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Endocrinologic Control of Men's Sexual Desire and Arousal/Erection

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ABSTRACT

Introduction: Several hormones and neurotransmitters orchestrate men's sexual response, including the appetitive (sexual desire) and consummative (arousal and penile erection) phases.

Aim: To provide an overview and recommendations regarding endocrinologic control of sexual desire and arousal and erection and their disturbances.

Methods: Medical literature was reviewed by the subcommittee of the International Consultation of Sexual Medicine, followed by extensive internal discussion, and then public presentation and discussion with other experts. The role of pituitary (prolactin, oxytocin, growth hormone, and α-melanocyte-stimulating hormone), thyroid, and testicular hormones was scrutinized and discussed.

Main Outcome Measures: Recommendations were based on grading of evidence-based medical literature, followed by interactive discussion.

Results: Testosterone has a primary role in controlling and synchronizing 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 that can be successfully corrected by appropriate treatments. Oxytocin and α-melanocyte-stimulating hormone are important in eliciting sexual arousal; however, 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.

Conclusion: Endocrine abnormalities are common in patients with sexual dysfunction. Their identification and treatment is strongly encouraged in disturbances of sexual desire and arousal.

Key Words: Sexual Desire; Erectile Dysfunction; Testosterone

INTRODUCTION

Cells communicate with one another through a discrete flow of molecules that consistently influence their behavior and activity. Two distinct classes of communicating molecules are recognized and classified according to their origin and fate: neurotransmitters and hormones. Hormones often are derived from endocrine glands and reach their target cells through the bloodstream, whereas neurotransmitters are locally generated and bioactive within the synaptic cleft. However, some communicating molecules often act as a neurotransmitter or as a hormone (eg, noradrenaline, OT, and α-MSH). Any interference with endocrine cell-to-cell communication because of over- (hyper-) or under- (hypo-) flow results in pathologic conditions. Because communication is very important in the dyadic field of sexual medicine, it obvious that endocrine disorders can greatly affect the sexual brain (desire) and the sexual body (arousal and erection).

This article presents a summary of the main endocrine control of men's sexual desire and arousal and erection as discussed by the authors at their presentation at the Fourth International Consultation of Sexual Medicine (Madrid, Spain, June 2015). After the past three International Consultations on Sexual Medicine, significant advances in the understanding of the endocrinology of male sexual function

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RECOMMENDATIONS

Recommendation 1
- Testosterone (T) significantly contributes to the regulation of male sexual desire (level 1A), and T treatment (TTh) can improve libido in hypogonadal (total T < 12 nmol/L) men (level 1A).
- T evaluation is strongly recommended in all men complaining of decreased sexual desire (level 1A).

Recommendation 2
- Dihydrotestosterone (DHT) and estrogens play a minor role in the regulation of male sexual desire (level 2B).
- DHT and estradiol (E2) evaluations are not recommended in men complaining of decreased sexual desire (level 3B).

Recommendation 3
- Adrenal hormones, including dehydroepiandrosterone (DHEA) and its sulfate (DHEAS; level 2A), and cortisol and aldosterone (level 3B) are not involved in the regulation of male sexual desire.
- Adrenal hormone evaluation is not recommended in men complaining of decreased sexual desire (level 1A).

Recommendation 4
- Prolactin (PRL) plays a major role in regulating male sexual desire (level 2A), acting through direct and indirect pathways (level 3B).
- PRL levels should be evaluated in all men complaining of decreased sexual desire (level 2A).
- Treating hyperprolactinemia restores sexual desire (level 2A).

Recommendation 5
- The contribution of thyroid hormones (THs) in the regulation of male sexual desire is contradictory (level 3B).
- TH evaluation is not recommended in men complaining of decreased sexual desire (level 2B).

Recommendation 6
- T regulates penile development and growth in early life, but not after puberty (level A).
- T targets several molecular pathways involved in the physiology of erections, including the nitric oxide and cyclic guanosine monophosphate (NO-cGMP) pathway (level A), RhoA-ROCK signaling, adrenergic response, and cavernous smooth muscle cell (SMC) turnover (level B).

Recommendation 7
- The decrease of circulating T levels is associated with a decrease in erectile function (EF; level 2B).
- TTh in hypogonadal men (total T level < 12 nmol/L) is associated with significant increases in self-reported measurements of EF that are proportional to the severity of hypogonadal status before treatment (level 1A).
- Basal and longitudinal assessments of T are recommended in men with erectile dysfunction (ED; level 1A).

Recommendation 8
- DHT exerts qualitatively similar effects as T on EF (level 2A), although it has been studied less extensively.
- Treatment with DHT and its analogs (mesterolone) cannot be recommended as an alternative to TTh to improve EF in hypogonadal men (level 4B).
- Measurement of DHT is not recommended in the assessment of EF (level 3A).

Recommendation 9
- The role of E2 on EF is controversial. Experimental evidence indicates that E2 downregulates phosphodiesterase type 5 (PDE5) expression (level 3C).
- Measurement of estrogens is not recommended in the assessment of EF (level 2C).

Recommendation 10
- DHEA and DHEAS are not involved in the regulation of male EF (level 2A).
- Glucocorticoid and mineralocorticoid in adrenal insufficiency might play a role in restoring EF (level 4C).

Recommendation 11
- PRL does not play a direct role in the regulation of male EF (level 3B).
- PRL evaluation is not recommended in patients complaining of ED (level 2B).
- Treating hyperprolactinemia might have indirect, positive effects on arousal and erection (level 3B)

Recommendation 12
- Conclusive data regarding the potential therapeutic role of oxytocin (OT) in male sexual dysfunctions are lacking (level 2B).

Recommendation 13
- Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are not involved in the regulation of male EF (level 3B).
- GH and IGF-1 levels should not be evaluated in men complaining of ED (level 2B).

Recommendation 14
- Animal models indicate that the melanocortin system is involved in the regulation of EF acting at a central level (level 2C).
- Available randomized controlled trials (RCTs) do not suggest analogs of α-melanocyte-stimulating hormone (α-MSH) for the treatment of ED because of associated adverse events (level 1B).

Recommendation 15
- Hyperthyroidism is significantly associated with an increased risk of ED (level 3B).
- Treating hyperthyroidism improves ED (level 3B).
- Sexual function should be assessed in all men with hyperthyroidism (level 3B).
- The prevalence of hyperthyroidism in men seeking medical care for ED is low (level 2B).
- TH evaluation is not recommended in all men complaining of ED (level 2B).
- The association between hypothyroidism and impairment of EF is contradictory (level 2C).
- Sexual function should not be assessed in all men with hypothyroidism (level 2B).
- The prevalence of hypothyroidism in men seeking medical care for ED is low (level 2B).
- TH evaluation is not recommended in all men complaining of ED (level 2B).

have been obtained. This report aims to provide recommendations focusing on the pathophysiology of male sexual dysfunctions, specifically on the endocrine aspects. In particular, the aim of this article was to scrutinize studies analyzing the effect of hormone alterations, and their treatments, on sexual desire and arousal and erection.

HORMONES AND SEXUAL DESIRE

Sex steroids (T, DHT, and E2)

There is much evidence documenting T as the fuel of male sexual desire.[1–7] However, the contribution of T in the age-related decline of male sexual desire is contradictory, at least in the general population. The Olmsted Longitudinal Study,[5] a stratified random sample of 414 men, failed to find any association between total T and sexual desire after adjusting for age. The Massachusetts Male Aging Study (MMAS)[6] found only a modest difference in mean T levels between subjects with and without low libido (0.12 nmol/L). In contrast to these reports, the European Male Aging Study (EMAS), a population-based survey performed on more than 3,400 men recruited from eight European centers,[7] clearly showed that a decreased frequency of sexual thoughts is one of the more specific symptoms associated with T deficiency. However, it is important to emphasize that the same study showed that the simultaneous presence of three sexual symptoms (low sexual desire, decreased morning erections, and ED) was the strongest predictor of low T, suggesting that sexual symptoms, in this combination, are the most sensitive and specific in identifying patients with low T levels.[7] Similar results were reported more recently by the Testosterone Trials (TTrials),[8] a survey performed in 788 community-dwelling men recruited from 12 sites in the United States. In addition, the Concord Health and Aging in Men Projects (CHAMP),[9] a prospective population-based observational study enrolling 1,226 men older than 70 years and followed for 2 years, found a consistent association between the decrease of T and the decrease of sexual desire. In particular,

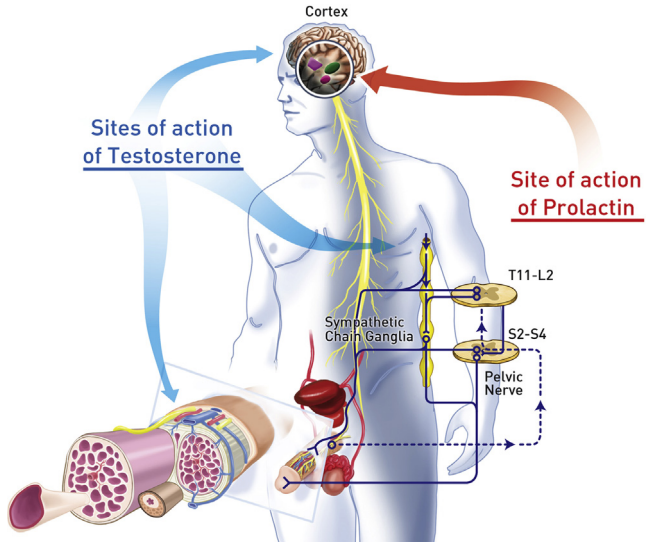

Figure 1. Sites of action of testosterone and prolactin in regulating male sexual desire and arousal and erection. Adapted from Isidori et al.[75] Figure 1 is available in color online at www.jsm.jsexmed.org.

Table 1. Characteristics and Outcomes of Randomized, Placebo-Controlled Clinical Studies Included in Meta-Analysis*

Study	Patients (T/placebo), n	Trial duration (wk)	Age (y)	T levels	Dose (daily)	Design	Sexual function tool used	EF domain	Libido domain
Eugonadal									
O'Carroll and Bancroft,[12] 1984	20/20	12	19–64	Eugonadal	Sustanon 250 mg/2 wk	Crossover	Specific questions on sexual function	−0.13 (−1.73 to 1.48), $P = .88$†; 0.34 (−0.59 to 1.27), $P = .48$‡	0.79 (−0.23 to 1.81), $P = .13$†; 0.09 (−0.83 to1.02), $P = .84$‡
Anderson et al,[13] 1992	16/15	4	21–41	Eugonadal	TE 200 mg/wk	parallel	SES score	−0.20 (−0.91 to 0.51), $P = .58$	0.08 (−0.62 to 0.78), $P = .82$
Aydin et al,[126] 1996	20/18	8	36.8	Eugonadal	TU 160 mg/d	Parallel	Specific questions on sexual function	0.16 (−0.57 to 0.89), $P = .67$	—
Svartberg et al,[14] 2004	15/14	26	54–75	Eugonadal	TE 250 mg/mo	Parallel	IIEF-5	0.90 (0.06–1.74), $P = .04$	—
Overall eugonadal								0.22 (−0.17 to 0.61), $P = .26$	0.25 (−0.24 to 0.74), $P = .32$
Mixed									
Benkert et al,[127] 1979	13/16	8	45–75	Eugonadal	TU 120 mg/d	Parallel	CGI scale	−0.26 (−1.08 to 0.56), $P = .54$	—
Gluud et al,[15] 1988	64/46	30	24–79	Mixed	TU 400 mg/d	Parallel	Specific questions on sexual function	0.27 (−0.11 to 0.65), $P = .17$	0.20 (−0.18 to 0.58), $P = .31$
Schiavi et al,[16] 1997	7/5	6	46–67	Mixed	TE 200 mg/2 wk	Crossover	BSF score	0.00 (−1.15 to 1.15), $P = 1.00$	2.40 (0.90–3.90), $P < .0001$
Rabkin et al,[17] 2000	39/35	6	67.7 ± 3.8	Mixed	TC 200 mg/2 wk	Parallel	CGI scale	—	0.76 (0.27–1.24), $P < .0001$
Haren et al,[18] 2005	39/37	48	68.5 ± 6.0	Mixed	TU 160 mg/d	Parallel	ADAM questionnaire	0.28 (−0.55 to 1.11), $P = .51$	0.50 (0.04–0.95), $P = .03$
Overall mixed								0.18 (−0.13 to 0.48), $P = .26$	0.64 (0.14–1.13), $P = .01$
Hypogonadal									
Nankin et al,[19] 1986	10/10	12	51–72	<12 nmol/L	TC 200 mg/2 wk	Crossover	Specific questions on sexual function	—	0.50 (−0.39 to 1.39), $P = .27$
Dobs et al,[20] 1998	7/6	8	41 ± 16	<8 nmol/L	Buccal T 10–20 mg/d	Parallel	WSF score	—	0.67 (−0.45 to 1.79), $P = .24$

(continued)

Table 1. Continued

Study	Patients (T/placebo), n	Trial duration (wk)	Age (y)	T levels	Dose (daily)	Design	Sexual function tool used	EF domain	Libido domain
Seidman et al,[128] 2001	13/17	6	35–71	<12 nmol/L	TE 200 mg/wk	Parallel	DSPS-M	0.91 (0.15–1.67), $P = .02$	—
Steidle et al,[21] 2003, Seftel et al,[22] 2004	106/99	40	56.8 ± 10.6	<12 nmol/L	TG 100 mg/d	Parallel	Specific questions on sexual function	0.29 (0.01–0.56), $P = .04$	0.36 (0.09–0.64), $P = .01$
Cavallini et al,[23] 2004	40/45	24	60–72	<12 nmol/L	TU 160 mg/d	parallel	IIEF-15	7.00 (5.86–8.14), $P < .0001$	4.00 (3.25–4.75), $P < .0001$
Chiang et al,[30] 2007	20/18	12	20–75	<12 nmol/L	TG 50 mg/d	Parallel	IIEF-EF score	0.40 (−0.26 to 1.05), $P = .23$	—
Jones et al,[24] 2011	103/102	52	59.9 ± 9.3	<12 nmol/L	TG 60 mg/d	Parallel	IIEF-15	0.08 (−0.21 to 0.37), $P = .59$	0.21 (−0.08 to 0.50), $P = .15$
Hackett et al,[25] 2013	92/98	30	33–83	<12 nmol/L	TU 1,000 mg/12 wk	Parallel	IIEF-15	0.33 (0.04–0.62), $P = .03$	0.31 (0.02–0.59), $P = .04$
Francomano et al,[130] 2014	20/20	240	57.5	<12 nmol/L	TU 1,000 mg/12 wk	Parallel	IIEF-EF score	1.03 (0.37–1.69), $P < .0001$	—
Overall total T < 12 nmol/L								0.29 (0.01–0.56), $P = .04$	0.97 (0.22–1.71), $P = .04$
Skakkebaek et al,[26] 1981	7.00 (5.86–8.14), $P < .0001$	7.00 (5.86–8.14), $P < .0001$	22–50	<8 nmol/L	TU 160 mg/d	Crossover	Specific questions on sexual function	1.76 (0.78–2.75), $P < .0001$	1.46 (0.52–2.40), $P < .0001$
Bancroft and Wu,[27] 1983	8/8	8	21–57	<8 nmol/L	TU 160 mg/d	Crossover	Specific questions on sexual function and real-time NPT	—	0.97 (−0.07 to 2.01), $P = .07$
Carani et al,[28] 1990	6/6	6	21–57	<8 nmol/L	TU 160 mg/d	Crossover	Specific questions on sexual function	—	2.25 (0.80–3.69), $P < .0001$
Clopper et al,[29] 1993	9/9	4	16–21	<8 nmol/L	TE 200 mg/2 wk	Crossover	Specific questions on sexual function and NPT	—	0.40 (−0.53 to 1.33), $P = .40$
Chiang et al,[30] 2009	20/20	12	20–75	<8 nmol/L	TG 50 mg/d	Parallel	IIEF-15 score	0.90 (0.25–1.55), $P = .01$	0.56 (−0.07 to 1.19), $P = .08$
Giltay et al,[87] 2010	0.08 (−0.21 to 0.37), $P = .59$	0.08 (−0.21 to 0.37), $P = .59$	35–69	<8 nmol/L	TU 1,000 mg/12 wk	Parallel	IIEF-5 score	0.29 (−0.02 to 0.60), $P = .07$	—

(continued)

Table 1. Continued

Study	Patients (T/placebo), n	Trial duration (wk)	Age (y)	T levels	Dose (daily)	Design	Sexual function tool used	EF domain	Libido domain
Aversa et al,[130] 2010	0.33 (0.04 −0.62), $P = .03$	0.33 (0.04 −0.62), $P = .03$	68.8 ± 6.5	<8 nmol/L	TU 160 mg/d, TU 1,000 mg/12wk	Parallel	IIEF-5 score	2.00 (1.21–2.79), $P < .0001$	—
Overall total T < 8 nmol/L								1.03 (0.37–1.69), $P < .0001$	0.98 (0.42–1.53), $P < .0001$

ADAM = Androgen Deficiency in the Aging Male; BA = controlled cohort before-and-after comparisons; BSF = Brief Sexual Function Questionnaire; CGI = Clinical Global Impression Scale; DSPS-M = Derogatis Sexual Performance Scale for Male; EF = erectile function; IIEF = International Index of Erectile Function; NPT = nocturnal tumescence test; SES = Frenken Sexual Experience Scale; T = testosterone; TC = testosterone cypionate; TE = testosterone enanthate; TG = testosterone gel; TU = testosterone undecanoate; WSF = Watts Sexual Function questionnaire.
*All data are reported as mean ± SD.
†Patients complaining of decreased sexual desire.
‡Patients complaining of erectile dysfunction.

men whose sexual desire decreased during the 2-year follow-up period showed a nearly 10% decrease in circulating T levels.[9] Incidence of secondary hypogonadism in a 4.3-year follow-up observational EMAS cohort was associated with new or worsening of low libido, ED, and infrequent spontaneous erections.[10] All these epidemiologic studies support the genuine association between androgens and sexual desire in humans.

The presence of androgen receptors in distinct areas of the human brain have been described as involved in the regulation of the male sexual response. Among these, the most important include the temporal, preoptic, hypothalamus, amygdala, midbrain, frontal, and prefrontal areas and cingulate gyrus (Brodmann area 24)[11] (Figure 1).

Corona et al[4] recently performed the largest meta-analysis published thus far scrutinizing the role of TTh on several aspects of male sexual function. Data on the effect of TTh on the libido component were available in 17 studies that together enrolled 1,111 individuals[12–30] (Table 1). Overall, TTh was found to improve libido, but this was not confirmed in those studies considering only eugonadal patients at enrollment (T levels < 12 nmol/L), without any differences in studies enrolling subjects with milder (T levels < 12 nmol/L) or more severe (T levels < 8 nmol/L) forms of hypogonadism (Table 1). Meta-regression analysis of the entire sample showed a trend toward an inverse relation between baseline mean T levels and the effect size on the libido component, which reached statistical significance when studies enrolling eugonadal or mixed eugonadal and hypogonadal subjects at baseline were excluded from the analysis.[4] Decreasing T using gonadotropin-releasing hormone analogs, as in healthy men for contraception purposes[31] or in patients with advanced prostate cancer,[32,33] produced a negative effect on libido.

RECOMMENDATION 1

- T significantly contributes to the regulation of male sexual desire (level 1A), and TTh can improve libido in hypogonadal (total T level < 12 nmol/L) men (level 1A).
- T evaluation is strongly recommended in all men complaining of decreased sexual desire (level 1A).

The role played by DHT in the control of male sexual desire is contradictory. In fact, patients with congenital 5α-reductase (5AR) type 2 deficiency (a rare genetic disorder characterized by a decreased conversion of T into DHT) after puberty often have normal sexual desire.[34] In line with this evidence, the CHAMP study did not report any association between mass-derived DHT and sexual desire.[9] However, recent evidence documented a decrease of sexual desire in patients taking 5AR inhibitors (5ARis), which cause a decrease in DHT circulating levels, suggesting a direct role in the regulation of male sexual desire.[35] Interestingly, in some cases, the decrease of sexual desire persisted even after 5ARi was withdrawn.[35] A possible explanation is that blocking 5AR in the brain could impair other 5AR

steroid metabolites that act as neurosteroids[35] to regulate sexual desire. In line with these data, there is significant corroborative evidence that administration of non-aromatization androgens such as DHT, nandrolone, or mesterolone can improve male sexual function. Oral DHT undecanoate treatment of agonadal men was reported to maintain sexual function for 9 weeks.[36] Similarly, daily DHT gel administration for 6 months to men with andropause symptoms and serum T levels lower than 15 nmol/L was more effective than placebo in restoring sexual function.[37]

Much less is known about the role of estrogens in human male sexual behavior.[38] In men with normal T levels, the administration of tamoxifen, an estrogen receptor antagonist, or testolactone, an aromatase inhibitor, did not modify sexual function.[38] No remarkable sexual dysfunction was reported in men affected by congenital estrogen deficiency, suggesting that estrogens are not strictly necessary for normal male sexual behavior.[38] A double-blinded, placebo-controlled RCT evaluating the effect of the non-aromatization androgen DHT on 114 healthy men older than 50 years showed no effect on any of 33 measurements of sexual function and mood, apart from a mild, but significant, decrease in overall sexual desire, which was reversible after treatment cessation.[39] However, an unexpected improvement in sexual desire and frequency of sexual activity occurred during transdermal E2 treatment in subjects affected by aromatase deficiency (a rare condition impairing estrogen formation), suggesting a possible role of estrogen in regulating male sexual desire.[38] In addition, Finkelstein et al,[40] in a double-blinded, placebo-controlled experimental model of gonadotropin-releasing hormone analog-induced hypogonadism performed in 400 healthy men, showed that estrogen and T deficiencies contributed to the decrease of sexual function. In particular, the enrolled men were previously treated with goserelin acetate to suppress endogenous T and E2 production and then randomly assigned to receive a placebo, T alone, or T gel and anastrozole to suppress the conversion of T to E2. In the group that received T alone, inhibition of estrogen synthesis compared with intact estrogen synthesis was associated with significant increases in the percentage of body fat, subcutaneous fat area, intra-abdominal fat area, and significant decreases in sexual desire and EF, confirming that E2 exerts an independent effect on these variables.[40]

In contrast, data from the EMAS did not indicate any association between E2 and overall sexual function in middle-aged and older men.[41] Similar results were reported in the CHAMP study and the TTrials.[8,9] Hence, more data are advisable to clarify the specific role of estrogen in male sexual function and, in particular, in the control of sexual desire.

RECOMMENDATION 2

- DHT and estrogens play a minor role in the regulation of male sexual desire (level 2B).
- DHT and E2 evaluations are not recommended in men complaining of decreased sexual desire (level 3B).

DHEA and Other Adrenal Hormones

An age-dependent decrease of circulating DHEA and DHEAS has been reported, suggesting a role for these adrenal hormones in the age-dependent impairment of several biological functions, including the sexual ones.[42,43] Granata et al[44] evaluated sexual function in a small prospective study involving 12 subjects with autoimmune primary adrenal insufficiency who were studied before (baseline) and after 2 months of adrenal hormone supplementation. They found that DHEAS levels did not correlate with any of the sexual parameters studied, including sexual desire, at baseline or in the recovery phase. Granata et al[44] also reported that subjects with adrenal insufficiency had lower scores in all domains, including sexual desire (as measured by the International Index of Erectile Function [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 mineralocorticoids in regulating male sexual desire.[44]

Several uncontrolled studies have indicated a positive effect of DHEA administration on sexual functions, including libido.[51] Corona et al[45] recently published a meta-analysis of 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. Similar results were reported in a recent double-blinded, placebo-controlled RCT enrolling 21 men with hypoactive sexual desire.[46]

The European Registry on Cushing's Syndrome documented that excess cortisol was associated with a 69% decrease of libido in affected men.[47] However, it is unknown whether cortisol played a direct role in the regulation of male sexual desire or whether the latter relation was the result of the morbidities associated with excess cortisol, including hypogonadism and mood disturbances.[47]

RECOMMENDATION 3

- Adrenal hormones, including DHEA and DHEAS (level 2A), and cortisol and aldosterone (level 3B) are not involved in the regulation of male sexual desire.
- Adrenal hormone evaluation is not recommended in men complaining of decreased sexual desire (level 1A).

Prolactin

An epidemiologic study conducted in middle-aged and elderly European men did not demonstrate any association between variation in PRL levels and sexual desire.[48] However, in this study, a low PRL level was associated with a negative change in sexual functioning compared with the previous year.[48] In apparent

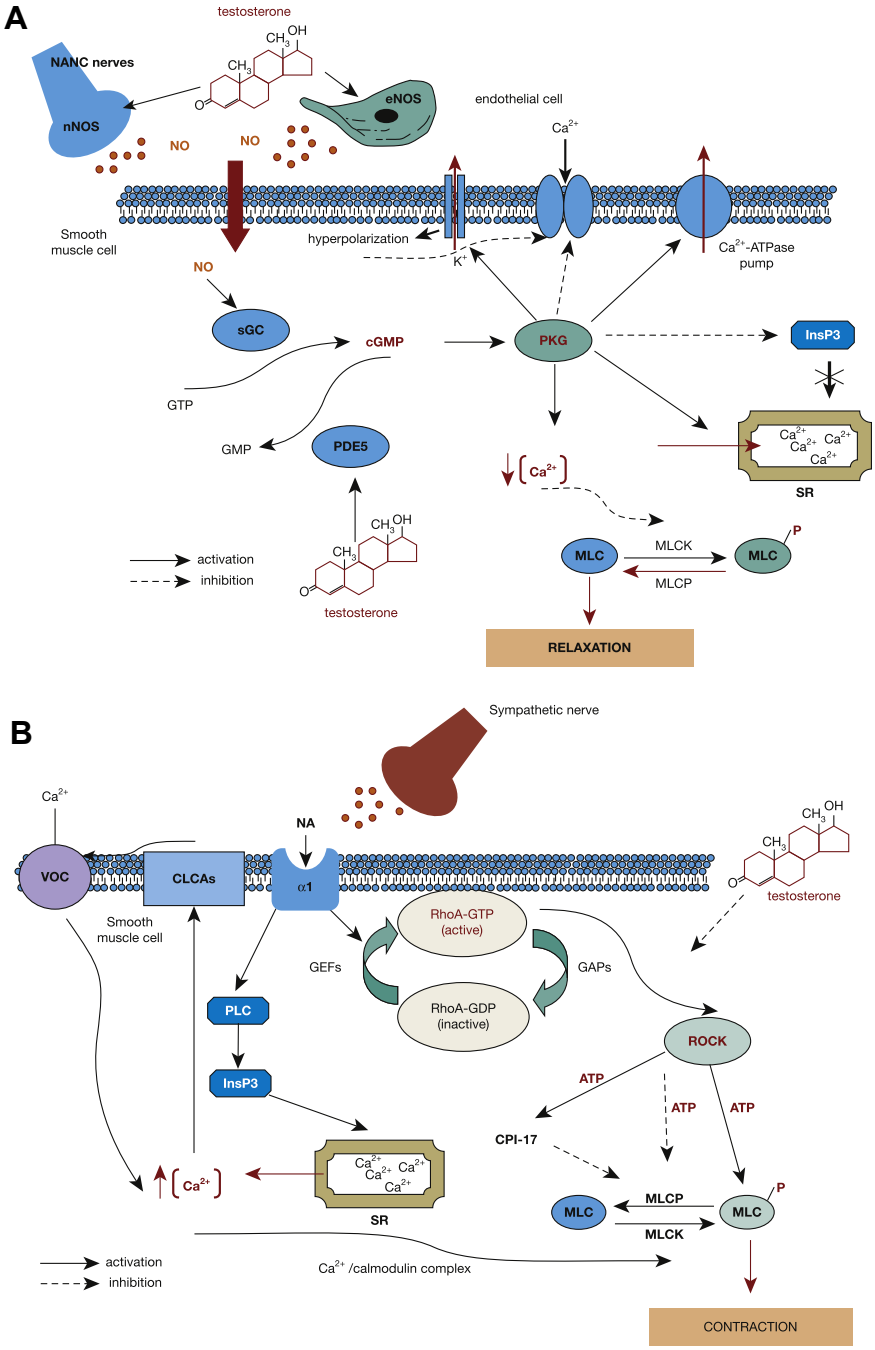

Figure 2. Role of testosterone in the mechanism of penile erection. Panel A depicts the generation of NO by NOS in NANC neurons (nNOS) or endothelial cells (eNOS). This step is positively regulated by testosterone. NO diffuses into smooth muscle cells and activates sGC, which in turn transforms GTP into cGMP. cGMP activates PKG, which, through the indicated pathways, decreases intracellular Ca^{2+} levels, leading to relaxation. PDE5 metabolizes cGMP into GMP, thereby limiting its effects. The latter event is positively controlled by testosterone. Panel B depicts the generation of InsP3 by NA binding to α_1-receptors. InsP3, by increasing Ca^{2+} levels, activates CLCAs, resulting in membrane depolarization and the opening of VOC. Increased Ca^{2+} flow promotes, through calmodulin, activation of MLCK and cell contraction. Cell contraction also is obtained by a second pathway, RhoA/ROCK, which increases, through a series of kinase activations, the sensitivity of MLC to Ca^{2+}. Testosterone is supposed to negatively regulate the latter event. Adapted from Corona and Maggi.[61] 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; sGC = soluble guanylate cyclase; SR = sarcoplasmic reticulum; VOC = voltage-operated channels. Figure 2 is available in color online at www.jsm.jsexmed.org.

contrast, in a cohort of men consulting for sexual dysfunction, a severely decreased libido was associated with a 10 times higher chance of having severe hyperprolactinemia (SHPRL; defined as PRL > 735 mU/L or 35 ng/mL), whereas no association was observed between mild hyperprolactinemia (defined as PRL > 420 mU/L or 20 ng/mL and < 735 mU/L or 35 ng/mL) and low desire.[49] Similar data were reported in a more recent study aimed at identifying risk factors related to primary decreased libido (ie, not associated with known conditions causing low libido, such as hypogonadism, hyperprolactinemia, psychopathology, and/or psychoactive medications) or secondary decreased libido (ie, associated with these conditions), involving more than 3,700 men with sexual dysfunction.[2] In subjects with SHPRL, decreased libido was almost universally present (84.2%), whereas only fewer than 1% of patients consulting for sexual dysfunction had SHPRL. However, in this cohort, two of three subjects with SHPRL had a pituitary tumor or some other organic problem; therefore, such patients must be identified.[2,49]

The mechanisms by which PRL regulates male sexual desire are not completely understood (Figure 1). A PRL-induced hypogonadism could explain, at least in part, the association between SHPRL and decreased libido.[42] In fact, PRL acutely increased the turnover of dopamine (DA) in several brain areas partly involved in the regulation of sexual behavior (ie, nigrostriatal and mesolimbic tracts) and of PRL secretion (ie, tuberoinfundibular tract).[1] In particular, in the tuberoinfundibular tract, chronic hyperprolactinemia resulted in an increase in DA secretion leading to suppression of gonadotropin-releasing hormone, low luteinizing hormone, and low T.[1,42] Accordingly, SHPRL-induced central hypogonadism is a common finding. However, a direct effect of increased PRL on sexual desire also was hypothesized.[1,42] In fact, PRL receptors were found in the diencephalic incertohypothalamic dopaminergic system, a pathway of short axons with terminals in the medial preoptic area, the most important area for the control of motivational and consummatory aspects of sexual behavior.[1,42] In the incertohypothalamic dopaminergic system in contrast to other areas, PRL inhibited, or did not increase, DA activity, supporting a direct, negative effect of PRL on sexual motivation.[1,42,50]

A detailed list of causes of hyperprolactinemia has been reported elsewhere.[42]

DA agonists (bromocriptine and cabergoline) are the first choice in treating hyperprolactinemia, in particular PRL-secreting adenomas, because of their higher efficacy in normalizing PRL levels and a higher frequency of pituitary tumor shrinkage.[42] In most cases, these PRL-lowering agents normalize hypoactive sexual desire, in addition to PRL and T levels. After treatment with dopaminergic drugs, hypoactive sexual desire normalizes in almost 70% to 90% of patients.[42]

As mentioned earlier, DA plays a crucial role acting as a neurotransmitter in regulating sexual excitation, particularly at the hypothalamic and mesolimbic levels.[11] Accordingly, many patients are treated off label with DA agonists to help increase sexual desire. Despite this evidence, the specific role of DA in regulating male sexual desire is not completely clear. The best clinical example in this regard is represented by patients with Parkinson disease (PD). Sexual dysfunction and decreased libido, in particular, are common in patients with PD and it is closely associated with depression and relationship dissatisfaction.[51] In addition, the use of DA agonist has been associated with an improvement of sexual desire and with impulse control disorders, a frequent complication of PD, with an estimated prevalence of 3% to 4%.[51,52] Nevertheless, it is not clear whether the known brain "lesions" related to PD (supposedly relevant for maintaining normal sexual function) have a decisive impact on the prevalence of sexual dysfunction observed in PD.[51] In fact, Lipe et al[53] reported no difference in the prevalence of sexual dysfunction when PD was compared with another, non-neurologic, chronic disease such as arthritis, suggesting that factors other than DA impairment might play a more important role. In support of this notion, Kummer et al[54] reported that age and depressive symptoms were the main predictors of loss of libido in patients with PD.

RECOMMENDATION 4

- PRL plays a major role in regulating male sexual desire (level 2A), acting through direct and indirect pathways (level 3B).
- PRL levels should be evaluated in all men complaining of decreased sexual desire (level 2A).
- Treating hyperprolactinemia restores sexual desire (level 2A).

Thyroid Hormones

Hypothyroidism in men is another endocrine condition previously associated with decreased libido. In a small prospective study, Carani et al[55] evaluated the prevalence of sexual dysfunctions in 48 men, 34 with hyperthyroidism and 14 with hypothyroidism, and their possible remission after normalizing TH levels. They found that low sexual desire was related to hypothyroidism and that it was restored after TH therapy. The mechanism of action of TH on sexual desire is unknown. Although a hypothyroidism-induced increase in PRL[42] might mediate the negative effects of low TH on sexual desire, a direct role of TH on the serotoninergic system has been postulated.[55] More recently, Corona et al[56] confirmed the association between low sexual desire and hypothyroidism in two different populations of subjects, including the aforementioned EMAS cohort and more than 3,000 patients consulting for sexual dysfunction. Hence, more studies are advisable to confirm the possible role of THs in the control of male sexual desire.

RECOMMENDATION 5

- The contribution of THs in the regulation of male sexual desire is contradictory (level 3B).
- TH evaluation is not recommended in men complaining of decreased sexual desire (level 2B)

HORMONES AND SEXUAL AROUSAL AND ERECTIONS

Sex Steroids (T, DHT, and E2)

Role of T: Summary of Evidence From Experimental Studies

Androgens are considered the major hormonal regulator of penile development and physiology[57] (Figure 1). In humans, T influences penile development, mainly because of extracellular stromal expansion.[58] Postnatal penile length and growth rate also seem to be correlated with the T surge occurring in the first months of life (mini-puberty).[59] However, no further correlation is seen in postpubertal adults. Most studies agree that androgen sensitivity and androgen receptor expression vary with age and stage of penile development. As a result, the role of T in adult ED has been the object of several controversies. Most early studies focused on androgen ablation in animal models, a condition that can hardly be transferred to the human physiology of an erection, with the few exceptions of bilateral orchiectomy for testicular cancer and androgen deprivation for prostate cancer. However, some recent studies on hypogonadism induced by a high-fat diet recapitulated the findings from castration studies.[59,60]

Part of the erectile response to T is mediated through an increased sexual desire, but several experimental studies have documented a direct role of T on cavernous SMCs involving NO, PDE5, RhoA-ROCK, cavernosal nerve function, and adrenergic response (Figures 1 and 2).[61]

All experimental studies agree on a castration-induced decrease in intracavernous pressure caused by decreased arterial inflow and altered veno-occlusion during erection. Although the data from surgical hypogonadism hardly represent a very small minority of cases of human male hypogonadism, the animal model of hypogonadism induced by a high-fat diet seems to recapitulate the findings of castration studies. The NO pathway clearly represents a major target of androgens[62,63] (Figure 2); however, studies of animals treated with L-N G-nitro arginine methyl ester also found additional NO-independent mechanisms that still required intact cGMP generation to control veno-occlusion.[64] Among the NO-independent targets of androgens is the RhoA-ROCK pathway[65] that keeps SMCs stably contracted by calcium sensitization; hypogonadism has been shown to induce activation of ROCK1,[60] counteracting SMC relaxation, but not ROCK2, which, conversely, is increased by T in endothelial cells[66] (Figure 2). Another NO-independent mechanism is the regulation of smooth muscle myosin isoforms,[67] and impaired renewal of subtunical cells also has been described in hypogonadism, contributing to impaired veno-occlusion.[68] Several, but not all,[69] studies found that PDE5 expression was regulated by androgens[63,70,71] (Figure 2). In general, experimental studies converge in showing that androgens are necessary to sustain the NO-cGMP pathway through direct[70,71] or indirect[72] mechanisms.[73] A recent study reported that estrogens inhibit, more than androgens stimulate, PDE5 expression and activity.[73]

Another recognized mechanism of androgen action is the regulation of α_1-adrenergic responsiveness of SMCs[63,74] (Figure 2). Consistent findings have pointed toward an effect of T on postganglionic parasympathetic neurons or, even further upstream, within the autonomic nervous system.[75] Therefore, androgens appear necessary to support adequate neuronal stimulation to the corpora cavernosa and maintain structural integrity in tissue as seen after the denervation from prostate surgery in men.[68,75]

RECOMMENDATION 6

- T regulates penile development and growth in early life, but not after puberty (level A).
- T targets several molecular pathways involved in the physiology of erections, including the NO-cGMP pathway (level A), RhoA-ROCK signaling, adrenergic response, and cavernous SMC turnover (level B).

Role of T: Summary of Evidence From Clinical Studies

Human studies are extremely heterogeneous in their assessment of EF; for the present synthesis, "overall EF" includes sexual-related and spontaneous erections, whereas "sexual-related EF" refers to the function exclusively assessed in the context of a sexual encounter (Sexual Encounter Profile, IIEF, and others).[4]

The EMAS and other cross-sectional surveys have reported lower T levels in approximately 30% of men with ED.[6,7,39,76–79] Longitudinal studies have confirmed this association by showing that an individual's decrease (change [Δ]) to the hypogonadal range, rather than its absolute value, predicts sexual decline.[9] However, this relation is weaker for EF compared with desire and still does not imply any causal association.[9,79]

Early studies found that the androgen dependency of EF in young men was maintained at threshold values that were far below those required to maintain the function of other target organs.[80] However, this finding does not automatically translate to elderly men with comorbidities (ie, the vast majority of men complaining of ED). Of note is that aging is associated with an increase in SHBG that can lower bioavailable T. This suggests that free T could be a better predictor of the association between EF and androgens. Although in principle this works, the direct measurement of free T, or its calculation by SHBG, is disadvantaged by the reliability vs. costs of proper assays and uncertainties in SHBG polymorphism and its affinity to T. In the past, most studies were performed using total rather than free T, and the EMAS[7] did not show a superiority of one or the other. Nevertheless, more data collected with an accurate direct measurement of free T in the future could indicate a stronger prediction of EF.

The few available RCTs addressing the role of T on ED have been extensively reviewed, with the largest and most updated meta-analysis confirming significant beneficial effects on overall EF, but only in men with a T level lower than 12 nmol/L.[4] Regression and subgroup analyses have emphasized a role for aging as a possible moderator of ED responsiveness to T. Specifically, data on sexual-related EF

Table 2. Characteristics and Outcomes of Phase 1 and 2 Studies Evaluating Effects of Oxytocin or α-MSH Analogs on Several Sexual Function Parameters

Study		Sample size	Population studied	Age (y)	Drug	Duration of treatment	Type of study	Erectile response	Side effects
Oxytocin									
Behnia et al,[98] 2014	—	29	Healthy heterosexual couples	—	Intranasal oxytocin application (24 IU)	Acute	Single arm	Psychometric questionnaires, ↑orgasm, ↑sexual satiety	—
Burri et al,[99] 1998	—	10	Healthy men	—	Intranasal oxytocin application (24 IU)	Acute	Double-blinded, placebo-controlled, balanced crossover	ASES, equivocal effects on sexual behavior	—
Scheele et al,[100] 2013	—	20	Healthy non-smoking male volunteers	25.5	Intranasal oxytocin application (24 IU)	Acute	Double-blinded, discovery and replication study	MRI, female partner's face more attractive vs unfamiliar women, augmented neural response to partner vs. familiar woman	—
MSH analog									
Royalty et al,[101] 2014	Single-dose trial design (part 1)	6	Healthy overweight and obese subjects	35.2	Long-acting α-MSH analog (0.03 mg/kg) MC4-NN2-0453	22 d	Randomized, double-blinded, placebo-controlled, 2-part trial	Erectile improvement (self-reported)	Skin hyperpigmentation (33%), headache (30%), decreased appetite (12%), injection-site hemorrhage
		6		32.3	Long-acting α-MSH analog MC4-NN2-0453 (0.06 mg/kg)				
		6		39.3	Long-acting α-MSH analog MC4-NN2-0453 (0.15 mg/kg)				
		6		35.2	Long-acting α-MSH analog MC4-NN2-0453 (0.30 mg/kg)				
		7		37.6	Long-acting α-MSH analog MC4-NN2-0453 (0.60 mg/kg)				

(continued)

Table 2. Continued

Study		Sample size	Population studied	Age (y)	Drug	Duration of treatment	Type of study	Erectile response	Side effects
		6		35.0	Long-acting α-MSH analog MC4-NN2-0453 (1.00 mg/kg)				
		6		31.8	Long-acting α-MSH analog (1.50 mg/kg)				
	Multiple-Dose Trial Design (Part 2)	25	Healthy obese subjects	43.8	Long-acting α-MSH analog MC4-NN2-0453 (0.75 mg/d)	210 d			
		50		38.6	long-acting α-MSH analog MC4-NN2-0453 (1.50 mg/d)				
		25		41.4	long-acting α-MSH analog MC4-NN2-0453 (3.00 mg/d)				
Rosen et al,[102] 2004	Phase 1 study (SC 0.3, 1, 3, 5, 7.5, 10 mg)	36	Healthy men	33.6	Melanocortin receptor agonist PT-141	Acute	Randomized, double-blinded, placebo-controlled, 2-phase trial	RigiScan, ↑duration of rigidity > 60% (min), ↑duration of rigidity > 80% (min; for dosage ≤1 mg)	Nausea, headache, flushing (average 30% of population for higher dosages)
	Phase 2 study (SC 4–6 mg)	25	Patients with ED not responsive to sildenafil	48	Melanocortin receptor agonist PT-141			RigiScan, ↑duration of rigidity > 60% (min), ↑duration of rigidity > 80% (min)	
Diamond et al,[103] 2004	Phase 1 study, nasal spray (4, 7, 10, 20 mg)	24	Healthy subjects	33.5	Melanocortin receptor agonist PT-141	Acute	Randomized, double-blinded, placebo-controlled, 2-phase trial	RigiScan, ↑duration of rigidity > 60% (min), ↑duration of rigidity > 80% (min)	Nausea, flushing
	Phase 2 study, nasal spray (7–20 mg)	24	Patients with ED responsive to sildenafil	50.9				RigiScan, ↑duration of rigidity > 60% (min), ↑duration of rigidity > 80% (min)	

(continued)

Table 2. Continued

Study		Sample size	Population studied	Age (y)	Drug	Duration of treatment	Type of study	Erectile response	Side effects
Wessells et al,[104] 2000	—	10	Psychogenic ED	47.4	Melanotan II 0.025 ± 0.157 mg/kg	Acute	Double blinded, placebo-controlled crossover	RigiScan, ↑duration of rigidity > 80% (min), ↑sexual desire	12 with severe nausea (12.9% of subjects)
		10	Organic ED	56.2					Nausea with stretching or yawning
Wessells et al,[105] 1998	—	10	Psychogenic ED	47	Melanotan II (0.025 mg/kg)	Acute	Double-blinded, placebo-controlled crossover study	RigiScan, ↑duration of rigidity > 80% (min)	Transient nausea with stretching and yawning
Safarinejad et al,[106] 2008	—	342	Patients with ED not responsive to sildenafil	28–59	Intranasal bremelanotide 10 mg		Double-blinded, placebo-controlled study	IIEF score, ↑sexual satisfaction domain	—
Krishna et al,[107] 2008	Treatments (placebo; 200-mg single oral dose of MK-0493; 500-mg single oral dose of MK-0493; 50-mg single oral dose of sildenafil)	20	Organic ED	35–50	Melanocortin 4 receptor agonist (MK-0493)	Acute	Randomized, double-blinded, placebo-controlled, 4-period crossover study	RigiScan, ↑duration of rigidity > 60% (min)	Nausea, vomiting

ASES = Acute Sexual Experience Scale; ED = erectile dysfunction; IIEF = International Index of Erectile Function; MRI = magnetic resonance imaging; MSH = melanocyte-stimulating hormone; SC = subcutaneous.

were available in 19 studies enrolling 1,431 individuals[12−18,21−26,30,81,125−130] (Table 1). Overall, TTh determined an improvement only in studies enrolling hypogonadal subjects (mean baseline T levels < 12 nmol/L), but not in those investigating eugonadal patients or mixed eugonadal and hypogonadal subjects. A sensitivity analysis performed in the few trials (n = 6) using IIEF-EF domain score as an outcome measurement confirmed the positive effect of TTh on the sexual-related EF component (IIEF-15 EF subdomain Δ increase of 3.726, 95% CI = 1.621−5.830, $P < .001$).

More recently, the concept of "compensated" or "subclinical hypogonadism" has been introduced, suggesting that when T decreases from a previously higher level, the increase in luteinizing hormone might become a confirmatory biomarker for insufficient androgenization.[82−84] Another relevant emerging aspect is the time course of T effects (ie, length of treatment necessary to achieve the maximum result). Recent systematic reviews[85] and RCTs[25,80,81] have found that although the effects on libido, ejaculation, and sexual activity occur within just 2 to 3 weeks, effects on EF could require up to 6 or even 12 months.

RECOMMENDATION 7

- The decrease of circulating T level is associated with a decrease in EF (level 2B).
- TTh in hypogonadal men (total T level < 12 nmol/L) is associated with significant increases in self-reported measurements of EF that are proportional to the severity of hypogonadal status before treatment (level 1A).
- Basal and longitudinal assessments of T are recommended in men with ED (level 1A).

Role of DHT

DHT is the most potent androgen involved in genital tissue development. No major discrepancies could be found when comparing the in vitro effects of T and DHT on EF. However, interest in the role of DHT has been renewed recently by patients complaining of sexual-related symptoms after exposure to 5ARis.[86] Studies have pointed toward a drug-related, rather than DHT-mediated, effect. In animal models, 5ARis have been associated with structural and functional alterations in penile tissue contributing to penile fibrosis that is mainly exerted through a modulation of cholinergic and adrenergic sensitivity, with no apparent change in PDE5.[87] However, the available evidence is insufficient to determine whether defective DHT, in the presence of normal T, impairs EF in men. The few trials performed on hypogonadal subjects treated with DHT alone or T plus 5ARi found similar effects on major EF domains.[37,88]

RECOMMENDATION 8

- DHT exerts qualitatively similar effects as T on EF (level 2A), but it has been less extensively studied.
- Treatment using DHT and its analogs (mesterolone) cannot be recommended as an alternative to TTh to improve EF in hypogonadal men (level 4B).
- Measurement of DHT is not recommended in the assessment of EF (level 3A).

Role of Estrogens

E2 was found to be required to maintain male sexual function in some, but not all, studies of selective estrogen deficiency.[36,41] The EMAS showed that E2 correlated with psychological symptoms of male aging,[41] but not with EF domains, confirming previous findings.[5,89] These studies found a robust, independent correlation between E2 and sexual dysfunction-associated distress and T associated with somatized anxiety in older men with ED.[90] A recent RCT found that aromatization played only a minor role in the maintenance of sexual function in healthy men, with some dependence on increasing age and obesity.[39] More recently, a longitudinal study found an association between estrone and the onset of ED during a 2-year follow-up.[9] Measurement of estrogens in men is not reliable with immunoassays; therefore, their use as biomarkers is possible only if adequate detection systems are available.

RECOMMENDATION 9

- The role of E2 on EF is controversial. Experimental evidence indicates that E2 downregulates PDE5 expression (level 3C).
- Measurement of estrogens is not recommended in the assessment of EF (level 2C).

DHEA and Other Adrenal Hormones

Past evidence documented a possible role of an age-dependent decrease of DHEAS in the pathogenesis of ED.[42,43] The MMAS found that DHEAS was the only hormone negatively correlated to the prevalence of ED among 17 investigated hormones, including T and E2.[91] In addition, Basar et al,[92] in a consecutive series of 348 men, reported that DHEAS and free T levels were significantly lower in men with sexual dysfunction as determined by the IIEF score. However, more recent data have advocated against an association between DHEA (and its DHEAS) and ED. A large placebo-controlled RCT evaluating the effect of DHEA in elderly men and women with an observational period up to 2 years failed to demonstrate a physiologically relevant beneficial effect on ED.[93] Similarly, Morales et al[94] reported that DHEA treatment (50 mg twice daily) did not induce significant differences in sexual performance outcomes compared with placebo as assessed by the IIEF, the Androgen Deficiency in the Aging Male questionnaire, the Aging Male Symptom Scale, and the Global Assessment Questionnaire. Similarly a meta-analysis evaluating the effect of DHEA administration in elderly men

indicated that DHEA supplementation did not improve the overall score of the IIEF-15 or EF domain total score.[45]

The prevalence of ED in patients with Cushing syndrome is unknown. In particular, no information has been reported in the European Registry on Cushing's Syndrome.[47] Granata et al[44] found that in subjects with adrenal insufficiency, treatment with glucocorticoids and mineralocorticoids independently improved the EF domain of the IIFF.

RECOMMENDATION 10

- DHEA and DHEAS are not involved in the regulation of male EF (level 2A).
- Glucocorticoid and mineralocorticoid in adrenal insufficiency might play a role in restoring EF (level 4C).

Prolactin

The relation between hyperprolactinemia and EF is under debate. Some researchers have suggested a possible pathogenic link between severe ED and SHPRL.[42] However, Corona et al[49] did not confirm a significant association between SHPRL and severe ED after adjustment for confounders, including T levels. Hence, SHPRL-induced hypogonadism could explain, at least in part, the association between ED and SHPRL. In apparent contrast with these findings, the same group reported that in subjects with sexual dysfunction, low PRL (<10 ng/mL or 210 mU/L) was associated with arteriogenic ED.[95] This finding was confirmed in the European general population by the EMAS.[48] Some experimental studies have indicated that acute, but not chronic, pharmacologic elevation of brain PRL is associated with a facilitated, rather than an impaired, sexual behavior, including increased penile erection, mounting, and intromission activity.[42] Similarly, in a population-based birth cohort study of men from the Philippines, basal PRL was inversely related to mating effort as indicated by the number of the men's lifetime sexual partners and the sexual activity in the month preceding the PRL measurement.[96] In that study, men without offspring who reported no sexual activity and/or the smallest number of sexual partners had the lowest concentrations of PRL.[96] All these findings indicate that PRL might have a more positive, than negative, effect on initiating or maintaining sexual behavior. It is still unclear how PRL might facilitate male sexual behavior. Different mechanisms could be advocated to explain these associations. In fact, low PRL in the peripheral circulation could mirror, within the hypothalamus, an increase of dopaminergic or a decrease of serotoninergic signaling. The latter possibility represents the most intriguing hypothesis.

RECOMMENDATION 11

- PRL does not play a direct role in the regulation of male EF (level 3B).
- PRL evaluation is not recommended in patients complaining of ED (level 2B).
- Treating hyperprolactinemia might have indirect, positive effects on arousal and erection (level 3B).

Oxytocin

OT is a nonapeptide synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and released by the posterior pituitary. In contrast to its clear function in female reproduction (regulation of milk ejection reflex and uterine contractility), the physiologic role in men is unclear. Animal models have indicated that OT plays a key role in the central control of penile erection, at the level of the paraventricular nuclei of the hypothalamus and of the spinal cord.[97] In particular, OT increases the activity of mesolimbic and mesocortical dopaminergic neurons originating in the ventral tegmental area and projecting to the nucleus accumbens and to the medial prefrontal cortex.[97] Accordingly, mesolimbic and mesocortical dopaminergic neurons play a key role in the motivational and rewarding properties of natural reinforcing stimuli, including sexual activity.[97] The mechanism by which OT induces penile erection and activates mesolimbic dopaminergic neurons when injected into the ventral subiculum or into the posteromedial nucleus of the amygdala is only partly understood. In these areas, OT also activates its own receptors that lead to the activation of NO synthase, thereby increasing NO production. NO in turn activates unknown efferent projections, which apparently increase glutamatergic neurotransmission in the ventral tegmental area.[97] In particular, DA released from these neurons is believed to mediate the transposition of the motivational aspects of natural stimuli into goal-directed behaviors, as in sexual activity, seeking a sexual partner, and sexual intercourse to achieve reward and satisfaction.[97] Altogether, these neural pathways might constitute a complex hypothetical circuit, which plays a role not only in the consummatory phase of sexual activity (EF and copulation) but also in the motivational and rewarding aspects of the anticipatory phase of sexual behavior.

Despite this strong experimental evidence, knowledge about the effects of OT on human sexual behaviors and partner interactions is scanty (Table 2).[98–107] In an uncontrolled observational study involving 29 healthy heterosexual couples, Behnia et al[98] analyzed the acute effects of intranasally administered OT (24 IU) on drive, arousal, orgasm, and refractory aspects of sexual behavior, together with partner interactions. They reported that men indicated higher levels of sexual satiety after sexual intercourse and women felt more relaxed and subgroups indicated an increased ability to share sexual desires or to empathize with their partners. However, the effect was small to moderate. In a previous small RCT with the same dose of OT administered intranasally, a lack of effect of active treatment was found on several sexual parameters, including arousal.[99] In a double-blinded, placebo-controlled RCT, a specific effect of intranasal OT was found in perceiving the partner as attractive, with magnetic resonance imaging–derived activation of brain regions involved in reward, such as the ventral tegmental area and the nucleus accumbens, but without a specific effect on arousal.[100]

Hence, there is a growing idea that OT in humans is important in pair bonding and in enhancing attractiveness during romantic love, as found in other mammals.[100]

RECOMMENDATION 12

- Conclusive data regarding the potential therapeutic role of OT in male sexual dysfunctions are lacking (level 2B).

Growth Hormone

GH is a 191-amino acid polypeptide synthesized and secreted under the control of GH-releasing hormone (positive) and somatostatin (negative) of somatotroph cells in the anterior pituitary. Its primary role is to promote linear bone growth. The physiologic role of GH on sexual function has not been fully elucidated. Experimental studies have shown that GH can induce dose-dependent relaxation of human corpus cavernosal strips in vitro and an increase in cGMP,[108,109] but the GH concentration needed to elicit a 30% relaxation was at least three orders of magnitude higher than the GH concentration changes recorded in cavernosal blood sampling during the physiologic process of erection in men.[110] Pastuszak et al[111] reported that IGF-1 levels correlated with sexual function score in 65 men scheduled for radical prostatectomy. In contrast to these findings, Miwa et al[112] did not find any correlation between peripheral GH levels and all aspects of the Aging Male Symptom Scale including sexual function in ambulatory men. In a small series of patients, cavernous GH levels in organic and psychogenic ED did not differ from peripheral levels.[113]

Although ED and decreased libido are often reported as symptoms of acromegaly in textbooks,[114] it is still unclear whether this is due to the excess of GH or a consequence of GH-related morbidities including secondary hypogonadism. Recently, Lotti et al[115] published the first study that systematically analyzed EF in 57 subjects with acromegaly. Although 42.1% of patients analyzed complained of ED, it was not related to several acromegaly-related parameters, including IGF-1 levels, type of treatment, duration of disease, or secondary hypogonadism. Conversely, subjects with ED and acromegaly had higher cardiovascular risk factors and worse impairment of penile vascular flow compared with subjects with acromegaly and without ED.[115] These data indicate that ED in acromegaly is not related to abnormalities of GH or IGF-1 or T levels but is associated with cardiac morbidities related to the disease. Hence, exposure to excess GH probably does not directly affect EF in vivo and caution is needed when results obtained by in vitro studies are transposed in vivo to humans. In line with these findings, GH replacement treatment did not modify sexual function in men with GH deficiency.[116]

RECOMMENDATION 13

- GH and IGF-1 are not involved in the regulation of male EF (level 3B).
- GH and IGF-1 levels should not be evaluated in men complaining of ED (level 2B).

Melanocortin

Melanocortins are a family of peptide hormones, including adrenocorticotrophic hormone and α-, β-, and γ-MSHs, derived from the cleavage of a large precursor peptide, namely proopiomelanocortin. Experimental animal models indicated that the interaction of α- and β-MSH with specific melanocortin receptors (MCR3 and MCR4) within the hypothalamus and limbic system led to a typical behavioral syndrome including grooming, stretching, and yawning, spontaneous penile erection and ejaculation, and increased sexual receptivity.[117] Two synthetic analogs of α-MSH have been developed for human use (melanotan; afamelanotide, formerly CUV1647; and bremelanotide, formerly PT-141). Phase 1 and 2 trials have been completed and are presented in Table 2[101–107] (for review, see Ückert et al[117]). However, in all studies, drug-related adverse effects were present, such as nausea, yawning, and flushing, which limited the attractiveness of this treatment. In addition, there were concerns regarding a possible increase in blood pressure.[117]

RECOMMENDATION 14

- Animal models indicate that the melanocortin system is involved in the regulation of EF acting at a central level (level 2C).
- Available RCTs do no suggest analogs of α-MSH for the treatment of ED because of associated adverse events (level 1B).

Thyroid Hormones

Although thyroid dysfunctions are often highlighted as common ED-associated conditions,[42] only a few evidence-based reports have investigated this aspect. In 2005, in a small Italian study, Carani et al[55] documented that hypo- and hyperthyroidism were commonly associated with ED (as detected by validated questionnaires). Similar results were confirmed in two other small studies from Italy[118] and Greece.[119] Interestingly, Carani et al[55] and Krassas et al[119] further documented that the correction of the underlying thyroid disorders restored EF. More recently, Corona et al[56] evaluated the relation between TH and EF in a large series (N = 3,203) of patients seeking medical care for sexual dysfunction and in the EMAS population. They found that hyperthyroidism, but not hypothyroidism, was associated with an increased risk of severe ED, after adjusting for confounding factors, including T and PRL levels. These associations were confirmed in nested case-control analyses comparing subjects with overt hyperthyroidism with controls matched for age, body mass index, smoking status, and T levels.[56] Similarly, in a retrospective analysis of a health insurance database representative of Taiwan's general population, Keller et al[120] reported that subjects with ED were 1.64 times more likely to have been previously diagnosed with hyperthyroidism compared with control individuals without ED. TH-α and TH-β receptors were described in rat and human corpora cavernosa endothelial cells

and SMCs.[121,122] Studies in animal models of hyperthyroidism indicated an impairment of NO-dependent relaxation of corpora cavernosa.[123] In rabbit corpora cavernosa strips, relaxation induced by acetylcholine and electrical field stimulation was impaired, whereas sensitivity to the NO donor, sodium nitroprusside, was unchanged.[123] These data suggest an effect of TH in penile NO formation, which has been demonstrated in a rat model.[125] Therefore, hyperthyroidism-associated ED could be due to a direct effect of TH on penile cognate receptors (for review, see Krassas et al[123]). Despite this evidence, Maseroli et al[124] reported that the prevalence of thyroid disorders in patients seeking medical care for ED was rather low (<1%) and not different from that observed in the general population of the same geographic area.

RECOMMENDATION 15

- Hyperthyroidism is significantly associated with an increased risk of ED (level 3B).
- Treating hyperthyroidism improves ED (level 3B).
- Sexual function should be assessed in all men with hyperthyroidism (level 3B).
- The prevalence of hyperthyroidism in men seeking medical care for ED is low (level 2B).
- TH evaluation is not recommended in all men complaining of ED (level 2B).
- The association between hypothyroidism and impairment of EF is contradictory (level 2C).
- Sexual function should not be assessed in all men with hypothyroidism (level 2B).
- The prevalence of hypothyroidism in men seeking medical care for ED is low (level 2B).
- TH evaluation is not recommended in all men complaining of ED (level 2B).

CONCLUSIONS

Several hormones modulate or even promote human sexual behavior, including libido and arousal. Although epidemiologic and intervention studies corroborate the crucial role of T in inducing and maintaining sexual desire and erection, results for other hormones are less clear. Hypothalamic neurohormones as OT and α-MSH are currently under active research for therapeutic purposes. However, results from pilot studies are disappointing for lack of consistency or for disappointing side effects. Aside from hypogonadism, other endocrine disorders are associated with sexual dysfunctions. However, apart from hyperprolactinemia, their investigation in men seeking medical care for sexual dysfunction is not recommended because of the current lack of convincing evidence.

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