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Goldman AL et al. Endocr Rev. (2017)

Sex differences in anxiety and depression: role of **testosterone**.
McHenry J et al. Front Neuroendocrinol. (2014)

[**Testosterone** deficiency, metabolic syndrome and diabetes mellitus].
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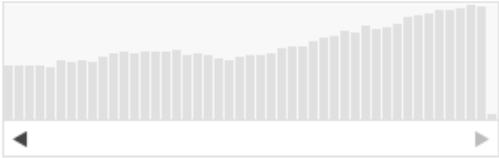

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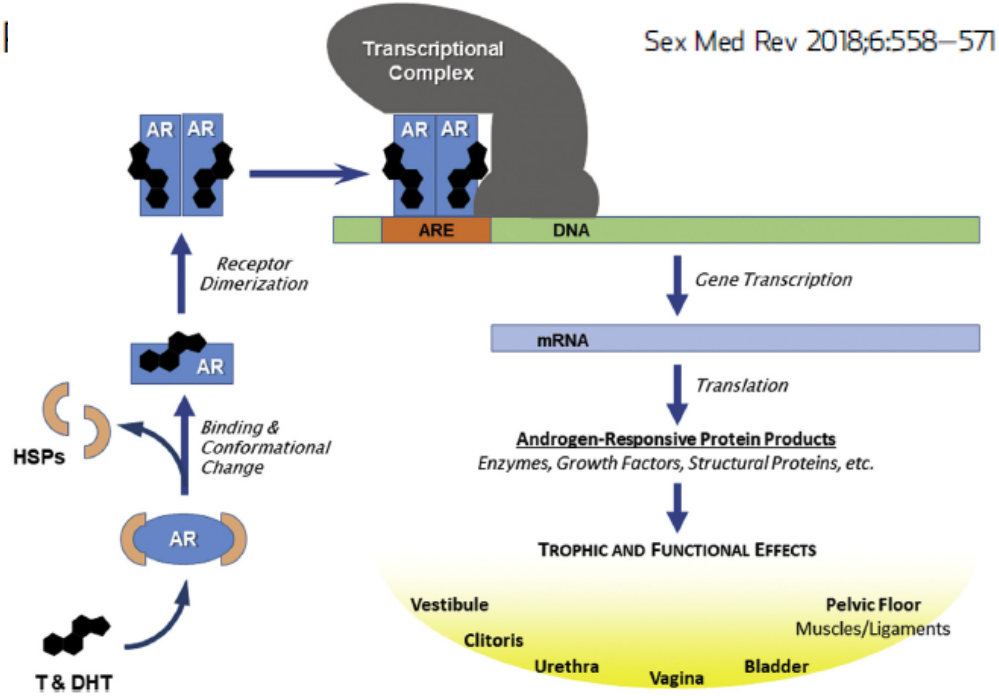
Role of Androgens in Female Genitourinary Tissue Structure and Function: Implications in the Genitourinary Syndrome of Menopause

Abdulmaged M. Traish, PhD,[1] Linda Vignozzi, MD, I
Noel N. Kim, PhD[5]

Sex Med Rev 2018;6:558–571

Androgens contribute to the maintenance of genitourinary tissue structure and function. The effects of androgens can be distinct from those of estrogens or can complement estrogenic action. Androgen mediated processes might be involved in the full or partial resolution of genitourinary syndrome of menopause symptoms in women.



Global Consensus Position Statement on the Use of Testosterone Therapy for Women

Susan R. Davis

J Clin Endocrinol Metab, October 2019, 104(10):4660–4666

It was considered of utmost importance that the diagnosis of HSDD (Hypoactive Sexual Desire Disorder/dysfunction) involves a full clinical assessment and that other factors contributing to FSD (Female Sexual arousal Disorder) must be identified and addressed before testosterone therapy is initiated. A blood total testosterone level should not be used to diagnose HSDD. Treatment should only be with formulations that achieve blood concentrations of testosterone that approximate premenopausal physiological concentrations.

Testosterone therapy for women with low sexual desire: a position statement from the Brazilian Society of Endocrinology and Metabolism

Arch Endocrinol Metab. 2019;63/3

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   Wu DH, Tian HJ, Yuan JN, Dong GP, Wu DW, Yang RW, Sun LY, Tang DX, Fu JF.
   Zhonghua Er Ke Za Zhi. 2019 Oct 2;57(10):786-791. doi: 10.3760/cma.j.issn.0578-1310.2019.10.011. Chinese.
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2. In utero and peripubertal metals exposure in relation to reproductive hormones and **sexual** maturation and progression among girls in Mexico City.
   Ashrap P, Sánchez BN, Téllez-Rojo MM, Basu N, Tamayo-Ortiz M, Peterson KE, Meeker JD, Watkins DJ.
   Environ Res. 2019 Oct;177:108630. doi: 10.1016/j.envres.2019.108630. Epub 2019 Aug 8.
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   Arch Endocrinol Metab. 2019 Jul 18;63(3):190-198. doi: 10.20945/2359-3997000000152. Review.
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1. Improvement of fertility parameters with Tribulus Terrestris and Anacyclus Pyrethrum treatment in male rats.

Haghmorad D, Mahmoudi MB, Haghighi P, Alidadiani P, Shahvazian E, Tavasolian P, Hosseini M, Mahmoudi M.

Int Braz J Urol. 2019 Sep-Oct;45(5):1043-1054. doi: 10.1590/S1677-5538.IBJU.2018.0843.

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Zhonghua Er Ke Za Zhi. 2019 Oct 2;57(10):786-791. doi: 10.3760/cma.j.issn.0578-1310.2019.10.011. Chinese.

PMID: 31594066

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3. [Testosterone substitution in elderly patients - the pros and cons].

Schmidt R, Palitzsch KD.

MMW Fortschr Med. 2019 Oct;161(17):59-62. doi: 10.1007/s15006-019-0965-y. Review. German. No abstract available.

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Comparison of Sexual Function and Serum Testosterone Levels in Mer [Addict Health. 2018]

Efficacy of oral estrogen plus testosterone gel to improve sexual function in pc [Climacteric. 2019]

[LONGITUDINAL CHANGES OF FREE TESTOSTER [Nihon Hinyokika Gakkai Zasshi....]

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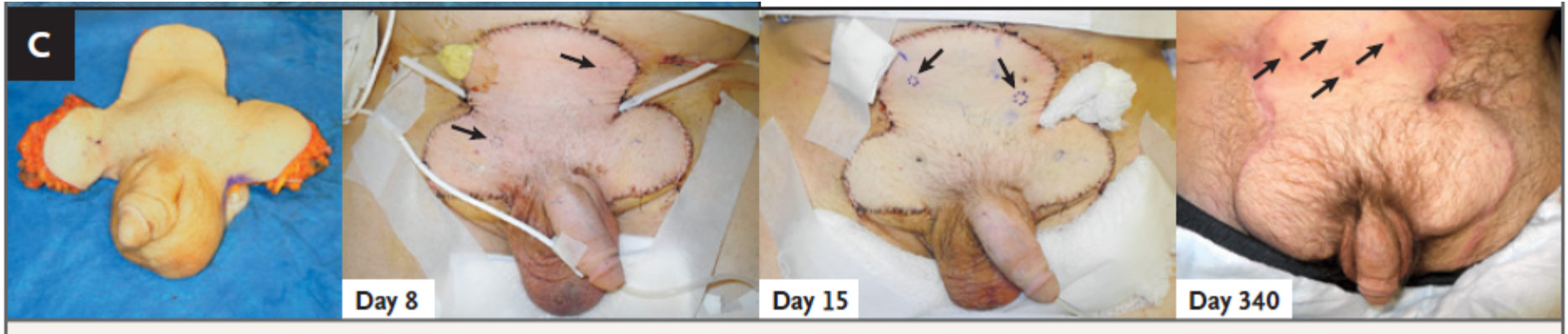

Testosterone e funzione sessuale
Francesco Romanelli

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Aromatase Inhibitors and Selective Estrogen Receptor Modulators: unconventional therapies for functional hypogonadism?
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Andrology. 2019 Nov 6. doi: 10.1111/andr.12725. [Epub ahead of print] Review.
PMID: 31696669
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2. Effects of immunocastration performed at two live weights on the growth **physiology**, temperament and testicular development of feral beef bulls.
Noya A, Ripoll G, Casasús I, Sanz A.
Anim Sci J. 2019 Nov 6. doi: 10.1111/asj.13307. [Epub ahead of print]
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3. Effects of chlorocholine chloride on pubertal development and reproductive functions in male rats.
Hou X, Hu H, Xiagedeer B, Wang P, Kang C, Zhang Q, Meng Q, Hao W.
Toxicol Lett. 2019 Nov 2. pii: S0378-4274(19)30348-0. doi: 10.1016/j.toxlet.2019.10.024. [Epub ahead of print]
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Androgen Therapy in Women.

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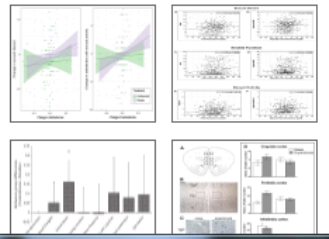

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Aromatase Inhibitors and Selective Estrogen Receptor Modulators: unconventional therapies for functional hypogonadism?

Marijke Awouters[1], Dirk Vanderschueren[2,3*], Leen Antonio[2,3*]

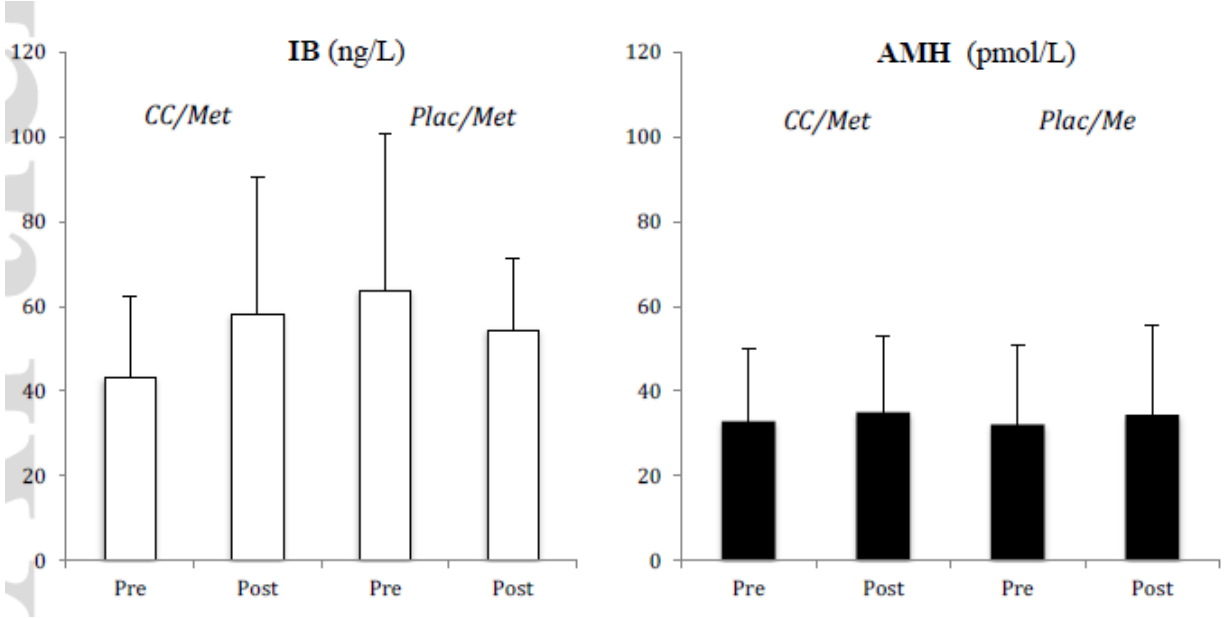
This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ANDR.12725

Conclusion: AIs are not recommended as treatment for functional hypogonadism because of insufficient efficacy as well as a decrease in BMD. SERMs might be an alternative for TRT, but more research is needed to evaluate their effect on hypogonadal signs and symptoms, as well as on their long-term safety profile.

Effect of clomiphene citrate treatment on the Sertoli cellsof dysmetabolic obese men with low testosterone levels.

Clinical Endocrinology. 2019;00 ; doi: 10.1111/CEN.14122

C. Pelusi[1], F. Fanelli[1], M. Baccini[1], V.Triggiani[2], N. Bartolomeo [3], M.D. Carbone[4], G. De Pergola[5], G. Di Dalmazi[1], U. Pagotto [1], R .Pasquali[1] and V. A. Giagulli[6]



Testosterone e funzione sessuale

Il testosterone è positivamente correlato con il desiderio sessuale, con meccanismo d'azione a livello cerebrale.

Il testosterone regola la funzione erettile attraverso un'azione su struttura, innervazione e funzione dei corpi cavernosi e su svariati meccanismi inter-cellulari, in particolare sulla produzione di ossido nitrico e sulla fosfo-diesterasi 5.

Il testosterone è in grado di modulare l'ejaculazione tramite un'azione a livello neurologico centrale e periferico.

A Critical Analysis of the Role of Testosterone in Erectile Function: From Pathophysiology to Treatment—A Systematic Review

Andrea M. Isidori[a], *Jacques Buvat*[b], *Giovanni Corona*[c], *Irwin Goldstein*[d], *Emmanule A. Jannini*[e], *Andrea Lenzi*[a], *Hartmut Porst*[f], *Andrea Salonia*[g], *Abdulmaged M. Traish*[h], *Mario Maggi*[i,*]

EUROPEAN UROLOGY 65 (2014) 99–112

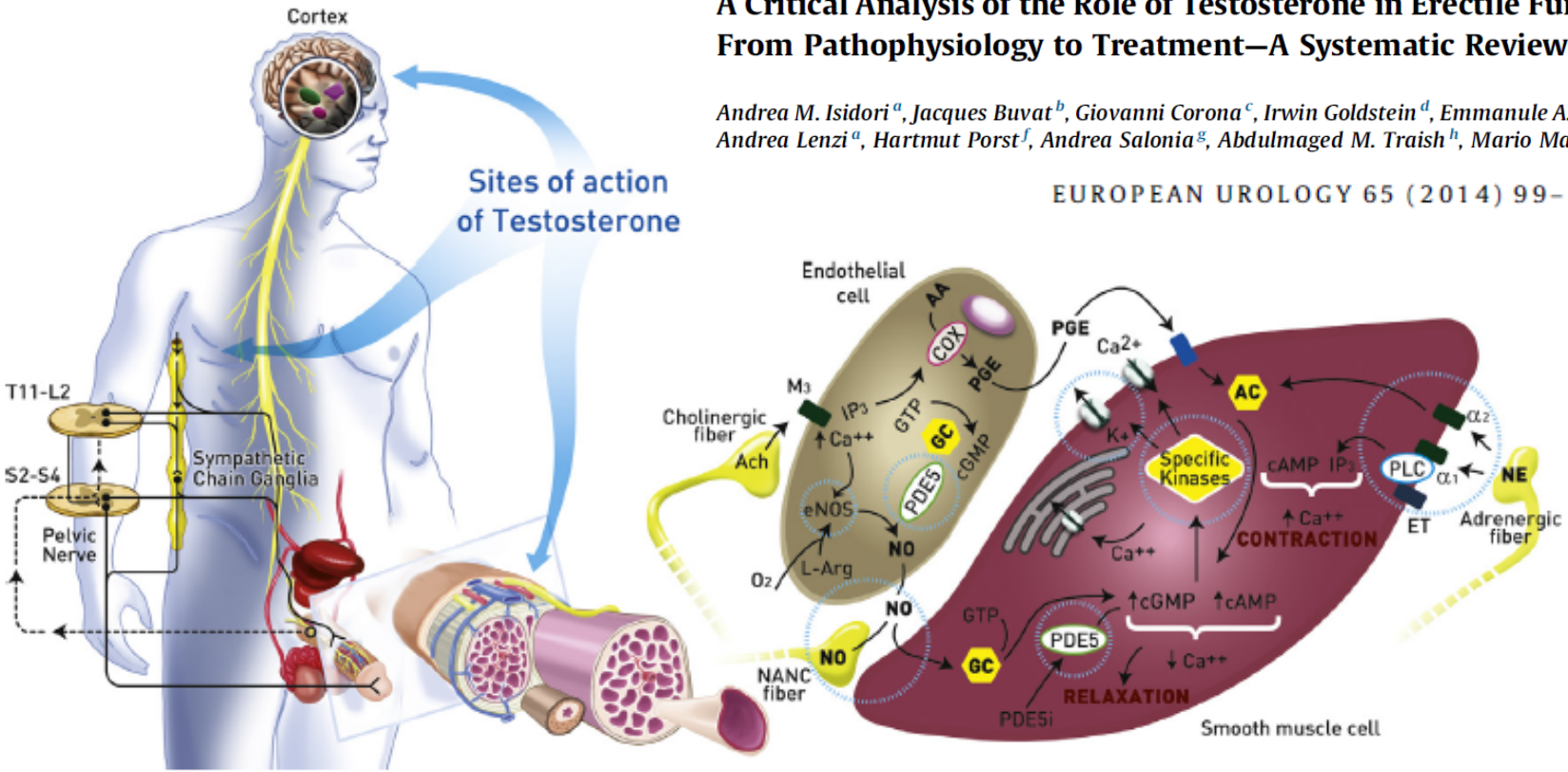
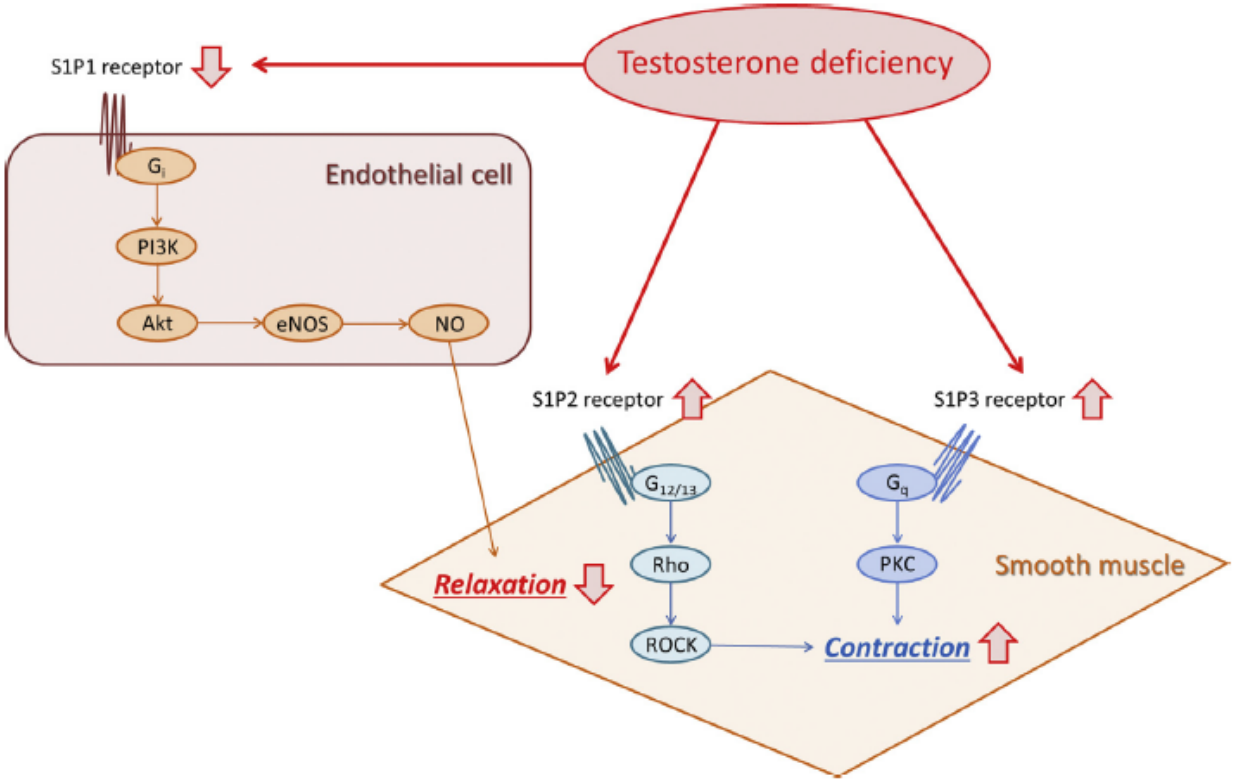


Fig. 2 – Sites of action of androgens in male sexual function. Blue arrows and dotted blue circles highlight the targets of testosterone. Ach = acetylcholin Ca^{2+} = calcium; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; eNOS = endothelial nitric oxide synthase; ET = endothelin; GC = guanylate cyclase; GTP = guanosine triphosphate; IP_3 = inositol triphosphate; K^+ = potassium; NANC = nonadrenergic-noncholinergic; NO = nitric oxide; PDE5 = phosphodiesterase type 5; PGE = prostaglandin E; AC = adenylate cyclase; NE = norepinephrine; PLC = phospholipase C.

Testosterone Deficiency and Endothelial Dysfunction: Nitric Oxide, Asymmetric Dimethylarginine, and Endothelial Progenitor Cells

Yuji Hotta, PhD,[1] Tomoya Kataoka, PhD,[2] and Kazunori Kimura, PhD[1,2] Sex Med Rev 2019;7:661-

Testosterone deficiency might cause endothelial dysfunction by decreasing NO levels through regulating the expression and activity of NO synthase and increasing ADMA expression. In addition, testosterone might affect the endothelial repair system by regulating the proliferation and migration of EPCs. Testosterone replacement therapy might be useful for treating endothelial dysfunction, considering that some reports have shown that this therapy improved NO bioavailability and EPC function



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

Giovanni Corona, MD, PhD,[1] Andrea M. Isidori, MD, PhD,[2] Antonio Aversa, MD, PhD,[2,3]
Arthur L. Burnett, MD, PhD,[4] and Mario Maggi, MD, PhD[5] *J Sex Med 2016;13:317–337.*

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 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).

EMAS position statement: Testosterone replacement therapy in the aging male

C. Dimopoulou et al. / Maturitas 84 (2016) 94–99

- Testing for testosterone deficiency should be only performed in men with symptoms of androgen deficiency; universal testosterone testing in aging males is not recommended (**1**|+◯◯◯).
- Symptoms compatible with androgen deficiency involve loss of libido, erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality and depressed mood (**1**|++◯◯).
- There is no consensus on the beneficial effects of TRT with regard to obesity, metabolic syndrome, type 2 diabetes mellitus, sexual function and osteoporosis (**2**|++◯◯).

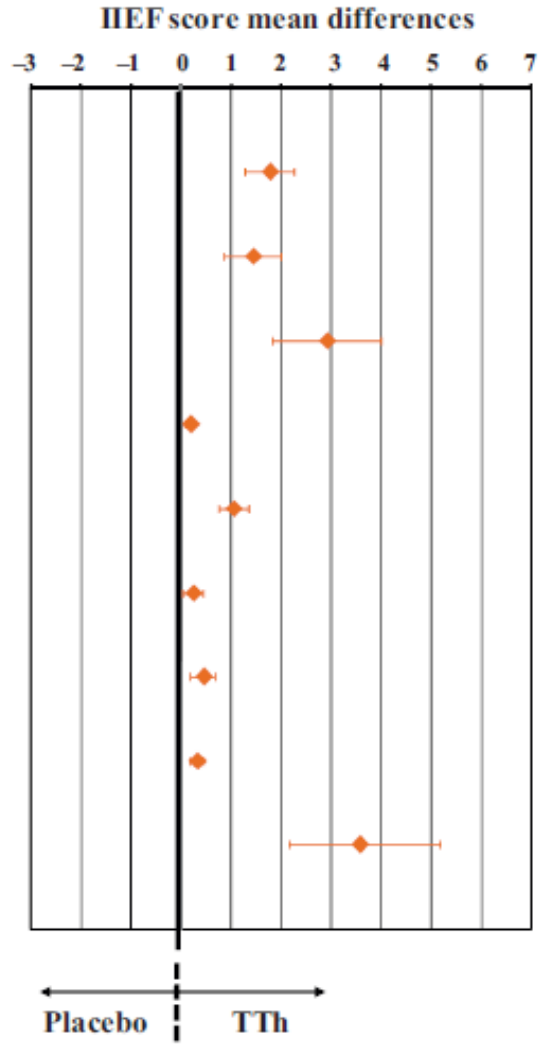
Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores

EUROPEAN UROLOGY 72 (2017) 1000–1011

Giovanni Corona[a], *Giulia Rastrelli*[b], *Abraham Morgentaler*[c], *Alessandra Sforza*[a], *Edoardo Mannucci*[b,d], *Mario Maggi*[b,*]

Evidence synthesis: Out of 137 retrieved articles, 14 were included in the study enrolling 2298 participants, with a mean follow-up of 40.1 wk and mean age of 60.2 ± 6.5 yr. Using IIEF-erectile function domain (IIEF-EFD) as the outcome, we found that TTh significantly improved erectile function compared with placebo (mean difference = 2.31 [1.41;3.22] IIEF-EFD score, $p < 0.0001$). Patients with more severe hypogonadism (total T < 8 nmol/l) reported greater changes in final IIEF-EFD score when compared with those with a milder T deficiency (total T < 12 nmol/l; 1.47 [0.90;2.03] and 2.95 [1.86;4.03] for total T < 12 nmol/l and <8 nmol/l, respectively, Q = 5.61, $p = 0.02$). The magnitude of the effect was lower in the presence of metabolic derangements, such as diabetes and obesity. Other aspects of sexual function, as evaluated by IIEF subdomains, were also improved with TTh including libido, intercourse satisfaction, orgasm, and overall sexual satisfaction.

A



IIEF domains	Diff. in mean	LL, 95% CI	UL, 95% CI	*p*	*N*
Overall erectile function domain	1.80	1.30	2.29	0.001	1806
TT < 12 nM	1.47	0.9	2.03	0.001	774
TT < 8 nM	2.95	1.86	4.03	0.001	1438
Libido domain	0.20	0.12	0.28	0.001	1269
Intercourse satisfaction domain	1.07	0.78	1.37	0.001	1269
Orgasm domain	0.27	0.06	0.48	0.010	1300
Paduch et al 2015 excluded	0.47	0.22	0.71	0.001	1224
Overall satisfaction	0.33	0.20	0.46	0.001	1269
Total IIEF-15 score	3.60	2.18	5.20	0.001	607

Evaluation and Management of Testosterone Deficiency: AUA Guideline

Mulhall THE JOURNAL OF UROLOGY® Vol. 200, 423-432, August 2018

Clinicians should make note of any patient-reported symptoms associated with low testosterone, such as reduced energy, reduced endurance, reduced sex drive, and changes in erectile function.[5,6]

14. **Patients should be informed that testosterone therapy may result in improvements in erectile function, low sex drive, anemia, bone mineral density, lean body mass, and/or depressive symptoms. (Moderate Recommendation; Evidence Level: Grade B)**

Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline

Shalender Bhasin J Clin Endocrinol Metab, May 2018, 103(5):1–30

Table 3. Symptoms and Signs Suggestive of T Deficiency in Men

Specific symptoms and signs
Incomplete or delayed sexual development
Loss of body (axillary and pubic) hair
Very small testes (<6 mL)
Suggestive symptoms and signs
Reduced sexual desire (libido) and activity
Decreased spontaneous erections, erectile dysfunction
Breast discomfort, gynecomastia
Eunuchoidal body proportions
Inability to father children, low sperm count
Height loss, low-trauma fracture, low BMD
Hot flushes, sweats

Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline

Sexual function. The commissioned systematic review and meta-analysis showed that T treatment in hypogonadal men with low libido is associated with significantly greater improvement in libido, erectile function, and sexual activity vs placebo (53–55). T does not significantly improve sexual function and activity in men who do not have low T concentrations in the hypogonadal range (56).

Phosphodiesterase 5 inhibitors can improve erectile function in eugonadal (57) and hypogonadal men (58). However, randomized controlled trials (RCTs) have failed to demonstrate further improvements in erectile function with the addition of T to an optimized regimen of phosphodiesterase 5 inhibitors (58, 59). T therapy does not improve ejaculatory function in men with low T concentrations and ejaculatory dysfunction (60).

The Efficacy and Adverse Events of Testosterone Replacement Therapy in Hypogonadal Men: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials

Oscar J. Ponce J Clin Endocrinol Metab, May 2018, 103(5):1745–1754

Results: We found four RCTs (including 1779 patients) at low risk of bias. Compared with placebo, TRT was associated with a small but significant increase in sexual desire or libido [standardized mean difference (SMD): 0.17; 95% confidence interval (CI), 0.01, 0.34; n = 1383], erectile function (SMD: 0.16; 95% CI, 0.06, 0.27; n = 1344), and sexual satisfaction (SMD: 0.16; 95% CI, 0.01, 0.31; n = 676) but had no effect on energy or mood. TRT was associated with an increased risk of developing erythrocytosis (relative risk: 8.14; 95% CI, 1.87, 35.40; n = 1579) compared with placebo but had no significant effect on lower urinary tract symptoms.

Conclusion: In hypogonadal men, TRT improves sexual desire, erectile function and sexual satisfaction; however, it increases the risk of erythrocytosis. (***J Clin Endocrinol Metab*** **103: 1745–1754, 2018)**

Lessons From the Testosterone Trials

Snyder et al Endocrine Reviews, June 2018, 39(3):369–386

ESSENTIAL POINTS

- Testosterone treatment of 1 year for older men with low testosterone improved all aspects of sexual function
- Testosterone treatment of 1 year for older men with low testosterone improved walking distance by a small amount
- Testosterone treatment of 1 year for older men with low testosterone did not improve vitality but slightly improved mood and depressive symptoms
- Testosterone treatment of 1 year for older men with low testosterone improved hemoglobin and corrected mild to moderate anemia
- Testosterone treatment of 1 year for older men with low testosterone markedly increased the volumetric bone mineral density and estimated bone strength
- Testosterone treatment of 1 year for older men with low testosterone increased the coronary artery plaque volume
- Testosterone treatment of 1 year for older men with low testosterone was not associated with more cardiovascular or prostate adverse events; however, the number of men and the duration of treatment were not sufficient to draw definitive conclusions about the risks of this treatment

Lessons From the Testosterone Trials

Snyder et al Endocrine Reviews, June 2018, 39(3):369–386

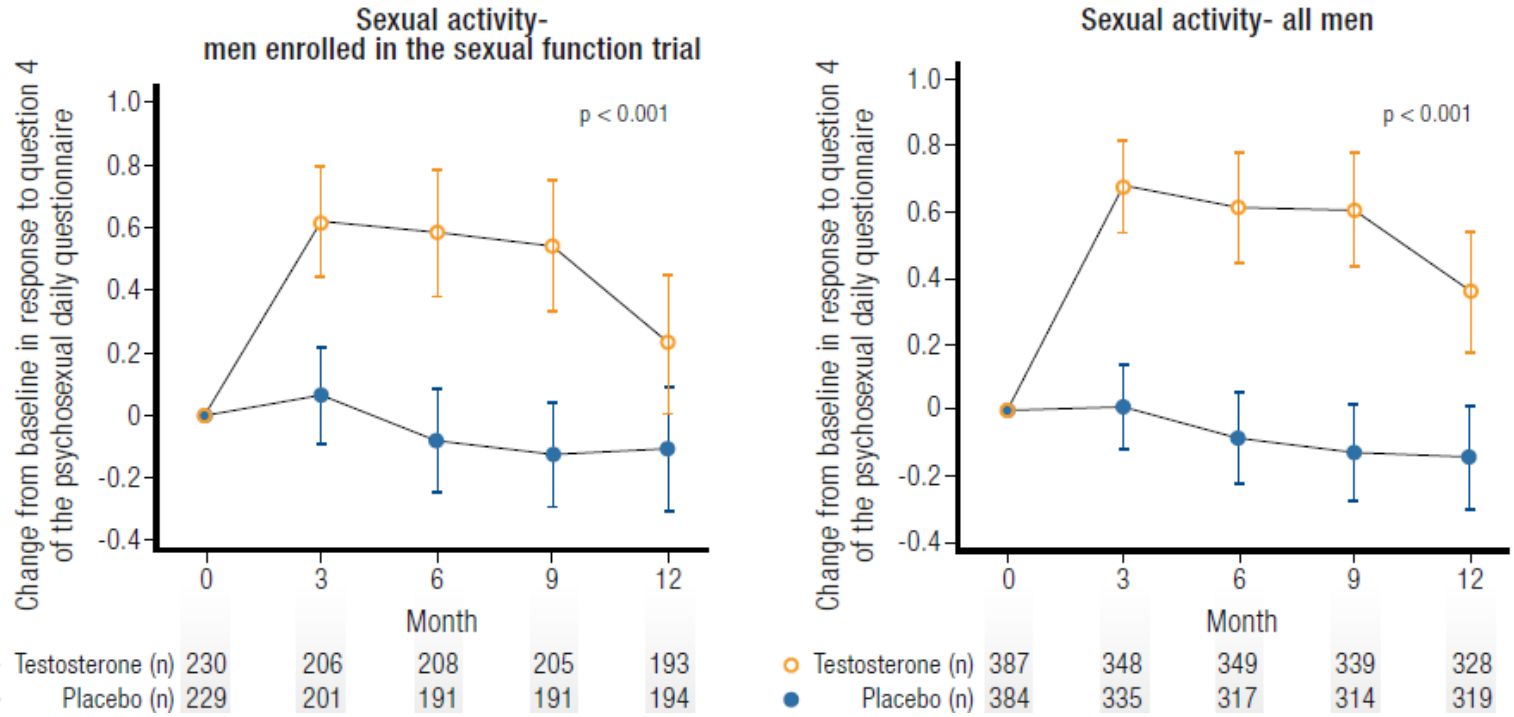
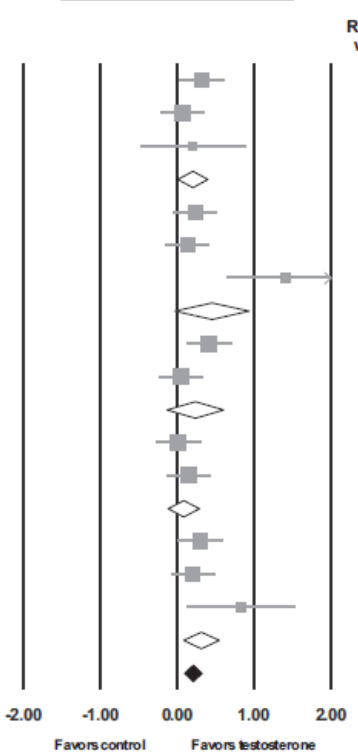


Figure 3. Effect of testosterone on sexual activity. Change from baseline in sexual activity, as assessed by the Psychosexual Daily Questionnaire, question 4, in (left) men taking testosterone or placebo and enrolled in the Sexual Function Trial and (right) all men enrolled in the TTrials. Data presented as means and 95% confidence intervals.

Testosterone therapy for sexual dysfunction in men with Type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials

M. Algeffari Diabet. Med. 35, 195–202 (2018)

Study name	Sexual Domains	Std diff in means	Lower limit	Upper limit	p-Value	Relative weight
Hackett, G (2013)	Erectile Function	0.326	0.036	0.615	0.027	45.98
Jones, (2011)	Erectile Function	0.079	-0.211	0.369	0.591	45.81
Dhindsa S, (2016)	Erectile Function	0.208	-0.477	0.892	0.553	8.21
		0.203	0.007	0.399	0.042	
Hackett, G (2013)	Intercourse satisfaction	0.240	-0.048	0.529	0.102	39.26
Jones, (2011)	Intercourse satisfaction	0.141	-0.146	0.429	0.336	39.29
Dhindsa S, (2016)	Intercourse satisfaction	1.410	0.649	2.171	0.000	21.46
		0.453	-0.032	0.937	0.067	
Hackett, G (2013)	Orgasm	0.425	0.134	0.715	0.004	49.75
Jones, (2011)	Orgasm	0.049	-0.237	0.335	0.736	50.25
		0.236	-0.132	0.604	0.209	
Hackett, G (2013)	Overall satisfaction	0.024	-0.264	0.311	0.871	50.20
Jones, (2011)	Overall satisfaction	0.147	-0.141	0.436	0.317	49.80
		0.085	-0.118	0.289	0.412	
Hackett, G (2013)	Sexual Desier	0.305	0.016	0.594	0.039	44.69
Jones, (2011)	Sexual Desier	0.209	-0.076	0.495	0.151	45.39
Dhindsa S, (2016)	Sexual Desier	0.834	0.122	1.545	0.022	9.93
		0.314	0.082	0.546	0.008	
		0.210	0.098	0.321	0.000	



What's new?

- We have performed the first meta-analysis evaluating the effectiveness of testosterone therapy on a range of sexual function domains in men with Type 2 diabetes.
- Evidence to date suggests that testosterone therapy may improve sexual desire and erectile function in men with Type 2 diabetes; however, heterogeneity among the results of included studies, limited participant numbers, and possible reporting bias greatly weaken these inferences.
- We conclude that testosterone therapy could be considered for men with Type 2 diabetes non-responsive to phosphodiesterase-5 inhibitors when risks and benefits of therapy are carefully considered, and other therapeutic options are unsuitable.

What are the benefits and harms of testosterone therapy for male sexual dysfunction?—a systematic review

K. Dimitropoulos et al.

IJIR: 27 March 2019

However, based on the data provided mainly by the RCTs included in this SR, it seems that TTh could indeed benefit hypogonadal and most probably borderline eugonadal men with sexual desire disorders, erectile dysfunction and impaired sexual satisfaction. These findings need to be approached cautiously, mainly due to the limitations having to do with the methodological inconsistency across studies. The need for robust and adequately designed clinical trials on T use for MSD is highlighted for future research, so that definitive results could be reached.

Diagnosis and Treatment of Testosterone Deficiency: Updated Recommendations From the Lisbon 2018 International Consultation for Sexual Medicine

Sex Med Rev 2019;7:636–649

Abraham Morgentaler, MD,[1] Abdulmaged Traish, PhD,[2] Geoffrey Hackett, MD,[3] T. Hugh Jones, MD,[4,5] and Ranjith Ramasamy, MD[6]

Recommendations

1. Sexual symptoms are a prominent presenting feature for men with TD (LOE 1, Grade A).
2. Testing for TD should be performed in men with decreased libido, ED, and/or difficulty achieving orgasm (LOE 2, Grade B).
3. Testosterone therapy may improve libido, erection quality, and other sexual symptoms (LOE 1, Grade A)
4. Testosterone therapy may salvage erectile function in men who have failed PDE5 inhibitors (LOE 2, Grade B).

Testosterone Replacement Therapy for Sexual Symptoms

Giulia Rastrelli, MD, PhD,[1] Federica Guaraldi, MD,[2,3] Yacov Reismann, MD,[4] Alessandra Sforza, MD,[3] Andrea M. Isidori, MD,[5] Mario Maggi, MD,[1] and Giovanni Corona, MD, Sex Med Rev 2019;7:464–475

Methods: A comprehensive PubMed literature search was performed.

Main Outcome Measure: Specific analysis of preclinical and clinical evidence on the role of T in regulating male sexual function was performed. In addition, available evidence supporting the role of TRT on several sexual outcomes was separately investigated.

Results: T represents an important modulator of male sexual response function. However, the role of T in sexual functioning is less evident in epidemiologic studies because other factors, including organic, relational, and intrapsychic determinants, can orchestrate their effect independently from the state of androgens. Nonetheless, it is clear that TRT can ameliorate several aspects of sexual functioning, including libido, erectile function, and overall sexual satisfaction. Conversely, data on the role of TRT in improving orgasmic function are more conflicting. Finally, further controlled studies are needed to investigate the combination of TRT and PDE5 inhibitors.

Conclusion: Positive effects of TRT are observed only in the presence of a hypogonadal status (ie, total T $<$ 12 nmol/L). In addition, TRT alone can be effective in restoring only milder forms of erectile dysfunction, whereas the combined therapy with other drugs is required when more severe vascular damage is present. **Rastrelli G,**

Testosterone Replacement Therapy for Sexual Symptoms

Giulia Rastrelli, MD, PhD,[1] Federica Guaraldi, MD,[2,3] Yacov Reismann, MD,[4] Alessandra Sforza, MD,[3] Andrea M. Isidori, MD,[5] Mario Maggi, MD,[1] and Giovanni Corona, MD, Sex Med Rev 2019;7:464–475

Table 2. Characteristics of the observational/registry studies evaluating the effect of testosterone replacement therapy on several sexual function parameters

						Sexual function parameters			
Study	No. of patients	Study name	Follow-up (mo)	T preparation	Mean age (y)	Libido	Erectile function	TRT + PDE5i	Ejaculation
Zitzmann et al[55]	1,438	IPASS	9–12	Long-acting injectable TU	49.2	↑	↑	↑	NA
Khera et al[56]	849	TRiUS	12	T gel 1%	51.2	↑	↑	NA	↑
Rosen et al[57]	750	RHYME	36	Mixed	59.1	↑	↑	↑	NA
Rastrelli et al[58]	1,954	SIAMS-NOI	12	Mixed	50.9	↑	↑	NA	↑
Permpongkosol et al[59]	428	Prospective registry	60	Long-acting injectable TU	65.6	↑	↑	NA	↑
Almehmadi et al[60]	261	Prospective registry	96	Long-acting injectable TU	58	NA	↑	NA	NA

IPASS = International, Post-Authorisation Surveillance Study Study; NA = not available; PDE5i = PDE5 inhibitor; RHYME = Registry of Hypogonadism in Men; SIAMO-NOI = Società Italiana di Andrologia e Medicina della sessualità-Osservatorio Nazionale Outcome Ipogonadismo; T = testosterone; TRiUS = Testim Registry in the United States; TRT = T replacement therapy; TU = testosterone undecanoate.

Testosterone R

Giulia Rastrelli, MD, P
Andrea M. Isidori, MD

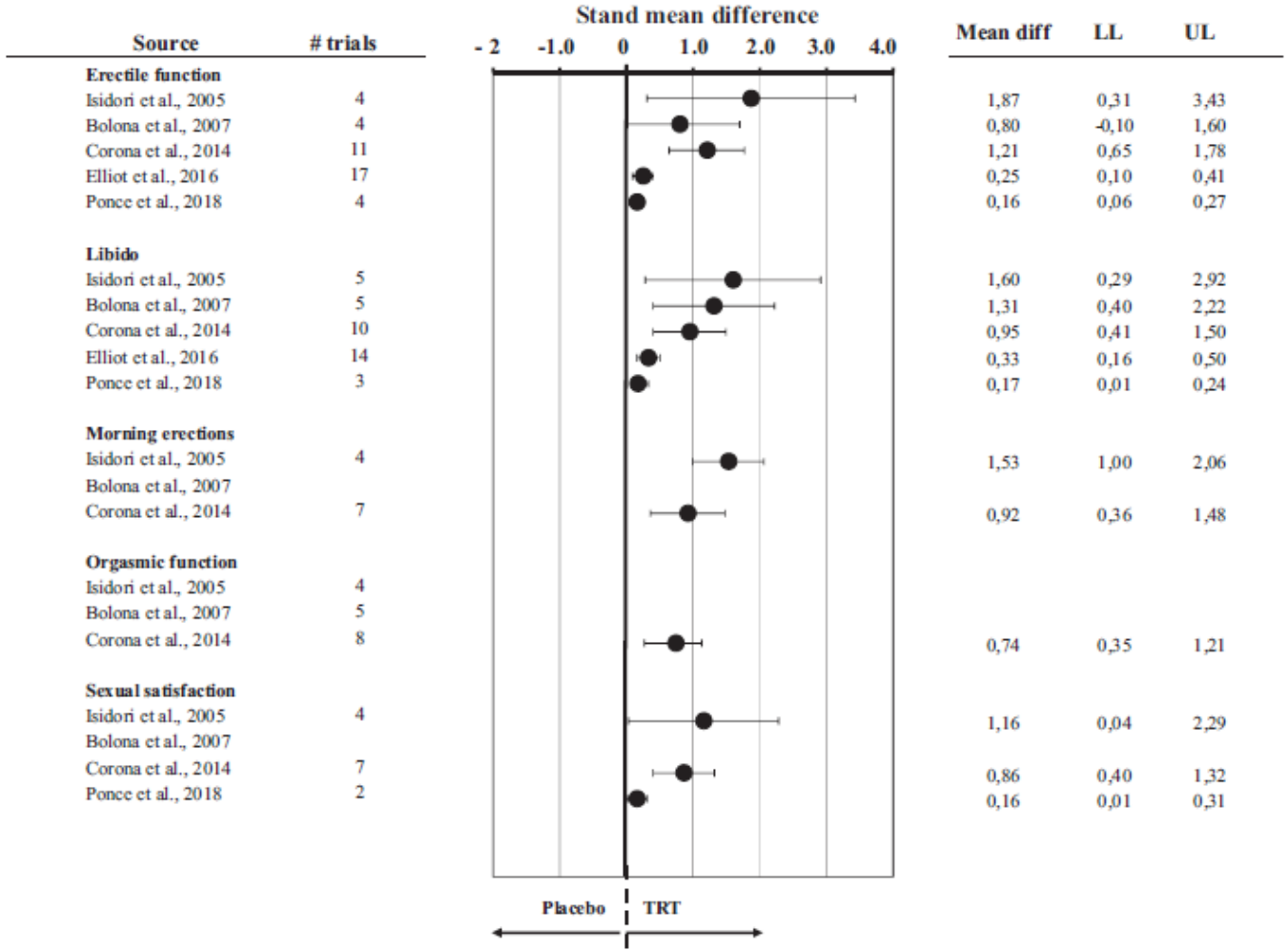
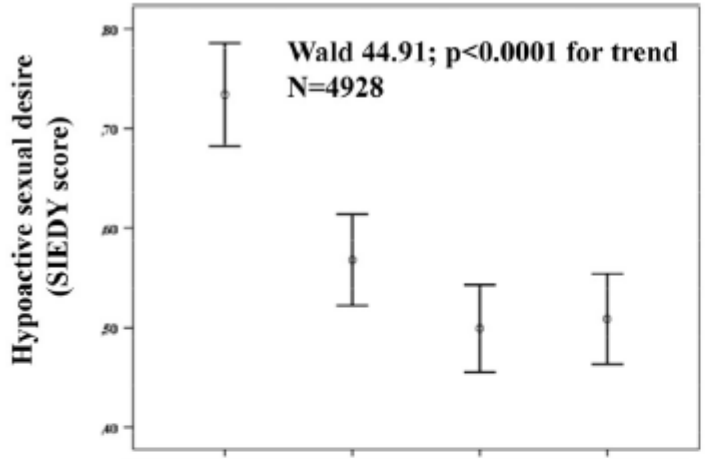
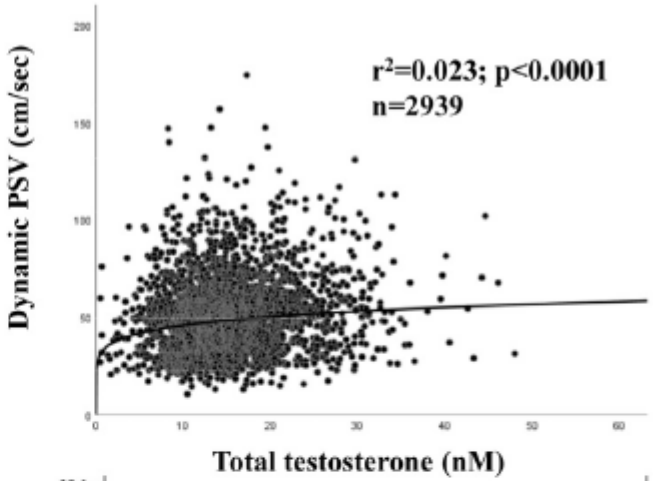


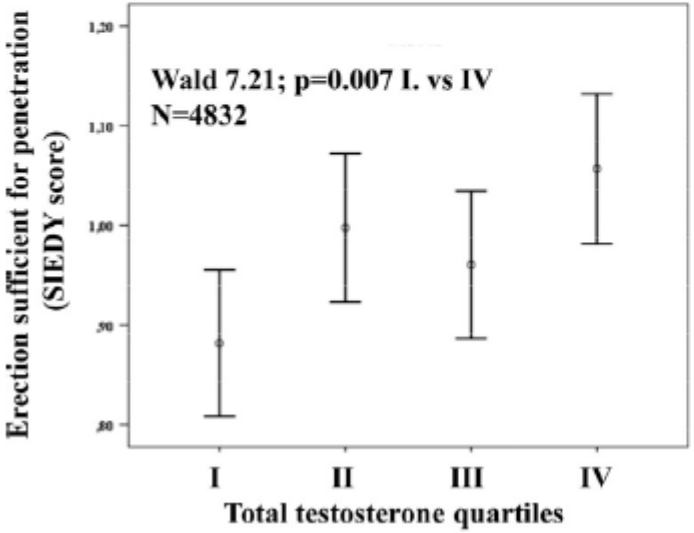
Figure 3. Summary of the results obtained by the available meta-analysis on the efficacy of testosterone replacement therapy (TRT) on sexual symptoms. Abbreviations: Diff = difference; LL = lower limit; UL = upper limit.

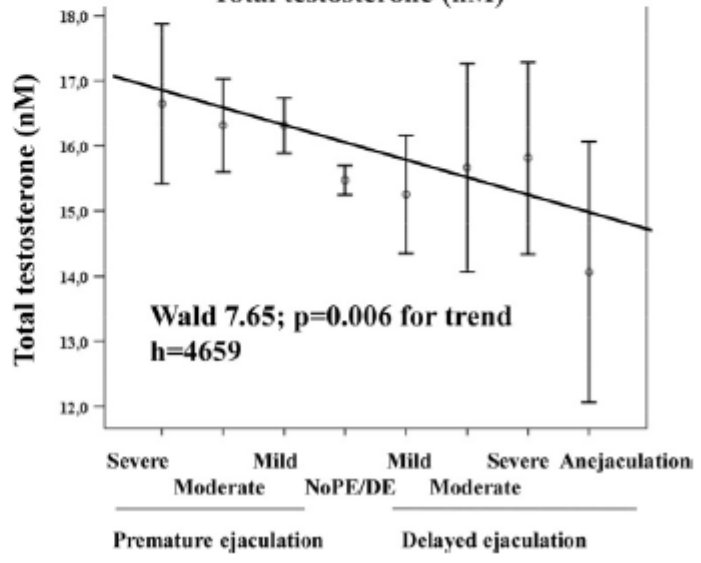
Testosterone Rep

Giulia Rastrelli, MD, PhD
Andrea M. Isidori, MD,[5]









Late-onset Hypogonadism and Testosterone Therapy – A Summary of Guidelines from the American Urological Association and the European Association of Urology

EUROPEAN UROLOGY FOCUS 5 (2019) 539–544

Mikkel Fode[a,*], *Andrea Salonia*[b,c], *Suks Minhas*[d], *Arthur L. Burnett*[e], *Alan W. Shindel*[f]

Table 1 – Summary of the main differences between the EAU and AUA guidelines.

EAU guidelines	AUA guidelines
Recommends measurement of free T in men with total T levels close to the lower normal range (8–12 nmol/l) or abnormal sex hormone-binding globulin levels	Does not recommend routine use of free T measurements
Defines the total T threshold of 12.1 nmol/l (349 ng/dl)	Defines the total T threshold of 10.4 nmol/l (300 ng/dl)
State that TT can improve sexual desire	Offers no definitive conclusion on the effects of TT on sexual desire
Does not directly state that TT can improve erections and recommends TT as an adjunctive ED in hypogonadal men with a poor response to PDE 5 inhibitors	States that TT may improve ED in hypogonadal men and considers TT as a first-line treatment
Recommends routine PSA monitoring in all patients on TT	Recommends only baseline DRE and PSA before treatment
Recommends that TT be "cautiously considered" at a minimum of 1 yr following curative treatment of low-risk PCA with no signs of recurrence	Recommends risk stratification of patients after curative PCA treatment and states that patients should be informed that there is inadequate evidence to quantify the risk-benefit ratio
States that TT may confer beneficial cardiac effects	States that the evidence on TT and cardiovascular risk is inconclusive

AUA = American Urological Association; DRE = digital rectal examination; EAU = European Association of Urology; ED = erectile dysfunction; PCA = prostate cancer; PDE 5 = phosphodiesterase type 5; PSA = prostate-specific antigen; T = testosterone; TT = testosterone therapy.

Guideline of guidelines: testosterone therapy for testosterone deficiency

Carolyn A. Salter and John P. Mulhall
2019 BJU International | doi:10.1111/bju.14899

Table 2 Populations for testosterone testing.

	Guideline						
	AUA	AACE	BSSM	EAU	Endocrine Society	ISSM	ISSAM
Chemotherapy	Yes	NR	NR	NR	NR	NR	NR
Testicular radiation	Yes	NR	NR	NR	NR	NR	NR
Chronic opioids	Yes	NR	Yes	Yes	Yes	Yes	Yes
Chronic corticosteroids	Yes	NR	Yes	Yes	Yes	Yes	Yes
Pituitary conditions	Yes	NR	NR	Yes	Yes	Yes	NR
DM	Yes	NR	Yes	Yes	Yes	Yes	Yes
Metabolic syndrome	NR	NR	NR	Yes	NR	Yes	Yes
Male infertility	Yes	NR	NR	Yes	Yes	Yes	NR
Decreased bone density	Yes	NR	NR	Yes	Yes	Yes	Yes
HIV/AIDS	Yes	NR	NR	Yes	Yes	Yes	NR
Unexplained anaemia	Yes	NR	NR	NR	NR	Yes	NR
ED	NR	NR	Yes	Yes	Yes	Yes	Yes
Low sex drive	NR	NR	Yes	Yes	Yes	Yes	Yes
COPD	NR	NR	No	Yes	NR	No	NR
Obesity	NR	NR	Yes	Yes	NR	Yes	Yes

COPD, chronic obstructive pulmonary disease; NR, no recommendation.

Roma, 7-10 novembre 2019

Testosterone e funzione sessuale
Francesco Romanelli

ITALIAN CHAPTER

«L'amore e il sesso stanno bene insieme, e va anche bene il sesso senza amore, e l'amore senza il sesso. Sono l'amore e il sesso individuali che vanno male.» ***Andy Warhol***

Testosterone e funzione sessuale

Roma, 7-

Conflitti di interesse

Ai sensi dell'art. 4.5 su "Docenti e moderatori dell'evento", pag. 8 del Manuale Nazionale di Accreditamento per l'erogazione di eventi ECM del 06/12/2018, dichiaro che negli ultimi 2 anni **non** ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.

Tanti auguri di buon compleanno per oggi 10 novembre 2019

Ennio Morricone 91

Mercedez 40

Eddie Irvine 54

What are the benefits and harms of testosterone therapy for male sexual dysfunction?—a systematic review

K. Dimitropoulos et al.

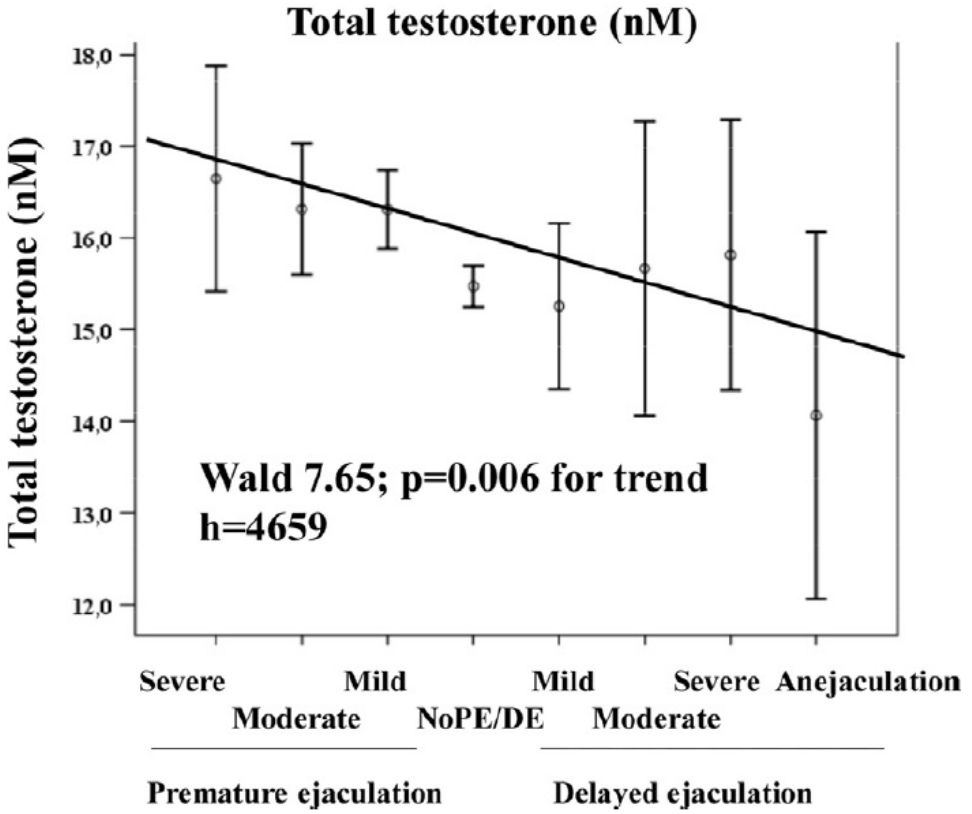
IJIR: 27 March 2019

The role of Testosterone Therapy (TTh) in the management of male sexual dysfunction remains unclear. Objective of the authors was to systematically review the relevant literature assessing the benefits and harms of TTh in men with sexual dysfunction. EMBASE, MEDLINE, Cochrane Systematic Reviews—Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane HTA, DARE, HEED), Google Scholar, WHO international Clinical Trials Registry Platform Search Portal, CINAHL databases and clinicaltrial.gov were searched systematically in March 2015 and an updated search was performed in March 2016. Randomized and non-randomized comparative studies assessing the benefits and harms of TTh in hypogonadal, borderline eugonadal and eugonadal men suffering from sexual dysfunction were included. Risk of bias and confounding assessments were performed. A narrative synthesis was undertaken. Of the 6410 abstracts identified, 36 studies were judged to be eligible for inclusion, including 25 randomized clinical trials (RCTs) and 11 non-randomized comparative studies (NRCSs), recruiting a total of 4944 patients. RCTs were judged to have low or unclear risk of bias, while NRCSs had high risk of bias and thus, overall quality of evidence was judged to be at least unclear. Based on the evidence mainly provided by the RCTs included in this systematic review, TTh could be considered for men with low or low-normal testosterone levels and problems with their sexual desire, erectile function and satisfaction derived from intercourse and overall sexual life. The exact testosterone formulation, dosage and duration of treatment remain to be clarified, while the safety profile of TTh also remains unclear. TTh could be used with caution in hypogonadal and most probably borderline eugonadal men to manage disorders of sexual desire, erectile function and sexual satisfaction. The overall low-to-moderate evidence quality highlights the need for robust and adequately designed clinical trials.

Testosterone Replacement Therapy for Sexual Symptoms

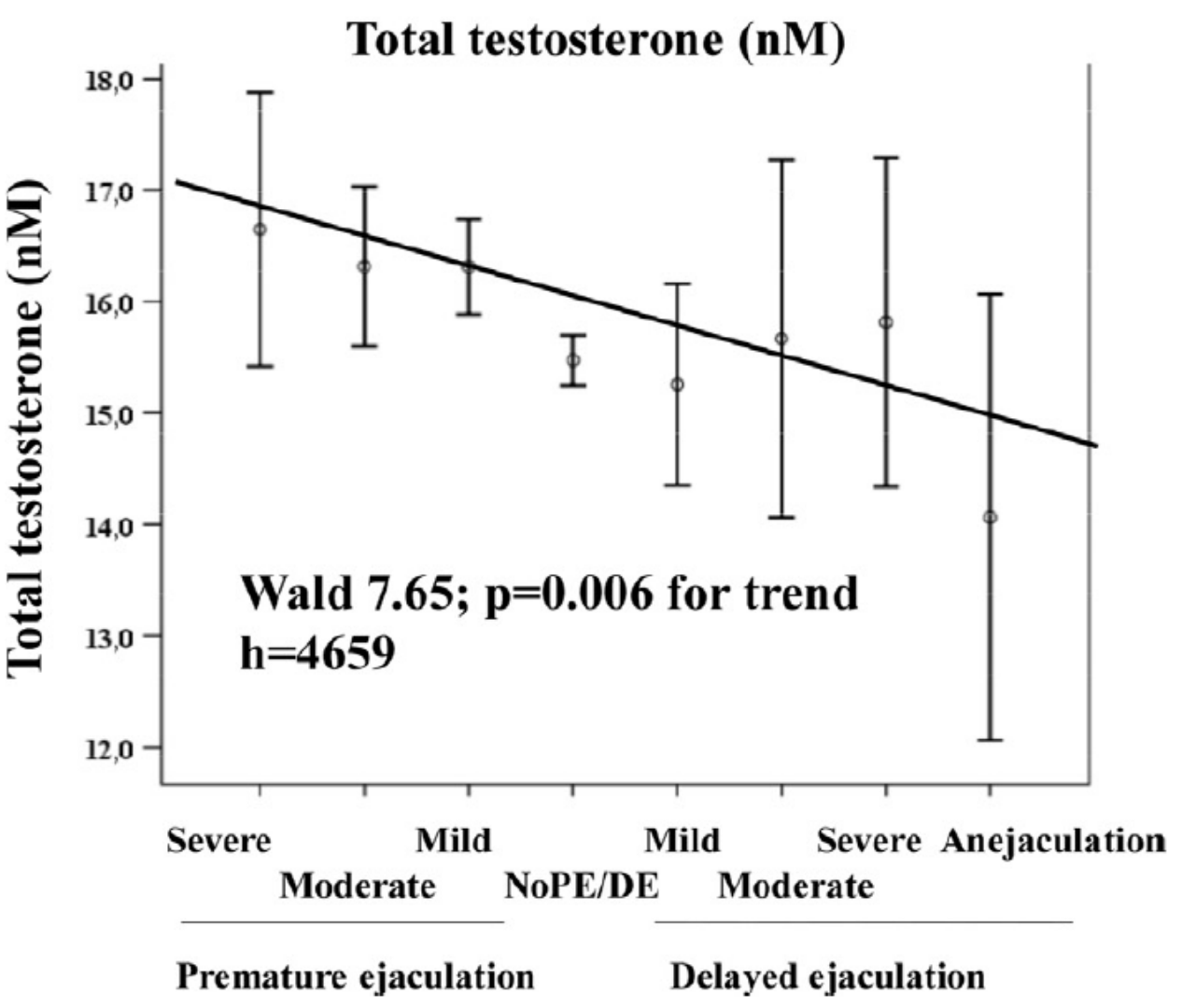
Giulia Rastrelli, MD, PhD,[1] Federica Guaraldi, MD,[2,3] Yacov Reismann, MD,[4] Alessandra Sforza, MD,[3] Andrea M. Isidori, MD,[5] Mario Maggi, MD,[1] and Giovanni Corona, MD, Sex Med Rev 2019;7:464–475

Overall, available data indicate that T represents an important modulator of all the steps involved in the regulation of the male sexual response cycle. This association is attenuated in the epidemiologic studies because, besides hormones, other factors including organic, relational and intrapsychic determinants can modulate androgens' role. Evidence arising from interventional studies confirms a possible role of TRT in ameliorating several aspects of sexual functioning including libido, erectile function and overall sexual satisfaction. Conversely, data on the role of TRT in improving orgasmic function are more conflicting and analyzed only in a limited number of RCTs. It is important to recognize that, whatever outcome is considered, the effects of TRT are clearly evident only in the presence of hypogonadal status (ie, total T < 12 nmol/L), whereas the positive effects of TRT are no longer confirmed for higher T levels. In addition, TRT alone can be effective in restoring only milder forms of ED, whereas the combined therapy with other drugs is required when more severe vascular damage is present.



Testosterone Replacem

Giulia Rastrelli, MD, PhD,[1] Federic
Andrea M. Isidori, MD,[5] Mario Ma



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

Giovanni Corona, MD, PhD,[1] Andrea M. Isidori, MD, PhD,[2] Antonio Aversa, MD, PhD,[2,3]
Arthur L. Burnett, MD, PhD,[4] and Mario Maggi, MD, PhD[5]
J Sex Med 2016;13:317–337.

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.

3. **The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs. (Moderate Recommendation; Evidence Level: Grade B)**

4. **Clinicians should consider measuring total testosterone in patients with a history of unexplained anemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction, and chronic corticosteroid use even in the absence of symptoms or signs associated with testosterone deficiency. (Moderate Recommendation; Evidence Level: Grade B)**

Clinicians should make note of any patient-reported symptoms associated with low testosterone, such as reduced energy, reduced endurance, diminished work and/or physical performance, fatigue, visual field changes (bitemporal hemianopsia), anosmia, depression, reduced motivation, poor concentration, impaired memory, irritability, infertility, reduced sex drive, and changes in erectile function.[5,6]

14. **Patients should be informed that testosterone therapy may result in improvements in erectile function, low sex drive, anemia, bone mineral density, lean body mass, and/or depressive symptoms. (Moderate Recommendation; Evidence Level: Grade B)**

Lessons From the Testosterone Trials

Snyder et al Endocrine Reviews, June 2018, 39(3):369–386

Lessons from the Sexual Function Trial

Testosterone improved most aspects of sexual function in older men with low testosterone, with the effect proportional to the increase in testosterone. The greater effects on sexual activity and libido than on erectile function are consistent with the postulated effects of testosterone and what has been observed in severely hypogonadal men. These results are also consistent with another placebo-controlled study for 16 weeks of a different testosterone gel in 751 men with a mean age 55 years who had low testosterone levels (22).

Late-onset Hypogonadism and Testosterone Therapy – A Summary of Guidelines from the American Urological Association and the European Association of Urology

EUROPEAN UROLOGY FOCUS 5 (2019) 539–544

Mikkel Fode[a,*], *Andrea Salonia*[b,c], *Suks Minhas*[d], *Arthur*

In summary, men with low sexual desire and ED may benefit from TT. Men with ED only should initially be offered ED-specific therapy. Given the complexity of human sexual responses, clinician judgment is of primary importance when instituting therapy. However, men with sexual dysfunction and normal T levels should not be offered TT [29].

There is no high-quality evidence of cognitive improvements with TT [38,39]. Data from RCTs have shown that TT may confer mild improvements in depressive symptoms and mood [33,40]. Evidence on TT effects on energy levels and QOL is conflicting [23,26,33,34,38,41].

Table 2 – Clinical symptoms and signs suggestive of LOH (adapted from the EAU and AUA guidelines).

General symptoms
Reduced energy and endurance
Diminished physical performance
Hot flushes
Physical changes
Reduced testis volume
Loss of body hair
Gynecomastia
Decrease in lean body mass and muscle strength
Visceral obesity
Sexual symptoms
Reduced sexual desire and sexual activity
Erectile dysfunction
Fewer and diminished nocturnal erections
Cognitive, mood, and quality-of-life–related symptoms
Changes in mood
Sleep disturbances
Depression
Diminished cognitive function
Associated conditions
Male-factor infertility
Metabolic syndrome
Insulin resistance and type 2 diabetes mellitus
Decrease in bone mineral density (osteoporosis) with low trauma fractures
Anemia

Long-term treatment with testosterone undecanoate injections in men with hypogonadism alleviates erectile dysfunction and reduces risk of major adverse cardiovascular events, prostate cancer, and mortality

THE AGING MALE
https://doi.org/10.1080/13685538.2019.1575354
Published online: 20 Feb 2019.

Farid Saad, Monica Caliber, Gheorghe Doros, Karim Sultan Haider & Ahmad

Results: TTh led to substantial and sustained reduction of ED; improvement in erectile function was significant for each successive year until year 9. This was accompanied by improvements in cardiometabolic risk factors and urinary function throughout the 12-year follow-up period. Benefits of TTh were stronger for patients with moderate/severe ED than for patients with no/minor ED. Incidence of prostate cancer, major adverse cardiovascular events, and mortality were significantly lower in men on TTh compared with untreated men.

Conclusion: Long-term TTh for up to 12 years alleviates ED, improves cardiometabolic risk factors, and reduces prostate cancer. Patients must stay on TTh consistently for a long time to achieve maximum benefits of TTh.

Male sexual dysfunction in obesity: The role of sex hormones and small fibre neuropathy

PLOS ONE | https://doi.org/10.1371/journal.pone.0221992 September 11, 2019

Jan Hoong Ho[1,2], Safwaan Adam[1,2], Shazli Azmi[2], Maryam Ferdousi[2], Yifen Liu[2], Alise Kalteniece[2], Shaishav S. Dhage[1,2], Brian G. Keevil[3], Akheel A. Syed[4], Basil J. Ammori[5], Tomás Ahern[6], Rachelle Donn[2], Rayaz A. Malik[2,7], Handrean Soran[1,2]*

Conclusion

Sexual dysfunction is highly prevalent in men with severe obesity. We found an association between small fibre neuropathy with erectile dysfunction with presence of diabetes a likely a significant contributing factor. We found no associations between testosterone levels with sexual symptoms (including frequency of sexual thoughts). The influence of small nerve fibre neuropathy on response to therapeutic interventions and whether interventions that improve small fibre neuropathy can improve erectile function in this population merits further study.

Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian society of endocrinology

A. M. Isidori · G. Balercia · A. E. Calogero · G. Corona · A. Ferlin · S. Francavilla · D. Santi · M. Maggi

J Endocrinol Invest (2015) 38:103–112

The decision as to whether or when to treat HG men to improve sexual symptoms remains problematic. ED generally has a multifactorial aetiology; vascular factors are predominant amongst the comorbidities and hamper the beneficial effects of TS. In young HG subjects, TS is often sufficient to improve sexual function. In older men, the low *T* level may be the consequence rather than the cause of ED [41]. A large number of HG ED patients could be safely treated with PDE5-I monotherapy and TS could be offered as an add-on treatment only for those with persistently low *T* levels, [39, 41]. The decision to start TS in older HG men depends on the patient's individual benefit/risk ratio.

11. We recommend TS for men with symptoms of low libido who have markedly reduced *T* levels ($T < 8$ nmol/L) to improve libido (1 ØØØO); whilst we suggest TS in men with *T* levels between 8 and 12 nmol/L (2 ØØØO).
12. We recommend that clinicians offer TS to men with erectile dysfunction (ED) who have markedly reduced *T* levels ($T < 8$ nmol/L), to improve erection (1 ØØØO).
13. In men with *T* levels between 8 and 12 nmol/L and ED, we suggest considering TS after having tried the established therapies to recover sexual function (2 ØØØO). In non-responders to phosphodiesterase 5 (PDE5) inhibitors who retain persistently low *T* levels, we suggest offering *T* therapy to improve erectile function (2 ØØOO).
14. We suggest that clinicians offer TS to men with low *T* levels ($T < 12$ nmol/L) to improve orgasmic function (2 ØOOO).

Guideline of guidelines: testosterone therapy for testosterone deficiency

Carolyn A. Salter and John P. Mulhall

2019 BJU International | doi:10.1111/bju.14899

We analysed the guidelines for testosterone therapy (TTh) produced by major international medical societies including: the American Urological Association, European Association of Urology, American Association of Clinical Endocrinologists, British Society for Sexual Medicine, Endocrine Society, International Society for Sexual Medicine, and the International Society for the Study of the Aging Male, and compared their recommendations.All the organisations were in general agreement concerning the following key points:

- Only men meeting the criteria for testosterone deficiency (TD) should be treated.
- Consider screening asymptomatic men with certain conditions that increase the risk of TD.
- Exogenous TTh causes impairment of spermatogenesis.
- There is no evidence that TTh causes prostate cancer.
- Men on TTh require careful laboratory monitoring.

Keywords

testosterone deficiency, testosterone, testosterone therapy, hypogonadism