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REVIEW

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Clinical practice update on testosterone therapy for male hypogonadism: Contrasting perspectives to optimize care

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Abstract

US Endocrine Society (ES) published a clinical practice guideline on testosterone therapy in men with hypogonadism, and Endocrine Society of Australia (ESA) a position statement on management of male hypogonadism. Both emphasize the importance of diagnosing men who are androgen deficient due to organic (classical or pathological) hypogonadism arising from disorders of the hypothalamus, pituitary or testes, who assuredly benefit from testosterone therapy. Both recognize that men with an intact gonadal axis may have low testosterone concentrations, for instance older men or men with obesity or other medical comorbidities. ES guidelines classify such symptomatic men as having organic (advanced age) or functional (obesity, medical comorbidities) hypogonadism, giving an option for testosterone therapy as a shared decision between clinicians and individual patients. ESA did not recommend testosterone therapy in these men. ES offers a reference range for total testosterone established in young men, while ESA cites age-standardized reference ranges. ES recommends using free testosterone as well as total testosterone to identify men with hypogonadism in conditions where sex hormone-binding globulin (SHBG) is altered, or when total testosterone is borderline. ESA recommends confirmatory biochemical testing with total testosterone, recognizing that this may be lower than expected if SHBG concentrations are low. Both emphasize the importance of identifying pre-existing prostate and cardiovascular disease prior to initiating testosterone therapy, with ES providing specific recommendations for PSA measurement, deferring testosterone therapy after major cardiovascular events and indications for pituitary imaging. These contrasting approaches highlight gaps in the evidence base where individualized patient management is required.

KEYWORDS

ageing, androgen deficiency, cardiovascular disease, free testosterone, male hypogonadism, prostate, testosterone

1 | INTRODUCTION

Hypogonadal men may present with symptoms and signs of androgen deficiency or with impaired fertility. Identifying and confirming the diagnosis in such men facilitates appropriate management including the use of testosterone therapy to reverse the symptoms and signs of androgen deficiency.[1,2] The US Endocrine Society (ES) published a Clinical Practice Guideline on testosterone therapy in men with hypogonadism.[1] The authors comprised ten experts in the field, nine from the United States and one from the UK, and updated the previous ES guideline.[3] They formulated and graded the evidence-based recommendations following the approach recommended by the Grading of

Recommendations, Assessment, Development and Evaluation Group (GRADE).[4] The Endocrine Society of Australia (ESA) published a Position Statement on the management of male hypogonadism, addressing assessment and indications for testosterone therapy[2] and treatment and therapeutic considerations.[5] The authors comprised eleven Australian endocrinologists with recognized clinical and/or research interests in this area, and updated a prior consensus guideline from ESA.[6]

While there are clear areas of agreement between the ES and ESA recommendations, there are also substantive differences. This review will summarize areas of agreement where the recommended clinical practice is widely accepted, and discuss in greater depth the rationale and evidence (or lack of evidence) underlying contrasting recommendations. The implications of the Testosterone Trials (T-Trials)[7,8] are considered. The contrasts between the ES and ESA recommendations provide insight into areas where the evidence base is incomplete, necessitating individualized management of men presenting with symptoms suggestive of androgen deficiency.

2 | ORGANIC OR PATHOLOGICAL HYPOGONADISM

Both ES and ESA recommend testosterone therapy for men with symptoms and signs of androgen deficiency (Figure 1) due to disorders of the hypothalamus, pituitary or testes. While ES preferred the broader term organic (also referred to as classical) hypogonadism,[1] these men are referred to as having pathological hypogonadism by ESA.[2] The ES recommends making a diagnosis of hypogonadism only in men with symptoms and signs consistent with testosterone deficiency and unequivocally and consistently low serum testosterone concentrations, defining a clinical syndrome related to the presence of low testosterone.[1] However, ES recognizes that these men fall into two categories, those with organic (or classical) hypogonadism, and men with an intact hypothalamo-pituitary-testicular (HPT) axis whose function is suppressed in various conditions but may be potentially reversible. These men are categorized as having functional hypogonadism (Figure 2). ESA recommends making a clinical diagnosis with a pathological basis, confirmed by hormone assays. The emphasis is on identifying men with pathological hypogonadism as the primary criterion for testosterone therapy, albeit with allowance for individualizing management in certain circumstances (Figure 3).

Both ES and ESA differentiate primary hypogonadism due to testicular disease (where gonadotrophin concentrations, luteinizing hormone [LH] and follicle-stimulating hormone [FSH], are elevated) from secondary disease involving the hypothalamus or pituitary (where LH and FSH are low or normal) (Figure 2). Both ES and ESA highlight the importance of assessing testicular volumes to identify

Symptoms and signs of androgen deficiency

ES Guideline

Non-specific symptoms and signs
- Decreased energy, motivation, initiative, self-confidence
- Feeling sad or blue, depressed mood
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild unexplained anemia (normochromic, normocytic)
- Reduced muscle bulk and strength
- Increased body fat, body mass index

Suggestive symptoms and signs
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections, erectile dysfunction
- Breast discomfort, gynecomastia
- Eunuchoidal body proportions
- Height loss, low-trauma fracture, low BMD
- Hot flushes, sweats

Specific symptoms and signs
- Incomplete or delayed sexual development
- Loss of body (axillary and pubic) hair
- Very small testes (<6 mL)

ESA Position Statement

Non-specific symptoms
- Lethargy, fatigue
- Decreased energy and/or endurance
- Low mood, irritability
- Poor concentration, sleepiness
- Impaired short term memory
- Deteriorating work performance
- Hot flushes

Organ-specific symptoms
- Bone: osteopenia, osteoporosis, fracture, loss of height
- Muscle: reduced muscle mass and strength
- Adipose tissue: increased fat mass
- Breast tissue: gynaecomastia

Sexual and reproductive symptoms
- Decreased libido
- (Erectile dysfunction*)

* uncommon as presenting feature and then only at very low testosterone concentrations

FIGURE 1 Symptoms and signs of androgen deficiency. ES material reproduced from Bhasin S, Brito JP, Cunningham GR, et al Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018; 103:1715-1744[1] with permission from Oxford University Press (publication of the Endocrine Society). ESA material reproduced from Yeap BB, Grossmann M, McLachlan RI, et al Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. Med J Aust 2016; 205:173-178[2] copyright 2016 The Medical Journal of Australia—reproduced with permission

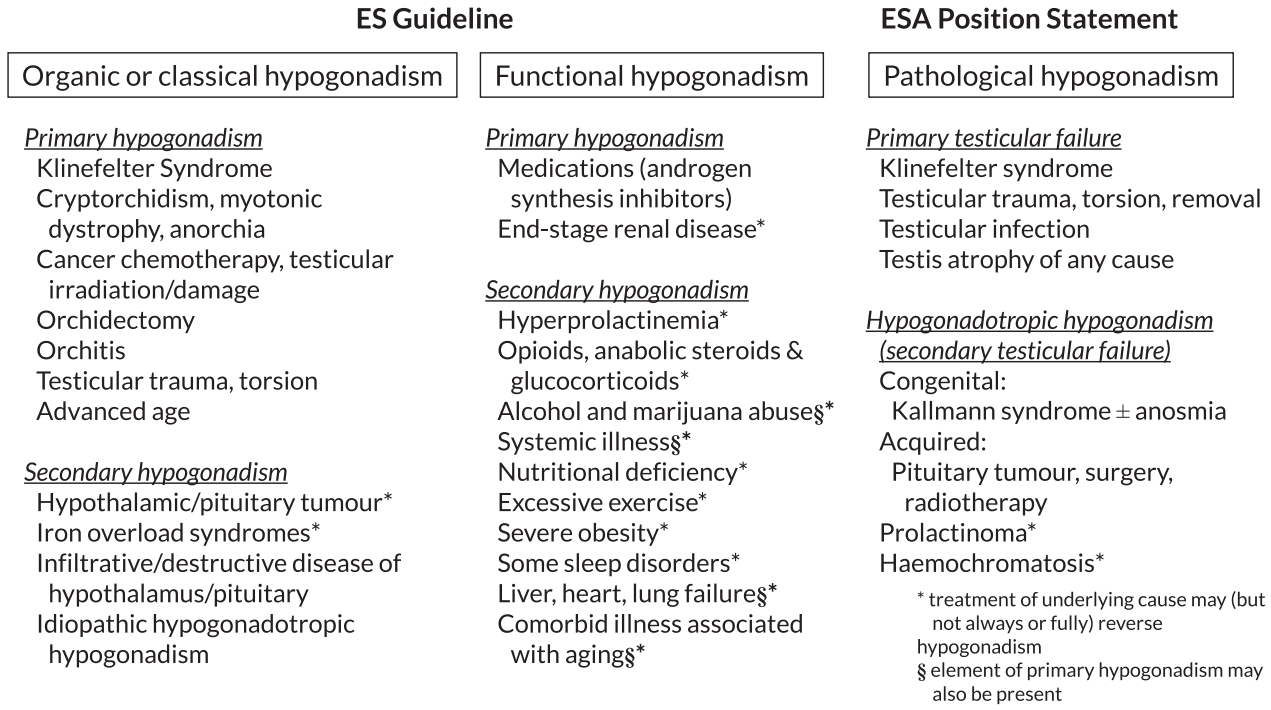

FIGURE 2 Causes of organic or pathological hypogonadism and of functional hypogonadism. ES material reproduced from Bhasin S, Brito JP, Cunningham GR, et al Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018; 103:1715-1744[1] with permission from Oxford University Press (publication of the Endocrine Society). ESA material reproduced from Yeap BB, Grossmann M, McLachlan RI, et al Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. Med J Aust 2016; 205:173-178[2] copyright 2016 The Medical Journal of Australia—reproduced with permission

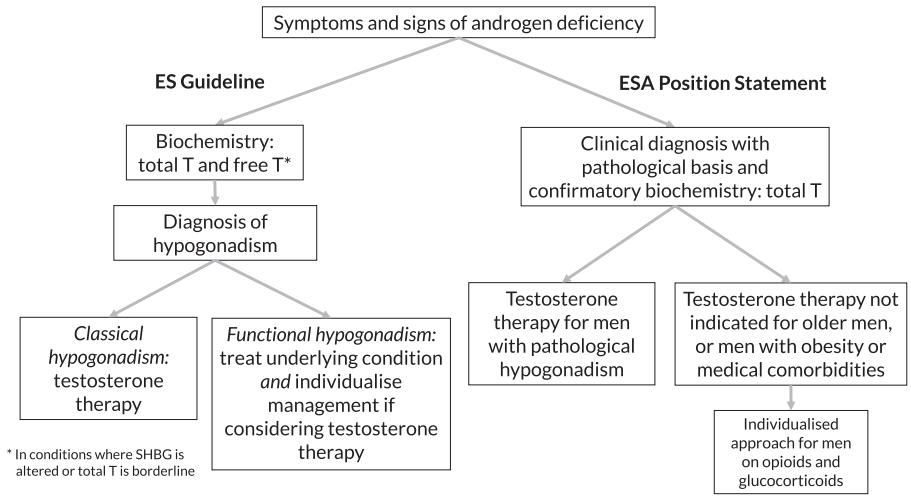

FIGURE 3 Management of men with symptoms and signs of androgen deficiency

men with primary hypogonadism from Klinefelter syndrome (with ES including very small testes <6 mL as a specific sign). Both emphasize that when fertility is desired this should be evaluated prior to initiation of testosterone therapy. ES and ESA emphasize the importance of determining the aetiology of hypogonadism in view of the recognized benefits of testosterone therapy in men with pathological hypogonadism.[1,2] The ES guideline includes advanced age as a possible cause of organic primary hypogonadism, and medications/drugs, obesity and comorbidities as possible causes of functional secondary hypogonadism (Figure 2).[1] ESA excludes age, obesity and medical comorbidities as causes of pathological hypogonadism in men with an intact HPT axis.[2] This resulted in discrepancies between the two sets of recommendations with respect to ageing men, men with obesity and men with medical comorbidities.

3 | AGEING, OBESITY AND MEDICAL COMORBIDITIES

3.1 | Ageing

The ES Guideline considered advanced age as a possible cause of organic primary hypogonadism (affecting only a small minority of the elderly male population) and comorbid illness associated with ageing as a cause of functional secondary hypogonadism (Figure 2).[1] In the ESA Position Statement, older age per se is not regarded as a cause of pathological hypogonadism and testosterone treatment is therefore not recommended in the absence of pathological hypogonadism (Figure 3).[2]

Across the male lifespan, testosterone concentrations decline from early adulthood into older age.[9] Studies in older men have delineated progressive longitudinal declines in circulating androgens and higher LH concentrations.[10-12] In the majority of ageing men, the gradually declining testosterone concentrations remain within the physiological range, without showing clear evidence of androgen deficiency.[13] However, a minority (1%-2% of the general population) of older men (aged ≥70 years) show progressive impairment of testicular function with low testosterone, elevated LH, multiple sexual symptoms and physical symptoms compatible with androgen deficiency—regarded by some but not all as constituting a syndrome of primary functional hypogonadism, also sometimes referred to as late-onset hypogonadism.[14,15]

In this setting, the T-Trials provide important evidence as to the benefits of testosterone in older men with symptoms consistent with hypogonadism and testosterone concentrations that are low when compared to younger men. In T-Trials involving 788 men aged ≥65 years with baseline testosterone <9.54 nmol/L, testosterone therapy over twelve months resulted in improvements in most aspects of sexual function in proportion to the increase in testosterone, some benefits in mood and depressive symptoms, but not in vitality or cognition.[7,8] While testosterone therapy did not improve walking distance in those whose walk speed was slow, in all T-Trial participants, testosterone did increase the distance walked.[7] There was increased volumetric bone mineral density and haemoglobin concentrations, and greater increase in coronary non-calcified plaque volume.[8] Although testosterone was not associated with more cardiovascular or prostate adverse events than placebo, a trial of a much larger number of men for a much longer period would be necessary to determine effects of testosterone on cardiovascular or prostate risk. These findings have attracted much interest as befitting the largest randomized controlled trial (RCT) of testosterone therapy reported to date. These important results show multiple benefits, albeit modest, over 12 months of testosterone therapy in older men, but further trials are needed to clarify longer-term health benefits and risks.[16]

The ES guideline clearly recognizes that there is considerable disagreement among experts on testosterone treatment in older men due to incomplete evidence, especially longer-term risks, and the non-specificity of (hypogonadal) symptoms. ES therefore recommends against routinely prescribing testosterone to all men ≥65 years with low testosterone concentrations.[1] ES suggests that in men >65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anaemia) and consistently and unequivocally low morning testosterone concentrations (see later), clinicians may consider *offering* testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits.[1] This approach allows experienced clinicians, on a shared decision-making basis, to select individual patients (probably those with severe/distressing symptoms and understanding of the uncertainties of risks) who could benefit from a trial of testosterone therapy (Figure 3).

The ESA position statement recommends testosterone therapy for men who have symptoms and signs of androgen deficiency due to disorders of the hypothalamus, pituitary or testes, and that such men should not be excluded from testosterone treatment solely due to age.[2] ESA does not recommend testosterone therapy in older men who may have lower testosterone concentrations compared with younger men, in the absence of pathological hypogonadism.

Both ES and ESA discourage the perception of testosterone as a treatment for "anti-ageing" or male rejuvenation,[17] and recognize the need for more evidence on the longer-term patient-important outcomes and risks of testosterone therapy in older men with functional hypogonadism.

3.2 | Obesity

In middle-aged and older men, obesity is consistently associated with lower circulating testosterone without elevation of LH and FSH,[18,19] and loss of excess weight in obese men is associated with recovery of endogenous testosterone production.[20-22] In men with class 1 and 2 obesity, this may be attributable to lower SHBG and hence lower testosterone concentrations. However, in men with BMI ≥40 kg/m^2, there is also a reduction in LH pulse amplitudes[23] as well as decreased total and free testosterone concentrations indicating a genuine functional suppression of the HPT axis (see[18] for review). Earlier studies conducted in class 1 and class 2 obese men reported normal libido, potency, secondary sexual characteristics and spermatogenesis.[24,25] However, more recent studies implicate obesity in low semen quality in men from the general population.[26,27] Furthermore, in obese middle-aged and older men, lower testosterone concentrations, sexual and physical symptoms, and lower Hb and lower bone density are often associated.[15,28] The ES, acknowledging the robust and consistent association between obesity and low T in men of all ages, formally classifies severe obesity as a cause of functional secondary hypogonadism (Figure 2).

Testosterone therapy results in a small gain of lean mass and corresponding reduction in fat mass.[29] By contrast, reducing excess weight results in substantial increases in circulating testosterone concentrations proportionate to the degree of weight loss.[30] In this respect, ES and ESA recommendations concur. ES states that in men with functional secondary hypogonadism, this may be reversible with treatment of underlying causes such as

obesity.[1] ESA recommends that obese men who may have reduced testosterone concentrations be encouraged to lose weight using a combination of diet and exercise.[2] Managing the obesity, may also have additional health benefits. In some instances, educating patients that obesity may be contributing to hypogonadism could motivate them to lose weight. Short-term studies have shown that testosterone treatment in carefully selected obese men may have modest benefits on symptoms of androgen deficiency and body composition even additive to diet alone.[31] However, both sets of guidelines refrained from commenting on the serial or adjunctive approach to treating obesity as the underlying cause of low testosterone (and if unsuccessful) with testosterone therapy.[30] Until more evidence is available, testosterone therapy alone cannot be routinely recommended for men with obesity-associated low testosterone concentrations.[18]

Obesity is a risk factor for insulin resistance and for type 2 diabetes, and men with lower testosterone concentrations are more likely to have or to develop metabolic syndrome or diabetes.[32,33] However, a meta-analysis of testosterone treatment in men with metabolic syndrome and/or type 2 diabetes found possible improvement in indices of insulin resistance without clear evidence of improvement in HbA1c.[34] Both ES and ESA do not recommend testosterone therapy in men with diabetes in the absence of pathological hypogonadism. Whether testosterone therapy would prevent progression from impaired glucose tolerance to type 2 diabetes, or revert newly diagnosed diabetes, in overweight middle-aged and older men with low-normal baseline testosterone concentrations is the question being addressed by a multicentre Australia-wide RCT with a 2-year duration of intervention.[35]

3.3 | Medical comorbidities

Both ES and ESA recognize that chronic diseases (not directly involving the hypothalamus, pituitary or testes) are associated with an increased risk of low testosterone concentrations. ES lists systemic illness, sleep disorders, end-stage renal disease, liver, heart and lung failure as causes of functional hypogonadism with elements of primary and secondary hypogonadism coexisting in many cases (Figure 2). ES emphasizes that functional secondary hypogonadism associated with medical comorbidities might be reversible by treating the underlying condition.[1] ES further states that the paucity of RCT data on efficacy or safety of T therapy precludes a general recommendation for T therapy in patients with chronic diseases (including severe obesity). ES advises clinicians to individualize their decision to treat or not treat these men with testosterone, based on careful consideration of the severity of symptoms, the degree of testosterone deficiency, confounding influence of comorbid illness, patient preferences, and the uncertainty of risks and benefits of testosterone therapy.[1]

Endocrine Society of Australia notes that in men (of any age) with intrinsically normal hypothalamo-pituitary-testicular (HPT) axis function, systemic illness and accumulation of comorbidities including renal, cardiac, inflammatory and mental health disorders, are associated with reduced testosterone concentrations.[2] In this setting, low testosterone concentrations are a biomarker for underlying poor health, and the use of testosterone therapy remains to be fully evaluated for safety and efficacy in randomized controlled trials.[2]

The distinction between men with and without organic or pathological hypogonadism is relevant to the anticipated response to testosterone therapy. In men with pathological hypogonadism, testosterone therapy consistently and predictably resolves symptoms of androgen deficiency.[36] However, in men with low testosterone due to systemic illness or accumulation of medical comorbidities, symptoms are non-specific and their response to testosterone therapy uncertain.

Both ES and ESA discuss the situation of men treated with systemic glucocorticoids or opioids, both of which are associated with reduced HPT axis function and low testosterone concentrations.[37,38] Where possible, removing these medications allows recovery of endogenous HPT axis function and is the preferred strategy. A therapeutic role for androgens in this setting needs to be established by well-designed randomized controlled trials.[2]

4 | TESTOSTERONE REFERENCE RANGES

Both ES and ESA recommend confirmatory biochemical testing, ideally with early morning, fasting blood sampling for assay of total testosterone concentrations, the need for repeat measurements and the importance of accurate testosterone assays.[1,2] ES, while recognizing that mass spectrometry methods generally offer higher precision than most immunoassays, recommends testosterone assays verified by the Centres for Disease Control (CDC) or an accuracy-based external quality control program. ESA gives preference to mass spectrometry assays where available. Acknowledging that the exact threshold levels (lower limits) of circulating testosterone for androgen deficiency are difficult to define accurately and may vary between individual androgen-dependent functions,[14,39] both guidelines recommend that testosterone results should be interpreted with the clinical findings of individual patients against reference intervals established in healthy eugonadal men from the general population.

However, there is divergence over the most appropriate reference range to be applied to interpreting the testosterone result. ES presents an internationally harmonized (by cross-calibrating four large population cohorts aged 19-89 years from the United States and Europe) reference range for total testosterone, measured by a high order mass spectrometry method at the CDC.[40] This allows local laboratories or national quality control schemes to standardize their results against the international reference, and for use in accurately calculating free testosterone (see below). ES cites a normal total testosterone reference range as 9.2-31.8 nmol/L in healthy non-obese men aged 19-39 years (2.5-97.5th percentile).[40] ESA cites mass spectrometry-based reference ranges for men aged 21-35 years with normal reproductive function (proven normal testes and semen analysis) as 10.4-30.1 nmol/L,[41] and for very healthy men aged 70-89 years as 6.4-25.7 nmol/L.[42] Some discrepancy

between the cited reference intervals is unsurprising given the differences in methods of testosterone assays, calibrators employed, and differences in the reference populations used to generate ranges. However, a more fundamental issue is the as yet unresolved debate as to whether lower testosterone concentrations due to ageing per se, can be associated with clinical sequelae of androgen deficiency.

The ES guidelines adopts a T-score approach (analogous to bone mineral density T-scores for the diagnosis of osteoporosis) with the reference range based on healthy non-obese men aged 19-39 years giving a cut-off for total testosterone concentration of 9.2 nmol/L.[40] It could be argued that this approach would potentially classify a large number of older men with testosterone <9.2 nmol/L as biochemically hypogonadal. However, it is supported by the results of the T-Trials showing improvements in some hypogonadal symptoms in older men with total testosterone <9.5 nmol/L, when their testosterone was increased from 8.1 nmol/L to 17.7 nmol/L the middle of the range for young men,[7] although those men did not have classical hypogonadism.

The ESA position statement utilizes an age-adjusted (*Z*-score) approach for its recommended reference range. Men without known hypothalamic, pituitary or testicular disease are expected to have total testosterone concentrations ≥10.4 nmol/L up to age 35 years, and ≥6.4 nmol/L at ≥70 years.[41,42] This approach enables older men with testosterone concentrations lower than expected for younger men, to be reassured that in the absence of pathological hypogonadism, androgen deficiency is unlikely and testosterone therapy is not indicated. Age-appropriate reference ranges are provided routinely for other analytes whose distribution varies with age, such as insulin-like growth factor-I,[43] bone turnover markers[44] and prostate-specific antigen (PSA).[45]

US Endocrine Society (ES) also recommends consideration of pituitary imaging when the clinical context is suggestive and when total testosterone concentrations are <5.2 nmol/L.[1] The ESA position statement did not offer any recommendation on pituitary imaging based on testosterone concentrations.

5 | TOTAL VS FREE TESTOSTERONE

US Endocrine Society (ES) places considerable importance on conditions that reduce or elevate sex hormone-binding globulin (SHBG) concentrations. ES lists obesity, insulin resistance, diabetes, use of exogenous androgens, glucocorticoids and some progestins, nephrotic syndrome, hypothyroidism, acromegaly and some polymorphisms in the SHBG gene as causes of low SHBG; and ageing, hyperthyroidism, liver disease, antiepileptic medications, HIV disease, use of estrogens and other polymorphisms in the SHBG gene as causes of high SHBG.[1] ES recommends measurement or calculation of free testosterone concentrations in men with conditions that alter SHBG and in men with borderline total testosterone.[1]

The interest in free testosterone concentrations stems from the "free hormone hypothesis", which postulates that free or unbound testosterone in the circulation is biologically active.[46] However, the validity of the free hormone hypothesis to assessing gonadal function in men remains under debate.[47,48] But the major obstacle is practical—to measure free testosterone accurately requires equilibrium dialysis or ultrafiltration, labour-intensive methodology that is costly and not routinely available.[47] Consequently for most clinicians, free testosterone concentrations are calculated using equations whose results may vary from each other.[49,50] Nevertheless, internal comparisons of calculated free testosterone using the same formula in a single laboratory are increasingly used to obtain quantitative information in conditions that alter circulating SHBG and when total testosterone concentrations are in the borderline range.[1] Support for this has come from the European Male Ageing Study, which showed that, compared to men with normal total and calculated free testosterone, men with normal total and low calculated free testosterone had a greater likelihood of sexual and physical symptoms.[28] Importantly, men with low total but normal free testosterone concentrations were more obese (and presumably had lower SHBG levels) and did not have associated sexual or physical symptoms. In men considered to have developed biochemical secondary hypogonadism over time, only those in whom both total and calculated free testosterone concentrations declined (but not when only total testosterone declined but free testosterone remained normal), experienced sexual symptoms.[51]

US Endocrine Society recognizes the practical difficulties in interpreting calculated free testosterone data, stemming from the current lack of standardization regarding free testosterone calculations and the lack of an established reference range, resulting in variability in the lower limits of the reference ranges quoted by different laboratories.[1] ES recommends that until a harmonized international reference range for free testosterone is available, local laboratory laboratories are encouraged to establish their own specific reference ranges for free testosterone measured by equilibrium dialysis or for calculated free testosterone (preferably calibrated against the equilibrium dialysis method).

The ESA recommends measuring total testosterone concentrations and when appropriate, interpreting these in relation to SHBG.[2] Thus, total testosterone concentrations may be low in men with low SHBG concentrations for example in the presence of obesity and insulin resistance (or exogenous androgens), without being indicative of androgen deficiency particularly when LH and FSH are normal. Men with high SHBG concentrations as seen with hyperthyroidism, liver disease and antiepileptic therapies, could have higher than expected total testosterone, without manifesting androgen excess.[2]

6 | SAFETY OF TESTOSTERONE TREATMENT

6.1 | Prostate safety

Prostate gland growth is androgen-sensitive, and androgen deprivation therapy causes regression of metastatic prostate cancer.[52] Given the potentially long time interval between development and clinical presentation,[53] testosterone therapy is unlikely to cause de novo prostate cancer, but may unmask pre-existing or latent disease.

Both ES and ESA specify presence of prostate cancer as a contraindication to testosterone therapy. ES notes that there has been no testosterone trial large and long enough to examine prostate cancer risk, and that testosterone therapy may increase the likelihood of detecting subclinical prostate cancer because of increased surveillance and rising prostate-specific antigen (PSA) concentrations which could lead to prostate biopsy.[1,54] In men with pathological hypogonadism not known to have prostate cancer, ESA found no convincing evidence that treatment with testosterone increased risk of malignant prostate disease (relative to eugonadal men).[5,55,56]

US Endocrine Society recommends against testosterone therapy in men with a palpable nodule or induration or PSA >4 ng/mL (or >3 ng/mL in men at high risk).[1] In men 55-69 years old with life expectancy >10 years, ES suggests discussing potential benefits and risks of prostate cancer detection and prostate monitoring, and engaging these men in shared decision-making. In men aged 40-69 years at increased risk of prostate cancer (eg, African Americans and men with affected first-degree relatives), ES suggests discussing potential risks and offering prostate monitoring options.[1] Monitoring comprises digital rectal examination and PSA testing at baseline and at 3-12 months after starting testosterone therapy, after which clinicians should follow standard local guidelines for prostate cancer screening based on age and race.[1] ESA recommends that where there is a reasonable possibility of substantive pre-existing prostate disease, digital rectal examination of the prostate and measurement of PSA be performed before testosterone therapy is commenced.[5] ESA also noted that monitoring of PSA during testosterone therapy is common practice.

Both ES and ESA note severe lower urinary tract symptoms (LUTS) as a precaution with respect to testosterone therapy, with ES noting that testosterone therapy does not worsen LUTS in men who do not have severe LUTS prior to treatment.[1] ES commented that although some clinicians have suggested considering patients with a history of organ-confined prostate cancer for T replacement on an individualized basis (if they have undergone radical prostatectomy, have undetectable PSA, and no detectable residual disease two or more years after surgery) the lack of data from RCTs precludes a general recommendation.[1]

6.2 | Cardiovascular safety

Epidemiological studies in older men have linked lower endogenous testosterone concentrations with higher risk of cardiovascular events, such as stroke,[57,58] and with all-cause mortality.[59] However, in one randomized controlled trial of older men with limited mobility, testosterone therapy was associated with an excess of adverse events.[60] There was no such signal in a similar trial of frail or intermediate-frail older men.[61] In T-Trials, seven men in each arm experienced cardiovascular adverse events, most of whom had pre-existing cardiovascular disease.[7,8] Retrospective case-control analyses, usually with major methodological limitations, show conflicting results with testosterone prescriptions being associated with increased[62] or decreased risk of myocardial infarction,[63] and reduced risk of major cardiovascular events or mortality.[64-66] Meta-analyses of testosterone trials have generally not found an excess of cardiovascular adverse events.[67,68] Whether testosterone exerts beneficial, neutral or adverse effects on the cardiovascular system remains unclear and needs elucidation in further studies.

US Endocrine Society notes that no randomized controlled trial large enough to determine effects of testosterone therapy on major cardiovascular events has been undertaken.[1,69] ES also noted that the US regulatory agency required labelling to warn of a possible increased risk of cardiovascular events with the use of testosterone, but the European regulatory agency concluded that there was no consistent evidence of increased risk of coronary heart disease associated with testosterone therapy in hypogonadal men.[1] ESA concluded that the evidence regarding testosterone therapy and cardiovascular outcomes is inconclusive.[5] Until better evidence is available, prudence might suggest using testosterone therapy with a degree of caution in older men with known cardiovascular disease, and optimizing management of cardiovascular risk factors and disease beforehand.

US Endocrine Society (ES) recommends against testosterone therapy in men who had a major cardiovascular event or stroke within the last 6 months, or those with thrombophilia.[1] Testosterone therapy is associated with a significantly higher frequency of erythrocytosis, and both ES and ESA recommend monitoring of haematocrit, advising that this be assessed 3-6 months after initiation of testosterone therapy and then on an annual basis.[1,5]

7 | IMPLICATIONS FOR CURRENT CLINICAL PRACTICE

Both ES and ESA highlight the priority to identify and treat men with symptoms and signs of androgen deficiency due to classical hypogonadism (Figures 1-3). However, the divergent views over recognition of a hypogonadal state in older men, men with obesity and/or diabetes, and men with medical comorbidities, and the role of testosterone therapy in these men reflect important areas where the current evidence base is incomplete.

The T-Trials in older men with functional hypogonadism demonstrated some benefits of testosterone therapy over 12 months for sexual function, physical function, bone strength and anaemia.[7,8,16] The T-Trials were not powered to assess the incident risks of prostate cancer or cardiovascular events, thus an important area for future research will be to establish the longer-term safety of testosterone therapy.

Both ES and ESA recognize the importance and primacy of careful clinical assessment, supported by confirmatory biochemical testing. ES presents an internationally harmonized single reference range for total testosterone based on healthy non-obese 19-35-year-old men. ES recommends the use of free testosterone in conditions that alter SHBG levels and when total testosterone concentrations are in the borderline range but acknowledges the current lack of an internationally standardized reference range for free testosterone. ESA cites age-standardized reference ranges for interpretation of total

testosterone, in conjunction with assessment of SHBG concentrations where appropriate.

Until new evidence is available, clinicians will continue to be challenged by the management of symptomatic older and obese men with comorbidities, where lower testosterone concentrations may be a biomarker for poorer health but could also contribute to an androgen deficiency state. In such men with functional hypogonadism, lifestyle interventions (for example to achieve loss of excess weight), management of comorbid illnesses and discontinuation of offending medications are recommended, but may be difficult to achieve.[30] Even when partially successful, these may not fully restore HPT axis function or resolve androgen deficiency-like symptoms. In this setting, ES suggests testosterone therapy may be tried in selected men who are fully informed as to the benefits and risks but ESA does not recommend testosterone therapy, placing emphasis on the need for better supporting evidence. Taken together, both the ES guidelines and ESA position statement acknowledge important gaps in the current evidence base that have led to differences in interpretation and approaches for optimising individualized management of older men with non-classical hypogonadism. In the interim, clinicians will need to decide for themselves how to reconcile these differences and to implement specific recommendations in practice, in order to optimize benefits and minimize risks for their patients.

CONFLICT OF INTEREST STATEMENT

BBY has received speaker honoraria and conference support from Bayer, Lilly and Besins Healthcare, research support from Bayer, Lilly and Lawley Pharmaceuticals, and has been a member of advisory committees for Lilly and Besins Healthcare. FCWW has received speaker honoraria from Bayer, Lilly and Besins Healthcare, research support from Lilly and Besins Healthcare, has been a member of advisory committees for Lilly and Besins Healthcare and consultant for Lilly, Besins Healthcare and Repros Therapeutics.

DISCLAIMER

The views expressed in this article are those of the authors as individuals, and do not represent the writing groups of the Endocrine Society guidelines nor the Endocrine Society of Australia position statement, nor do they represent the Endocrine Society or the Endocrine Society of Australia.

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