Sexual dysfunctions in men affected by autoimmune Addison's disease before and after short-term gluco- and mineralocorticoid replacement therapy. *J Sex Med*. 2013;**10**(8):2036–2043. https://doi.org/10.1111/j.1743-6109.2012.02673.x
58. Corona G, Rastrelli G, Giagulli VA, et al. Dehydroepiandrosterone supplementation in elderly men: a meta-analysis study of placebo-controlled trials. *J Clin Endocrinol Metab*. 2013;**98**(9):3615–3626. https://doi.org/10.1210/jc.2013-1358
59. Bloch M, Meiboom H, Zaig I, Schreiber S, Abramov L. The use of dehydroepiandrosterone in the treatment of hypoactive sexual desire disorder: a report of gender differences. *Eur Neuropsychopharmacol*. 2013;**23**(8):910–918. https://doi.org/10.1016/j.euroneuro.2012.09.004
60. Amodru V, Ferriere A, Tabarin A, et al. Cushing's syndrome in the elderly: data from the European registry on Cushing's syndrome. *Eur J Endocrinol*. 2023;**188**(4):395–406. https://doi.org/10.1093/ejendo/lvad008
61. Bancroft J. The endocrinology of sexual arousal. *J Endocrinol*. 2005;**186**(3):411–427. https://doi.org/10.1677/joe.1.06233
62. Lyons DJ, Hellysaz A, Broberger C. Prolactin regulates tuberoinfundibular dopamine neuron discharge pattern: novel feedback control mechanisms in the lactotrophic axis. *J Neurosci*. 2012;**32**(23):8074–8083. https://doi.org/10.1523/JNEUROSCI.0129-12.2012
63. Duskin-Bitan H, Shimon I. Prolactinomas in males: any differences? *Pituitary*. 2020;**23**(1):52–57. https://doi.org/10.1007/s11102-019-01009-y
64. Lookingland KJ, Moore KE. Effects of estradiol and prolactin on incertohypothalamic dopaminergic neurons in the male rat. *Brain Res*. 1984;**323**(1):83–91. https://doi.org/10.1016/0006-8993(84)90267-1
65. Shimon I, Benbassat C. Male prolactinomas presenting with normal testosterone levels. *Pituitary*. 2014;**17**(3):246–250. https://doi.org/10.1007/s11102-013-0497-x
66. Corona G, Wu FC, Rastrelli G, et al. Low prolactin is associated with sexual dysfunction and psychological or metabolic disturbances in middle-aged and elderly men: the European male aging study (EMAS). *J Sex Med*. 2014;**11**(1):240–253. https://doi.org/10.1111/jsm.12327
67. Corona G, Mannucci E, Fisher AD, et al. Effect of hyperprolactinemia in male patients consulting for sexual dysfunction. *J Sex Med*. 2007;**4**(5):1485–1493. https://doi.org/10.1111/j.1743-6109.2007.00569.x
68. Corona G, Rastrelli G, Bianchi N, et al. Hyperprolactinemia and male sexual function: focus on erectile dysfunction and sexual desire. *Int J Impot Res*. 2024;**36**(4):324–332. https://doi.org/10.1038/s41443-023-00717-1
69. Petersenn S, Fleseriu M, Casanueva FF, et al. Diagnosis and management of prolactin-secreting pituitary adenomas: a pituitary society international consensus statement. *Nat Rev Endocrinol*. 2023;**19**(12):722–740. https://doi.org/10.1038/s41574-023-00886-5
70. Khare S, Lila AR, Patt H, et al. Gender differences in macroprolactinomas: a single Centre experience. *Endocr Connect*. 2016;**5**(1):20–27. https://doi.org/10.1530/EC-15-0105
71. Hashimoto D, Fujimoto K, Nakata M, et al. Developmental and functional roles of androgen and interactive signals for external genitalia and erectile tissues. *Reprod Med Biol*. 2024;**23**(1):e12611. https://doi.org/10.1002/rmb2.12611
72. Baskin LS, Sutherland RS, DiSandro MJ, Hayward SW, Lipschutz J, Cunha GR. The effect of testosterone on androgen receptors and human penile growth. *J Urol*. 1997;**158**(3):1113–1118. https://doi.org/10.1016/S0022-5347(01)64400-8
73. Tenuta M, Carlomagno F, Cangiano B, et al. Somatotropic-testicular Axis: a crosstalk between GH/IGF-I and gonadal hormones during development, transition, and adult age. *Andrology*. 2021;**9**(1):168–184. https://doi.org/10.1111/andr.12918
74. MacLean DB, Matsui H, Suri A, Neuwirth R, Colombel M. Sustained exposure to the investigational Kisspeptin analog, TAK-448, down-regulates testosterone into the castration range in healthy males and in patients with prostate cancer: results from two phase 1 studies. *J Clin Endocrinol Metab*. 2014;**99**(8):E1445–E1453. https://doi.org/10.1210/jc.2013-4236
75. Ciocca G, Limoncin E, Carosa E, et al. Is testosterone a food for the brain? *Sex Med Rev*. 2016;**4**(1):15–25. https://doi.org/10.1016/j.sxmr.2015.10.007
76. Corona G, Maggi M. The role of testosterone in erectile dysfunction. *Nat Rev Urol*. 2010;**7**(1):46–56. https://doi.org/10.1038/nrurol.2009.235
77. Lugg J, Ng C, Rajfer J, González-Cadavid N. Cavernosal nerve stimulation in the rat reverses castration-induced decrease in penile NOS activity. *Am J Phys*. 1996;**271**(2 Pt 1):E354–E361. https://doi.org/10.1152/ajpendo.1996.271.2.E354
78. Traish AM, Park K, Dhir V, Kim NN, Moreland RB, Goldstein I. Effects of castration and androgen replacement on erectile function in a rabbit model. *Endocrinology*. 1999;**140**(4):1861–1868. https://doi.org/10.1210/endo.140.4.6655
79. Reilly CM, Lewis RW, Stopper VS, Mills TM. Androgenic maintenance of the rat erectile response via a non-nitric-oxide-dependent pathway. *J Androl*. 1997;**18**(6):588–594. https://doi.org/10.1002/j.1939-4640.1997.tb02435.x
80. Sopko NA, Hannan JL, Bivalacqua TJ. Understanding and targeting the rho kinase pathway in erectile dysfunction. *Nat Rev Urol*. 2014;**11**(11):622–628. https://doi.org/10.1038/nrurol.2014.278
81. Vignozzi L, Morelli A, Filippi S, et al. Testosterone regulates RhoA/rho-kinase signaling in two distinct animal models of chemical diabetes. *J Sex Med*. 2007;**4**(3):620–632. https://doi.org/10.1111/j.1743-6109.2007.00440.x
82. Liao W, Huang W, Guo Y, Xin M, Fu X. Testosterone promotes vascular endothelial cell migration via upregulation of ROCK-2/moesin cascade. *Mol Biol Rep*. 2013;**40**(12):6729–6735. https://doi.org/10.1007/s11033-013-2788-8
83. Yuan P, Li X, Ju XW, Jiang J, Jiang R. Downregulation of the expression of galanin impairs erectile function in hypoandrogenic rats. *Sex Med*. 2023;**11**(3):qfad029. https://doi.org/10.1093/sexmed/qfad029
84. Zhang XH, Melman A, Disanto ME. Update on corpus cavernosum smooth muscle contractile pathways in erectile function:

a role for testosterone? *J Sex Med*. 2011;**8**(7):1865–1879. https://doi.org/10.1111/j.1743-6109.2011.02218.x
85. Traish AM, Toselli P, Jeong SJ, Kim NN. Adipocyte accumulation in penile corpus cavernosum of the orchiectomized rabbit: a potential mechanism for veno-occlusive dysfunction in androgen deficiency. *J Androl*. 2005;**26**(2):242–248. https://doi.org/10.1002/j.1939-4640.2005.tb01091.x
86. Morelli A, Filippi S, Mancina R, et al. Androgens regulate phosphodiesterase type 5 expression and functional activity in corpora cavernosa. *Endocrinology*. 2004;**145**(5):2253–2263. https://doi.org/10.1210/en.2003-1699
87. Zhang XH, Morelli A, Luconi M, et al. Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum. *Eur Urol*. 2005;**47**(3):409–416. https://doi.org/10.1016/j.eururo.2004.10.021
88. Yang R, Huang YC, Lin G, et al. Lack of direct androgen regulation of PDE5 expression. *Biochem Biophys Res Commun*. 2009;**380**(4):758–762. https://doi.org/10.1016/j.bbrc.2009.01.144
89. Andric SA, Janjic MM, Stojkov NJ, Kostic TS. Testosterone-induced modulation of nitric oxide-cGMP signaling pathway and androgenesis in the rat Leydig cells. *Biol Reprod*. 2010;**83**(3):434–442. https://doi.org/10.1095/biolreprod.110.083626
90. Vignozzi L, Filippi S, Comeglio P, et al. Estrogen mediates metabolic syndrome-induced erectile dysfunction: a study in the rabbit. *J Sex Med*. 2014;**11**(12):2890–2902. https://doi.org/10.1111/jsm.12695
91. Gur S, Alzweri L, Yilmaz-Oral D, et al. Testosterone positively regulates functional responses and nitric oxide expression in the isolated human corpus cavernosum. *Andrology*. 2020;**8**(6):1824–1833. https://doi.org/10.1111/andr.12866
92. Xiong W, Kong X, Jiang J, Yang Z, Jiang R. Low androgen status inhibits erectile function by inducing eNOS uncoupling in rat corpus cavernosum. *Andrology*. 2020;**8**(6):1875–1883. https://doi.org/10.1111/andr.12844
93. Zhao YH, Wu ZX, Zhao X, Jiang J, Jiang R. Low androgen level impairs erectile function of rat by regulating the Ng/CaN/AKT/eNOS pathway in penile corpus cavernosum. *Andrology*. 2022;**10**(6):1189–1196. https://doi.org/10.1111/andr.13202
94. Fu OZ, Kun ZL, Liu QW, Jiang J, Jiang R. Effect of low androgen levels on transient receptor potential channels expression in rat penile corpus cavernosum tissue and its relationship with erectile function. *Andrologia*. 2022;**54**(8):e14477. https://doi.org/10.1111/and.14477
95. Reilly CM, Stopper VS, Mills TM. Androgens modulate the alpha-adrenergic responsiveness of vascular smooth muscle in the corpus cavernosum. *J Androl*. 1997;**18**(1):26–31. https://doi.org/10.1002/j.1939-4640.1997.tb01873.x
96. Isidori AM, Buvat J, Corona G, et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review. *Eur Urol*. 2014;**65**(1):99–112. https://doi.org/10.1016/j.eururo.2013.08.048
97. Mitsui Y, Yamabe F, Hori S, et al. Significant inverse association of testosterone level with penile deformity severity in Japanese males with Peyronie's disease. *Int J Urol*. 2023;**30**(1):36–42. https://doi.org/10.1111/iju.15055
98. Köhler TS, Kim J, Feia K, et al. Prevalence of androgen deficiency in men with erectile dysfunction. *Urology*. 2008;**71**(4):693–697. https://doi.org/10.1016/j.urology.2007.11.073
99. Tsertsvadze A, Fink HA, Yazdi F, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. *Ann Intern Med*. 2009;**151**(9):650–661. https://doi.org/10.7326/0003-4819-151-9-200911030-00150
100. Kupelian V, Shabsigh R, Travison TG, Page ST, Araujo AB, McKinlay JB. Is there a relationship between sex hormones and erectile dysfunction? Results from the Massachusetts male aging study. *J Urol*. 2006;**176**(6):2584–2588. https://doi.org/10.1016/j.juro.2006.08.020
101. Rochira V, Carani C. Aromatase deficiency in men: a clinical perspective. *Nat Rev Endocrinol*. 2009;**5**(10):559–568. https://doi.org/10.1038/nrendo.2009.176
102. Ahern T, Swiecicka A, Eendebak RJAH, et al. Natural history, risk factors and clinical features of primary hypogonadism in ageing men: longitudinal data from the European male ageing study. *Clin Endocrinol*. 2016;**85**(6):891–901. https://doi.org/10.1111/cen.13152
103. Rastrelli G, Carter EL, Ahern T, et al. Development of and recovery from secondary hypogonadism in aging men: prospective results from the EMAS. *J Clin Endocrinol Metab*. 2015;**100**(8):3172–3182. https://doi.org/10.1210/jc.2015-1571
104. Isidori AM, Balercia G, Calogero AE, et al. Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian society of endocrinology. *J Endocrinol Investig*. 2015;**38**(1):103–112. https://doi.org/10.1007/s40618-014-0155-9
105. Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. Testosterone treatment and sexual function in older men with low testosterone levels. *J Clin Endocrinol Metab*. 2016;**101**(8):3096–3104. https://doi.org/10.1210/jc.2016-1645
106. Boeri L, Capogrosso P, Ventimiglia E, et al. Does calculated free testosterone overcome Total testosterone in protecting from sexual symptom impairment? Findings of a cross-sectional study. *J Sex Med*. 2017;**14**(12):1549–1557. https://doi.org/10.1016/j.jsxm.2017.10.070
107. Rastrelli G, O'Neill TW, Ahern T, et al. Symptomatic androgen deficiency develops only when both total and free testosterone decline in obese men who may have incident biochemical secondary hypogonadism: prospective results from the EMAS. *Clin Endocrinol*. 2018;**89**(4):459–469. https://doi.org/10.1111/cen.13756
108. Antonio L, Wu FCW, O'Neill TW, et al. Low free testosterone is associated with hypogonadal signs and symptoms in men with normal total testosterone. *J Clin Endocrinol Metab*. 2016;**101**(7):2647–2657. https://doi.org/10.1210/jc.2015-4106
109. Taniguchi H, Shimada S, Kinoshita H. Testosterone therapy for late-onset hypogonadism improves erectile function: a systematic review and meta-analysis. *Urol Int*. 2022;**106**(6):539–552. https://doi.org/10.1159/000520135
110. Yang HJ, Kim KH, Kim DS, et al. The effect of testosterone replacement on sexual function in the elderly: a systematic review and meta-analysis. *World J Mens Health*. 2023;**41**(4):861–873. https://doi.org/10.5534/wjmh.220171
111. Lee H, Hwang EC, Oh CK, et al. Testosterone replacement in men with sexual dysfunction. *Cochrane Database Syst Rev*. 2024;**1**(1):CD013071. https://doi.org/10.1002/14651858.CD013071.pub2
112. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. *N Engl J Med*. 2016;**374**(7):611–624. https://doi.org/10.1056/NEJMoa1506119
113. Saad F, Aversa A, Isidori AM, Zafalon L, Zitzmann M, Gooren L. Onset of effects of testosterone treatment and time span until maximum effects are achieved. *Eur J Endocrinol*. 2011;**165**(5):675–685. https://doi.org/10.1530/EJE-11-0221
114. Skakkebaek NE, Bancroft J, Davidson DW, Warner P. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. *Clin Endocrinol*. 1981;**14**(1):49–61. https://doi.org/10.1111/j.1365-2265.1981.tb00364.x
115. Giltay EJ, Tishova YA, Mskhalaya GJ, Gooren LJG, Saad F, Kalinchenko SY. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. *J Sex Med*. 2010;**7**(7):2572–2582. https://doi.org/10.1111/j.1743-6109.2010.01859.x
116. Rosen RC, Wu F, Behre HM, et al. Quality of life and sexual function benefits of long-term testosterone treatment: longitudinal results from the registry of hypogonadism in men (RHYME).

J Sex Med. 2017;**14**(9):1104–1115. https://doi.org/10.1016/j.jsxm.2017.07.004
117. Hackett G, Cole N, Saghir A, Jones P, Strange RC, Ramachandran S. Testosterone undecanoate improves sexual function in men with type 2 diabetes and severe hypogonadism: results from a 30-week randomized placebo-controlled study. *BJU Int*. 2016;**118**(5):804–813. https://doi.org/10.1111/bju.13516
118. Munk NE, Knudsen JS, Comerma-Steffensen S, Simonsen U. Systematic review of Oral combination therapy for erectile dysfunction when phosphodiesterase type 5 inhibitor monotherapy fails. *Sex Med Rev*. 2019;**7**(3):430–441. https://doi.org/10.1016/j.sxmr.2018.11.007
119. Kim JW, Oh MM, Park MG, et al. Combination therapy of testosterone enanthate and tadalafil on PDE5 inhibitor nonreponders with severe and intermediate testosterone deficiency. *Int J Impot Res*. 2013;**25**(1):29–33. https://doi.org/10.1038/ijir.2012.32
120. Corona G, Maseroli E, Rastrelli G, et al. Characteristics of compensated hypogonadism in patients with sexual dysfunction. *J Sex Med*. 2014;**11**(7):1823–1834. https://doi.org/10.1111/jsm.12549
121. Tajar A, Forti G, O'Neill TW, et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European male ageing study. *J Clin Endocrinol Metab*. 2010;**95**(4):1810–1818. https://doi.org/10.1210/jc.2009-1796
122. Giannetta E, Gianfrilli D, Barbagallo F, Isidori AM, Lenzi A. Subclinical male hypogonadism. *Best Pract Res Clin Endocrinol Metab*. 2012;**26**(4):539–550. https://doi.org/10.1016/j.beem.2011.12.005
123. Isidori AM, Aversa A, Calogero A, et al. Adult- and late-onset male hypogonadism: the clinical practice guidelines of the Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE). *J Endocrinol Investig*. 2022;**45**(12):2385–2403. https://doi.org/10.1007/s40618-022-01859-7
124. Kacker R, Traish AM, Morgentaler A. Estrogens in men: clinical implications for sexual function and the treatment of testosterone deficiency. *J Sex Med*. 2012;**9**(6):1681–1696. https://doi.org/10.1111/j.1743-6109.2012.02726.x
125. O'Connor DB, Lee DM, Corona G, et al. The relationships between sex hormones and sexual function in middle-aged and older European men. *J Clin Endocrinol Metab*. 2011;**96**(10):E1577–E1587. https://doi.org/10.1210/jc.2010-2216
126. Gooren LJG. Human male sexual functions do not require aromatization of testosterone: a study using tamoxifen, testolactone, and dihydrotestosterone. *Arch Sex Behav*. 1985;**14**(6):539–548. https://doi.org/10.1007/BF01541754
127. Chen T, Wu F, Wang X, et al. Different levels of estradiol are correlated with sexual dysfunction in adult men. *Sci Rep*. 2020;**10**(1):12660. https://doi.org/10.1038/s41598-020-69712-6
128. Belladelli F, Boeri L, Fallara G, et al. Hyperestrogenism is associated with sexual function impairment in men-findings from a cross-sectional, real-life study. *Andrology*. 2024;**12**(1):179–185. https://doi.org/10.1111/andr.13470
129. De Rocco PM, Selice R, Di Mambro A, de Toni L, Foresta C, Garolla A. Estradiol-testosterone imbalance is associated with erectile dysfunction in patients with Klinefelter syndrome. *J Clin Med*. 2021;**10**(11):2319. https://doi.org/10.3390/jcm10112319
130. Helo S, Ellen J, Mechlin C, et al. A randomized prospective double-blind comparison trial of clomiphene citrate and Anastrozole in raising testosterone in Hypogonadal infertile men. *J Sex Med*. 2015;**12**(8):1761–1769. https://doi.org/10.1111/jsm.12944
131. Soares AH, Horie NC, Chiang LAP, et al. Effects of clomiphene citrate on male obesity-associated hypogonadism: a randomized, double-blind, placebo-controlled study. *Int J Obes*. 2018;**42**(5):953–963. https://doi.org/10.1038/s41366-018-0105-2
132. Traish AM, Hassani J, Guay AT, Zitzmann M, Hansen ML. Adverse side effects of 5α-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. *J Sex Med*. 2011;**8**(3):872–884. https://doi.org/10.1111/j.1743-6109.2010.02157.x
133. Howell S, Song W, Pastuszak A, Khera M. Differential gene expression in post-finasteride syndrome patients. *J Sex Med*. 2021;**18**(9):1479–1490. https://doi.org/10.1016/j.jsxm.2021.05.009
134. Pinsky MR, Gur S, Tracey AJ, Harbin A, Hellstrom WJG. The effects of chronic 5-alpha-reductase inhibitor (dutasteride) treatment on rat erectile function. *J Sex Med*. 2011;**8**(11):3066–3074. https://doi.org/10.1111/j.1743-6109.2011.02425.x
135. Sansone A, Kliesch S, Dugas M, et al. Serum concentrations of dihydrotestosterone are associated with symptoms of hypogonadism in biochemically eugonadal men. *J Endocrinol Investig*. 2021;**44**(11):2465–2474. https://doi.org/10.1007/s40618-021-01561-0
136. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. *J Clin Endocrinol Metab*. 2002;**87**(4):1467–1472. https://doi.org/10.1210/jcem.87.4.8138
137. Bhasin S, Travison TG, Storer TW, et al. Effect of testosterone supplementation with and without a dual 5α-reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial. *JAMA*. 2012;**307**(9):931–939. https://doi.org/10.1001/jama.2012.227
138. Traish AM, Kang HP, Saad F, Guay AT. Dehydroepiandrosterone (DHEA)–a precursor steroid or an active hormone in human physiology. *J Sex Med*. 2011;**8**(11):2960–2982. https://doi.org/10.1111/j.1743-6109.2011.02523.x
139. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. *J Urol*. 1994;**151**(1):54–61. https://doi.org/10.1016/S0022-5347(17)34871-1
140. Basar MM, Aydin G, Mert HC, et al. Relationship between serum sex steroids and aging male symptoms score and international index of erectile function. *Urology*. 2005;**66**(3):597–601. https://doi.org/10.1016/j.urology.2005.03.060
141. Nair KS, Rizza RA, O'Brien P, et al. DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med*. 2006;**355**(16):1647–1659. https://doi.org/10.1056/NEJMoa054629
142. Morales A, Black A, Emerson L, Barkin J, Kuzmarov I, Day A. Androgens and sexual function: a placebo-controlled, randomized, double-blind study of testosterone vs. dehydroepiandrosterone in men with sexual dysfunction and androgen deficiency. *Aging Male*. 2009;**12**(4):104–112. https://doi.org/10.3109/13685530903294388
143. Yadav A, Mishra RK. Sub-chronic restraint stress suppresses sexual potency and erection efficiency by targeting the hypothalamic-pituitary-testicular Axis and the nitric oxide/cyclic guanosine monophosphate/phosphodiesterase 5α pathway in adult rats. *Neuroendocrinology*. 2023;**113**(4):442–456. https://doi.org/10.1159/000528131
144. Valassi E. Clinical presentation and etiology of Cushing's syndrome: data from ERCUSYN. *J Neuroendocrinol*. 2022;**34**(8):e13114. https://doi.org/10.1111/jne.13114
145. Hasenmajer V, De Alcubierre D, Ferrari D, et al. Exploring sexual function in adrenal insufficiency: findings from the dual RElease hydrocortisone versus conventionAl glucocorticoid replaceMent therapy in hypocortisolism (DREAM) trial. *Andrology*. 2024Mar 28 Online ahead of print;**13**(2):302–313. https://doi.org/10.1111/andr.13635
146. Molinari C, Grossini E, Mary DASG, et al. Prolactin induces regional vasoconstriction through the beta2-adrenergic and nitric oxide mechanisms. *Endocrinology*. 2007;**148**(8):4080–4090. https://doi.org/10.1210/en.2006-1577
147. Chang AS, Grant R, Tomita H, Kim HS, Smithies O, Kakoki M. Prolactin alters blood pressure by modulating the activ-

ity of endothelial nitric oxide synthase. *Proc Natl Acad Sci USA*. 2016;**113**(44):12538–12543. https://doi.org/10.1073/pnas.1615051113
148. Xu ZH, Pan D, Liu TY, et al. Effect of prolactin on penile erection: a cross-sectional study. *Asian J Androl*. 2019;**21**(6):587–591. https://doi.org/10.4103/aja.aja_22_19
149. Rudman Y, Duskin-Bitan H, Masri-Iraqi H, Akirov A, Shimon I. Predicting hypogonadotropic hypogonadism persistence in male macroprolactinoma. *Pituitary*. 2022;**25**(6):882–890. https://doi.org/10.1007/s11102-022-01259-3
150. Sehemby M, Lila AR, Sarathi V, et al. Predictors of chronic LH-testosterone Axis suppression in male Macroprolactinomas with Normoprolactinemia on Cabergoline. *J Clin Endocrinol Metab*. 2020;**105**(12):e4551–e4557. https://doi.org/10.1210/clinem/dgaa650
151. Corona G, Mannucci E, Jannini EA, et al. Hypoprolactinemia: a new clinical syndrome in patients with sexual dysfunction. *Journal of Sexual Medicine*. 2009;**6**(5):1457–1466. https://doi.org/10.1111/j.1743-6109.2008.01206.x
152. Corona G, Rastrelli G, Comeglio P, et al. The metabolic role of prolactin: systematic review, meta-analysis and preclinical considerations. *Expert Rev Endocrinol Metab*. 2022;**17**(6):533–545. https://doi.org/10.1080/17446651.2022.2144829
153. Wang T, Lu J, Xu Y, et al. Circulating prolactin associates with diabetes and impaired glucose regulation: a population-based study. *Diabetes Care*. 2013;**36**(7):1974–1980. https://doi.org/10.2337/dc12-1893
154. Haring R, Völzke H, Vasan RS, et al. Sex-specific associations of serum prolactin concentrations with cardiac remodeling: longitudinal results from the study of health Pomerania (SHIP). *Atherosclerosis*. 2012;**221**(2):570–576. https://doi.org/10.1016/j.atherosclerosis.2012.01.017
155. El-Eshmawy MM, Elkhamisy EM, Elsayed E, Kamal S. Impact of gender on the association between low serum prolactin and left ventricular mass in subjects with prediabetes. *Diabetes Metab J*. 2017;**41**(3):195–204. https://doi.org/10.4093/dmj.2017.41.3.195
156. Muldoon MF, Mackey RH, Korytkowski MT, Flory JD, Pollock BG, Manuck SB. The metabolic syndrome is associated with reduced central serotonergic responsivity in healthy community volunteers. *J Clin Endocrinol Metab*. 2006;**91**(2):718–721. https://doi.org/10.1210/jc.2005-1654
157. Muldoon MF, Mackey RH, Sutton-Tyrrell K, Flory JD, Pollock BG, Manuck SB. Lower central serotonergic responsivity is associated with preclinical carotid artery atherosclerosis. *Stroke*. 2007;**38**(8):2228–2233. https://doi.org/10.1161/STROKEAHA.106.477638
158. Carosa E, Di Sante S, Rossi S, et al. Ontogenetic profile of the expression of thyroid hormone receptors in rat and human corpora cavernosa of the penis. *J Sex Med*. 2010;**7**(4_Part_1):1381–1390. https://doi.org/10.1111/j.1743-6109.2009.01701.x
159. Özdemirci S, Yildiz F, Utkan T, et al. Impaired neurogenic and endothelium-dependent relaxant responses of corpus cavernosum smooth muscle from hyperthyroid rabbits. *Eur J Pharmacol*. 2001;**428**(1):105–111. https://doi.org/10.1016/S0014-2999(01)01268-7
160. Korkmaz FN, Yilmaz-Oral D, Asker H, et al. Combined levothyroxine and testosterone treatment for restoring erectile dysfunction in propylthiouracil-induced hypothyroid rats. *J Sex Med*. 2023;**20**(6):732–741. https://doi.org/10.1093/jsxmed/qdad034
161. Krassas GE, Tziomalos K, Papadopoulou F, Pontikides N, Perros P. Erectile dysfunction in patients with hyper- and hypothyroidism: how common and should we treat? *J Clin Endocrinol Metab*. 2008;**93**(5):1815–1819. https://doi.org/10.1210/jc.2007-2259
162. Carani C, Isidori AM, Granata A, et al. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. *J Clin Endocrinol Metab*. 2005;**90**(12):6472–6479. https://doi.org/10.1210/jc.2005-1135
163. Veronelli A, Masu A, Ranieri R, Rognoni C, Laneri M, Pontiroli AE. Prevalence of erectile dysfunction in thyroid disorders: comparison with control subjects and with obese and diabetic patients. *Int J Impot Res*. 2006;**18**(1):111–114. https://doi.org/10.1038/sj.ijir.3901364
164. Nikoobakht MR, Aloosh M, Nikoobakht N, Mehrsay AR, Biniaz F, Karjalian MA. The role of hypothyroidism in male infertility and erectile dysfunction. *Urol J*. 2012;**9**(1):405–409
165. Krysiak R, Szkróbka W, Okopień B. The effect of l-thyroxine treatment on sexual function and depressive symptoms in men with autoimmune hypothyroidism. *Pharmacol Rep*. 2017;**69**(3):432–437. https://doi.org/10.1016/j.pharep.2017.01.005
166. Keller J, Chen YK, Lin HC. Hyperthyroidism and erectile dysfunction: a population-based case-control study. *Int J Impot Res*. 2012;**24**(6):242–246. https://doi.org/10.1038/ijir.2012.24
167. Cannarella R, Calogero AE, Aversa A, Condorelli RA, La Vignera S. Is there a role for Levo-thyroxine for the treatment of arterial erectile dysfunction? The clinical relevance of the mean platelet volume. *J Clin Med*. 2020;**9**(3):742. https://doi.org/10.3390/jcm9030742
168. Corona G, Wu FCW, Forti G, et al. Thyroid hormones and male sexual function. *Int J Androl*. 2012;**35**(5):668–679. https://doi.org/10.1111/j.1365-2605.2012.01266.x
169. Maseroli E, Corona G, Rastrelli G, et al. Prevalence of endocrine and metabolic disorders in subjects with erectile dysfunction: a comparative study. *J Sex Med*. 2015;**12**(4):956–965. https://doi.org/10.1111/jsm.12832
170. Kjaergaard AD, Marouli E, Papadopoulou A, et al. Thyroid function, sex hormones and sexual function: a Mendelian randomization study. *Eur J Epidemiol*. 2021;**36**(3):335–344. https://doi.org/10.1007/s10654-021-00721-z
171. Becker AJ, Uckert S, Stief CG, et al. Possible role of human growth hormone in penile erection. *J Urol*. 2000;**164**(6):2138–2142. https://doi.org/10.1016/S0022-5347(05)66985-6
172. Ückert S, Scheller F, Stief CG, et al. Potential mechanism of action of human growth hormone on isolated human penile erectile tissue. *Urology*. 2010;**75**(4):968–973. https://doi.org/10.1016/j.urology.2009.05.046
173. Becker AJ, Ückert S, Stief CG, et al. Serum levels of human growth hormone during different penile conditions in the cavernous and systemic blood of healthy men and patients with erectile dysfunction. *Urology*. 2002;**59**(4):609–614. https://doi.org/10.1016/S0090-4295(01)01594-1
174. Pastuszak AW, Liu JS, Vij A, et al. IGF-1 levels are significantly correlated with patient-reported measures of sexual function. *Int J Impot Res*. 2011;**23**(5):220–226. https://doi.org/10.1038/ijir.2011.31
175. Brill KT, Weltman AL, Gentili A, et al. Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. *J Clin Endocrinol Metab*. 2002;**87**(12):5649–5657. https://doi.org/10.1210/jc.2002-020098
176. Lotti F, Rochira V, Pivonello R, et al. Erectile dysfunction is common among men with acromegaly and is associated with morbidities related to the disease. *J Sex Med*. 2015;**12**(5):1184–1193. https://doi.org/10.1111/jsm.12859
177. Pivonello R, Auriemma RS, Delli Veneri A, et al. Global psychological assessment with the evaluation of life and sleep quality and sexual and cognitive function in a large number of patients with acromegaly: a cross-sectional study. *Eur J Endocrinol*. 2022;**187**(6):823–845. https://doi.org/10.1530/EJE-22-0263
178. Pallotti F, Costa D, Hirsch MN, et al. Erectile function and androgen and estrogen beta receptor gene polymorphisms in acromegalic men. *J Endocrinol Investig*. 2024;**47**(1):141–147. https://doi.org/10.1007/s40618-023-02131-2

179. Chen Z, Shao X, He M, et al. Erectile dysfunction is associated with excessive growth hormone levels in male patients with acromegaly. *Front Endocrinol (Lausanne)*. 2021;**12**:633904. https://doi.org/10.3389/fendo.2021.633904
180. Kapicloglu S, Mollamehmetoglu M, Kutlu N, Can G, Ozgur GK. Inhibition of penile erection in rats by a long-acting somatostatin analogue, octreotide (SMS 201-995). *Br J Urol*. 1998;**81**(1): 142–145. https://doi.org/10.1046/j.1464-410x.1998.00520.x
181. Monzani ML, Pederzoli S, Volpi L, Magnani E, Diazzi C, Rochira V. Sexual dysfunction: a neglected and overlooked issue in adult GH deficiency: the management of AGHD study. *J Endocr Soc*. 2021;**5**(3):bvab002. https://doi.org/10.1210/jendso/bvab002
182. Argiolas A, Argiolas FM, Argiolas G, Melis MR. Erectile dysfunction: treatments, advances and new therapeutic strategies. *Brain Sci*2023 15th ed. 2023;**13**(5):802. https://doi.org/10.3390/brainsci13050802
183. Melis MR, Argiolas A. Oxytocin, erectile function and sexual behavior: last discoveries and possible advances. *Int J Mol Sci*. 2021;**22**(19):10376. https://doi.org/10.3390/ijms221910376
184. Wen YX, Fan LY, Yang AY, et al. Oxytocinergic neurons, but not oxytocin, are crucial for male penile erection. *Neuropharmacology*. 2023;**235**:109576. https://doi.org/10.1016/j.neuropharm.2023.109576
185. Lazzari VM, Becker RO, de Azevedo MS, et al. Oxytocin modulates social interaction but is not essential for sexual behavior in male mice. *Behav Brain Res*. 2013;**244**:130–136. https://doi.org/10.1016/j.bbr.2013.01.025
186. Cera N, Vargas-Cáceres S, Oliveira C, et al. How relevant is the systemic oxytocin concentration for human sexual behavior? *A Systematic Review Sex Med*. 2021;**9**(4):100370. https://doi.org/10.1016/j.esxm.2021.100370
187. Ückert S, Becker AJ, Ness BO, et al. Oxytocin plasma levels in the systemic and cavernous blood of healthy males during different penile conditions. *World J Urol*. 2003;**20**(6):323–326. https://doi.org/10.1007/s00345-002-0300-5
188. Burri A, Heinrichs M, Schedlowski M, Kruger THC. The acute effects of intranasal oxytocin administration on endocrine and sexual function in males. *Psychoneuroendocrinology*. 2008; **33**(5):591–600. https://doi.org/10.1016/j.psyneuen.2008.01.014
189. Behnia B, Heinrichs M, Bergmann W, et al. Differential effects of intranasal oxytocin on sexual experiences and partner interactions in couples. *Horm Behav*. 2014;**65**(3):308–318. https://doi.org/10.1016/j.yhbeh.2014.01.009
190. Van der Ploeg LHT, Martin WJ, Howard AD, et al. A role for the melanocortin 4 receptor in sexual function. *Proc Natl Acad Sci USA*. 2002;**99**(17):11381–11386. https://doi.org/10.1073/pnas.172378699
191. Semple E, Hill JW. Sim1 neurons are sufficient for MC4R-mediated sexual function in male mice. *Endocrinology*. **159**(1): 439–449. https://doi.org/10.1210/en.2017-00488
192. Jorgenson E, Matharu N, Palmer MR, et al. Genetic variation in the SIM1 locus is associated with erectile dysfunction. *Proc Natl Acad Sci USA*. 2018;**115**(43):11018–11023. https://doi.org/10.1073/pnas.1809872115
193. Bovijn J, Jackson L, Censin J, et al. GWAS identifies risk locus for erectile dysfunction and implicates hypothalamic neurobiology and diabetes in Etiology. *Am J Hum Genet*. 2019;**104**(1): 157–163. https://doi.org/10.1016/j.ajhg.2018.11.004
194. Patel DP, Pastuszak AW, Hotaling JM. Genetics and erectile dysfunction: leveraging early foundations for new discoveries. *Int J Impot Res*. 2022;**34**(3):252–259. https://doi.org/10.1038/s41443-020-00372-w
195. Faulkner LD, Dowling AR, Stuart RC, Nillni EA, Hill JW. Reduced melanocortin production causes sexual dysfunction in male mice with POMC neuronal insulin and leptin insensitivity. *Endocrinology*. 2015;**156**(4):1372–1385. https://doi.org/10.1210/en.2014-1788
196. Ückert S, Bannowsky A, Albrecht K, Kuczyk MA. Melanocortin receptor agonists in the treatment of male and female sexual dysfunctions: results from basic research and clinical studies. *Expert Opin Investig Drugs*. 2014;**23**(11):1477–1483. https://doi.org/10.1517/13543784.2014.934805
197. Isidori A, Di Luigi L, Conte D. ACTH 1-17 and sexual behavior. *Ric Clin Lab*. 1984;**14**(2):247–251. https://doi.org/10.1007/BF02904979
198. Wessells H, Levine N, Hadley ME, Dorr R, Hruby V. Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. *Int J Impot Res*. 2000; **12**(Suppl 4):S74–S79. https://doi.org/10.1038/sj.ijir.3900582
199. Wessells H, Fuciarelli K, Hansen J, et al. Synthetic melanotropic peptide initiates erections in men with psychogenic erectile dysfunction: double-blind, placebo controlled crossover study. *J Urol*. 1998;**160**(2):389–393. https://doi.org/10.1016/S0022-5347(01)62903-3
200. Kim S, Cho MC, Cho SY, Chung H, Rajasekaran MR. Novel emerging therapies for erectile dysfunction. *World J Mens Health*. 2021;**39**(1):48–17. https://doi.org/10.5534/wjmh.200007
201. Dreyer BA, Amer T, Fraser M. Melanotan-induced priapism: a hard-earned tan. *BMJ Case Rep*. 2019;**12**(2):e227644. https://doi.org/10.1136/bcr-2018-227644
202. Mallory CW, Lopategui DM, Cordon BH. Melanotan tanning injection: a rare cause of priapism. *Sex Med*. 2021;**9**(1):100298. https://doi.org/10.1016/j.esxm.2020.100298
203. Rosen RC, Diamond LE, Earle DC, Shadiack AM, Molinoff PB. Evaluation of the safety, pharmacokinetics and pharmacodynamic effects of subcutaneously administered PT-141, a melanocortin receptor agonist, in healthy male subjects and in patients with an inadequate response to Viagra. *Int J Impot Res*. 2004;**16**(2):135–142. https://doi.org/10.1038/sj.ijir.3901200
204. Diamond LE, Earle DC, Rosen RC, Willett MS, Molinoff PB. Double-blind, placebo-controlled evaluation of the safety, pharmacokinetic properties and pharmacodynamic effects of intranasal PT-141, a melanocortin receptor agonist, in healthy males and patients with mild-to-moderate erectile dysfunction. *Int J Impot Res*. 2004;**16**(1):51–59. https://doi.org/10.1038/sj.ijir.3901139
205. Safarinejad MR, Hosseini SY. Salvage of sildenafil failures with bremelanotide: a randomized, double-blind, placebo controlled study. *J Urol*. 2008;**179**(3):1066–1071. https://doi.org/10.1016/j.juro.2007.10.063
206. Safarinejad MR, Hosseini SY. Expression of concern: salvage of sildenafil failures with Bremelanotide: a randomized, double-blind, placebo controlled study. *J Urol*. 2023;**10**: 101097JU0000000000003117. https://doi.org/10.1097/JU.0000000000003117
207. Dhillon S, Keam SJ. Bremelanotide: first approval. *Drugs*. 2019;**79**(14):1599–1606. https://doi.org/10.1007/s40265-019-01187-w
208. Royalty JE, Konradsen G, Eskerod O, Wulff BS, Hansen BS. Investigation of safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of a long-acting α-MSH analog in healthy overweight and obese subjects. *J Clin Pharmacol*. 2014;**54**(4):394–404. https://doi.org/10.1002/jcph.211
209. Hussain A, Farzam K. *Setmelanotide*. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan.
210. Patel B, Koysombat K, Mills EG, et al. The emerging therapeutic potential of Kisspeptin and neurokinin B. *Endocr Rev*. 2024;**45**(1):30–68. https://doi.org/10.1210/endrev/bnad023
211. Mills EG, Yang L, Abbara A, Dhillo WS, Comninos AN. Current perspectives on Kisspeptins role in behaviour. *Front Endocrinol (Lausanne)*. 2022;**13**:928143. https://doi.org/10.3389/fendo.2022.928143
212. Gresham R, Li S, Adekunbi DA, Hu M, Li XF, TO'Byrne K. Kisspeptin in the medial amygdala and sexual behavior in male rats. *Neurosci Lett*. 2016;**627**:13–17. https://doi.org/10.1016/j.neulet.2016.05.042
213. Mills EG, Ertl N, Wall MB, et al. Effects of Kisspeptin on sexual brain processing and penile tumescence in men with hypoactive

sexual desire disorder: a randomized clinical trial. *JAMA Netw Open*. 2023;**6**(2):e2254313. https://doi.org/10.1001/jamanetworkopen.2022.54313

214. Bhardwaj S, Kumar P, Jerome A, et al. Serum kisspeptin: new possible biomarker for sexual behaviour and sperm concentration in buffalo bulls. *Reprod Domest Anim*. 2020;**55**(9):1190–1201. https://doi.org/10.1111/rda.13761
215. Comninos AN, Wall MB, Demetriou L, et al. Kisspeptin modulates sexual and emotional brain processing in humans. *J Clin Invest*. 2017;**127**(2):709–719. https://doi.org/10.1172/JCI89519

Sexual Medicine Reviews, 2025, 13, 433–455
https://doi.org/10.1093/sxmrev/qeaf025
Invited Review