CLINICAL PRACTICE UPDATE: TESTOSTERONE DEFICIENCY SYNDROME GUIDELINES

TESTOGEL® testosterone

Conditions that lead to hypogonadism, like Klinefelter's Syndrome, remain underdiagnosed.[1] Is it a patient who may have Klinefelter's Syndrome? Or a patient who has presented as simply tired and lethargic, and has lost interest in their sex life and you've considered testosterone as part of their treatment plan only to find it's just too hard and confusing?

Yet evidence is increasingly supporting a bi-directional link between low levels of testosterone and metabolic conditions like diabetes and obesity.[2] Guidelines now include various metabolic comorbidities as potential triggers to screen for testosterone levels,[3] but what exactly should you be looking for?

Sure, official recommendations have been published to guide physicians to better diagnose and treat patients with testosterone deficiency (TD),[4] but there's discordance. So how to make sense of it all? Here's seven golden rules to keep in mind when delving into the testosterone management space.

1. Consider the guideline author and audience

This one's a no-brainer, but it helps to put the recommendations in the context of who is writing them and for whom are they being written. National and international society clinical practice guidelines can often reflect the experience and interests of the specialty concerned and do not always agree.[4] Urologists and primary care physicians may have different standard operating procedures than endocrinologists and sexual medicine physicians.[5]

In this review we'll consider national and international guidelines for the diagnosis and management of testosterone deficiency (TDS) – which you'll also see referred to as 'male hypogonadism' – from urological, sexual medicine and endocrinological societies (Table 1).

TABLE 1. Guidelines for the management of TDS

UROLOGY, SEXUAL MEDICINE AND MULTIDISCIPLINARY GUIDELINES		ENDOCRINOLOGY GUIDELINES	
SOCIETY	REFERENCE	SOCIETY	REFERENCE
American Urological Association (AUA)	Mulhall 2018	American Association of Clinical Endocrinologists (AACE)	Petak 2002
British Society for Sexual Medicine (BSSM)	Hackett 2017	Endocrine Society of Australia (ESA)	Yeap 2016a and Yeap 2016b
Canadian Medical Association (CMA)	Morales 2015	US Endocrine Society (ES)	Bhasin 2018
European Academy of Andrology (EAA)	Corona 2020		
European Association of Urology (EAU)	Dohle 2019		
International Society for the Study of the Aging Male (ISSAM)	Lunenfeld 2015		
International Society for Sexual Medicine (ISSM)	Khera 2016		

2. Be clear on how TDS is defined

The good news is that for the most part, the diagnostic criteria for defining TDS is generally similar across all guidelines (Table 2).[6-16] A diagnosis of TDS requires the clinical manifestation of TD (signs and symptoms), together with documented biochemical evidence of TD.

However, what guidelines do not seem to align on is what TDS looks like. Clinical manifestations of TDS are variable (Table 2).[6-16] Some guidelines get 'more specific' and 'less specific', as in the BSSM, ES, EAA and the EAU guidelines, while some others choose to list common conditions. One thing the majority of guidelines do agree on is that the use of validated questionnaires is not recommended to define which patients are candidates for T therapy. Screening questionnaires, while sensitive, generally have low specificity.[17]

TABLE 2. Comparison of the societal recommendations for the diagnosis, management and monitoring of TDS

	GUIDELINE									
	ESA[6,7]	BSSM[8]	AUA[9]	ES[10]	AACE[11]	ISSM[12]	EAU[13]	CMA[14]	ISSAM[15]	EAA[16]
CLASSIFICATION OF TDS SYMPTOMS	Non-specific, organ-specific and sexual and reproductive symptoms and signs	Sexual, cardiometabolic, physical and psychological symptoms and signs	Symptoms associated with low testosterone; Signs associated with low testosterone	Specific, suggestive and non-specific symptoms and signs	Sexual and non-sexual symptoms, and signs	Sexual, physical, psychological, cognitive symptoms	More specific sexual, physical and psychological symptoms; less specific sexual, physical and psychological symptoms.	Sexual, somatic and psychological symptoms and signs	Sexual and non-sexual symptoms, and signs	Specific and less-specific symptoms and less-specific signs
TT										
THRESHOLD (NMOL/L)	7.4 in young men and 6.6 men older than 70y	8	10.4	9.2	N/A	12	8	Local laboratory ranges	12.1	8
ASSAY	LCMS	Reliable assay	LCMS	Reliable assay	N/A	LCMS	LCMS or immunoassay	Reliable assay	LCMS	Reliable assay
TIMING	Early morning	Early morning; fasting	Early morning	Early morning; fasting	Early morning	Early morning	Early morning; fasting	Early morning	Early morning	Early morning; fasting
REPEATED TEST REQUIRED	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
FT										
WHEN TO BE USED	Not recommended	If TT low-normal; if SHBG abnormal	[illegible] equivocal range	[illegible] plus SHBG-altering condition	[illegible] If low or low-normal TT	[illegible] not confirmed with TT; in obese men	If TT low-normal; if SHBG abnormal	with TT in equivocal range	If TT does not correspond with clinical presentation; Obese men	If TT low-normal; if SHBG abnormal
THRESHOLD (PMOL/L)	N/A	225	N/A	N/A	N/A	N/A	220	N/A	225-243	220
ASSAY	N/A	Calculated	Equilibrium dialysis	Equilibrium dialysis or calculated	Equilibrium dialysis	Equilibrium dialysis or calculated	N/A	N/A	Equilibrium dialysis or calculated	Equilibrium dialysis or calculated
BORDERLINE TT LEVELS (NMOL/L)		8-12		N/A	N/A	Low-normal, especially in obese or older men	8-12	Symptomatic		8-12
TREATMENT FOR BORDERLINE T LEVELS		TRT trial for 3-6 months based on symptoms		N/A	N/A	TRT trial of 6-12 months if symptomatic	N/A	TRT trial for 3 months	N/A	TRT trial for 3-6 months
ASSESSMENT OF T CLINICAL RESPONSE AND SIDE EFFECTS	3 months, annually	3, 6 and 12 months, annually	Every 6-12 months	3-6 and 12 months, annually	3 to 4 month intervals	3, 6 and 12 months, annually	3, 6 and 12 months, annually	3 and 6 months, annually	3-4 and 12 months, annually	3 and 12 months, annually
TARGET T RANGE FOLLOWING TREATMENT (NMOL/L)		15-30	15.6-20.8	Mid-normal	9.7-27.8	Mid-normal	Mid-normal	14-17.5	Normal	Mid-normal

CLICK TO ENLARGE

AACE: American Association of Clinical Endocrinologists; AUA: American Urological Association; BSSM: British Society for Sexual Medicine; EAA: European Academy of Andrology; ES: Endocrine Society (US); ESA: Endocrine Society of Australia; FT: Free testosterone; ISSAM: International Society for the Study of the Aging Male; ISSM: International Society for Sexual Medicine; N/A: no recommendation made; TT: total testosterone.

3. Who to test?

There is consensus amongst guidelines that there is no evidence supporting the universal screening for TDS and that serum T should be measured in men exhibiting classical clinical features of TDS. However, differences exist around what constitutes the symptomatic patient, and this is where much of the recommendations appear to differ. Some guidelines still refrain from screening men with comorbidities, while others have now added a long laundry list of comorbidities in whom screening should be performed (Table 2).[6-16]

4. Total? Free? How should T levels be assessed?

Accurate T assays are important to a diagnosis of TDS. The laboratory findings for TDS includes total T (TT), free T (FT), sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH), and luteinising hormone (LH). While the analysis of TT is warranted, the laboratory thresholds for a diagnosis of TDS vary amongst the organisations and no consensus has been reached regarding the lower TT threshold defining TDS (Table 2).[6-16] In addition, there are no generally accepted lower limits of normal TT, ranging from 9.2 nmol/L to 12.1 nmol/L.[10,15]

T is a highly-variable hormone and its levels are influenced by age, genetic background, ethnicity, lifestyle factors and comorbidities with significant intra-individual variations. Therefore, the diagnostic approach recommended by most guidelines is at least 2 measurements of TT, preferable 4 weeks apart. All guidelines agree that liquid chromatography /mass spectrometry (LCMS) should be used to measure TT where possible but also recognise that this technology may not be available at every institution. The validity of free T remains under debate. Free T is commonly calculated, but the result can vary according to the method of calculation and there is no established reference range for calculated free T.[17]

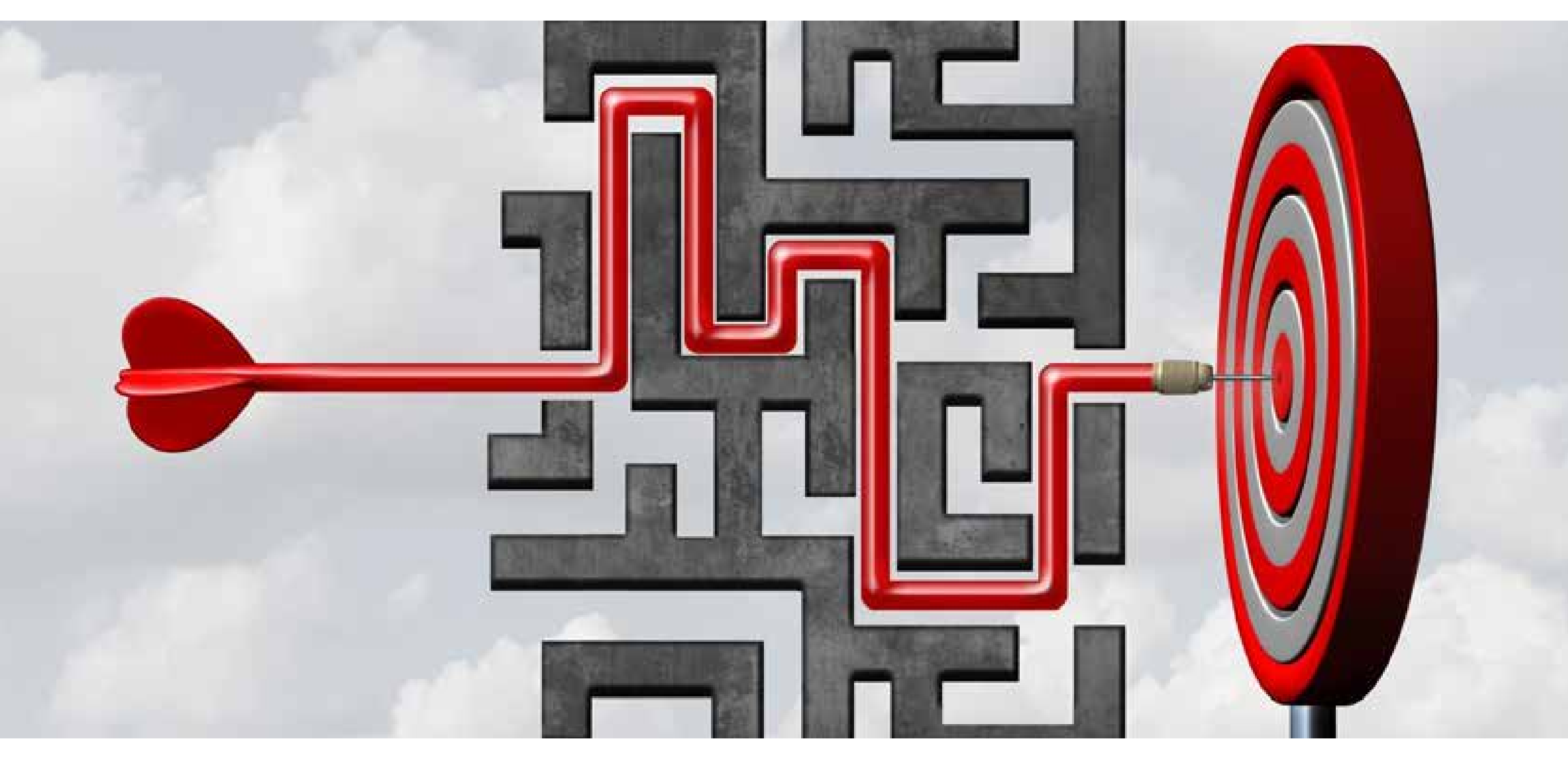
The assessment of gonadotropins is required to determine the origin of the TD.[8] Guidelines discuss how, in patients with low T, serum LH should be measured to establish the aetiology of TDS. Serum prolactin levels should also be measured in patients with low testosterone levels combined with low or low/normal LH levels to screen for hyperprolactinemia. In men with repeated low T, normal prolactin and low-normal LH values, the AUA guidelines recommend a diagnosis of TDS and treating with T therapy.[9]

5. Is it a yes or a no? Interpreting the test result

So, you've got his results in front of you and it's borderline. What do you do? It's unhelpful that guidelines are not clear cut on this. It comes down to the numbers AND the clinical situation. The ISSM and BSSM endorses a trial of T therapy for at least 6 months in symptomatic men with consistently lower TT levels of 8-12 nmol/L, and high levels of LH (indicating Leydig cell impairment) or SHBG (indicating lower free T calculated by mass action formula).[8,12] Similarly, the CMA advocates a 3 month trial of T therapy in men with uncertain biochemical results but a convincing clinical picture.[14]

With a verified diagnosis of TDS i.e., in the presence of characteristic symptoms with unequivocal biochemical findings of low T, all guidelines agree that testosterone replacement therapy is indicated.

In some cases, guidelines get specific about whether the cause is 'reversible' or 'irreversible'.[17] For example, the ES and ESA guidelines do not recommend T treatment for men with intrinsically intact HPT axis and potentially reversible suppressed function due to other causes, such as obesity.[18] However other urological, sexual medicine and endocrinological societies focus less on differentiating between irreversible and potentially reversible hypogonadism and generally define TDS as an over-arching diagnosis.



6. Time to take action, what to do?

The EAA and EAU recommend that patients should be encouraged to improve lifestyle, obese men should be encouraged to lose weight and comorbidities treated before starting T therapy[13] while the AUA and BSSM state that patients with TDS who are overweight or obese should be counselled regarding weight loss programs concurrent with T therapy.[9] The ESA considers low T in this context to be a consequence of underlying poor health and does not support T treatment in these men.

In symptomatic men with low serum T and erectile dysfunction, the EUA encourages the use of PDE5-inhibitors ahead of T therapy. The ISSM particularly encourages HCPs to consider T therapy in men that are suspected will not adequately adhere to the recommended modifications to diet, behaviour and exercise. The EAU confirmed weight loss to be the first approach for all overweight and obese men with TDS, while recognising the increase in TT levels observed after lifestyle measures to be modest and the benefit possibly lower compare with TRT.[13]

7. What target do you aim for?

While the goal of testosterone therapy is the normalisation of TT levels combined with improvement in symptoms or signs, the guidelines are divergent with respect to the recommended target serum TT levels in patients with TDS (Table 2).[6-16]

All patients should undergo a baseline measurement of haemoglobin/haematocrit (Hct) prior to commencing T therapy and if the Hct exceeds 50%, TRT should be withheld until the aetiology is formally investigated. While one on TRT, Hct over 54% warrants intervention, such as dose reduction or temporary discontinuation. While the incidence of polycythaemia for one particular T formulation compared to another cannot be determined, trials have indicated that injectable T is associated with the greatest treatment-induced increases in haemoglobin/Hct.[14] Most groups advise checking T levels at 3, 6 and 12 months and then annually thereafter with dose adjustments or change of preparation as necessary (Table 2).[6-16]

The guidelines generally accepted that TRT is not harmful to prostate health however PSA should always be evaluated. In cases of rising PSA levels > 1.4 ng/mL within 1 year from starting TRT or if PSA level is >4 ng/mL at any follow-up, the ES and EAA recommend urological consultation. In contrast, the ESA position statement recommends against routine PSA monitoring because it could lead to over-diagnosis.[7]

The EAA recommends the use of transdermal T as the preferred preparation in the initiation of T treatment, particularly in older subjects with comorbidities.[16] Cessation of TRT should be considered in patients with normalised T levels but no improvement in signs or symptoms of TDS 3-6 months after commencement of treatment.[9,16]

Conclusions

There are considerable differences in recommendations for diagnosis of TDS and eligibility for T therapy may vary depending on the guidelines used. While clinical guidelines represent the best evidence available from the experts, guideline recommendations should never replace clinical expertise.

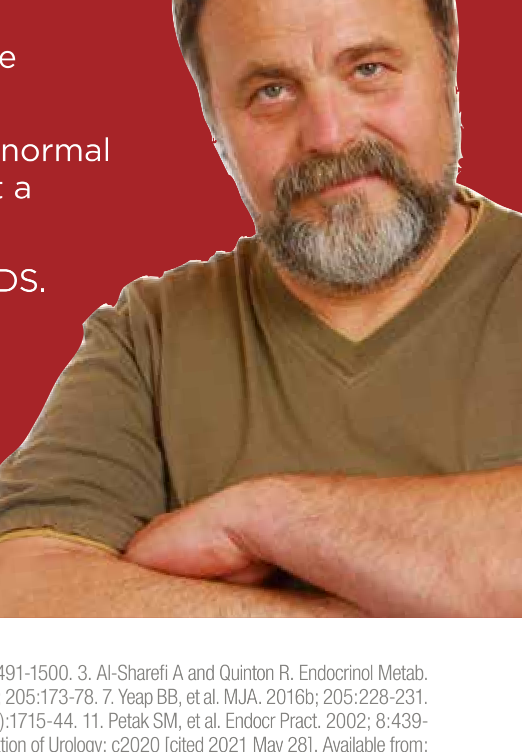
Testosterone therapy guidance diverges on the following points:

- Terminology: some guidelines remain with male hypogonadism while some guidance refers to the new descriptor, TDS.
- Laboratory thresholds for a diagnosis of TDS and the influence of LH, SHBG and free T levels on prescribing practices.
- Disagreement whether threshold levels be applied irrespective of the patient's age and/or comorbidities.
- Whether HPT axis suppression due to comorbidities such as obesity should be considered a form of hypogonadism.
- Patients that should be screened for low T, even in the absence of relevant signs or symptoms.
- Whether obesity or the presence of metabolic syndrome is a valid reason for investigating TDS.
- T treatment for men with borderline T levels.
- Monitoring criteria.

ALIGNMENTS AND DISCORDANCE

All major organisations generally agree on the following for the management of men with TDS:

- The formal definition of TDS was consistent and included abnormal clinical findings and biochemistry. Low TT is used to support a diagnosis of TDS.
- There is no evidence supporting the universal screening for TDS.
- Only men meeting the criteria for TDS should be offered treatment.
- Certain conditions increase the risk of TDS. Consider screening asymptomatic men with these conditions for TD.
- On-going laboratory monitoring is recommended for men on testosterone therapy.



References: 1. Bearelly P and Oates R. F1000Res. 2019;8:F1000 Faculty Rev-112. 2. Ottarsdottir K, et al. Endocr Connect. 2018;7(12):1491-1500. 3. Al-Sharefi A and Quinton R. Endocrinol Metab. 2020; 35:526-40. 4. Park HJ, et al. J Clin Med. 2019; 8:410. 5. Hackett G. Ther Adv Urol. 2016; 8:147-60. 6. Yeap BB, et al. MJA. 2016a; 205:173-78. 7. Yeap BB, et al. MJA. 2016b; 205:228-231. 8. Hackett G, et al. J Sex Med. 2017; 14:1504-23. 9. Mulhall JP, et al. J Urol. 2018; 200:423-32. 10. Bhasin S, et al. JCEM. 2018; 103(5):1715-44. 11. Petak SM, et al. Endocr Pract. 2002; 8:439-456. 12. Khera M, et al. J Sex Med. 2016; 13:1787-1804. 13. Dohle GR, et al. Male hypogonadism [Internet]. Arnhem: European Association of Urology; c2020 [cited 2021 May 28]. Available from: https://uroweb.org/guideline/male-hypogonadism. 14. Morales A, et al. CMAJ. 2015; 187:1369-77. 15. Lunenfeld B, et al. Aging Male. 2015; 18:5–15. 16. Corona G, et al. Andrology. 2020; 8:970-87. 17. Giagulli VA, et al. Andrology. 2020;8:1628-1641. 18. Yeap BB & Wu FCW. Clin Endocrinol. 2019; 90:56-65.

BESINS HEALTHCARE Innovating for Wellbeing

Besins Healthcare Australia Pty Ltd. ABN 68 164 882 062.
Suite 5.02, 12 Help St Chatswood NSW 2067.
Office phone (02) 9904 7473.
For medical information call 1800 BESINS (237 467). www.besins-healthcare.com.au
TES-1322. Approval date Novmeber 2021.

TESTOGEL® testosterone