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Position statement

EMAS position statement: Testosterone replacement therapy in older men

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A B S T R A C T

Introduction: Late-onset hypogonadism is the clinical entity characterised by low testosterone concentrations associated with clinical symptoms in the absence of organic disease in ageing men. It has been associated with metabolic syndrome, reduced bone mineral density, and increased cardiovascular morbidity and mortality risk. Although testosterone replacement therapy (TRT) reverses most of these conditions in young hypogonadal men, the risk/benefit ratio of TRT in older men is debatable.

Aim: To update the 2015 EMAS statement on TRT in older men with new research on late-onset hypogonadism and TRT.

Materials and methods: Literature review and consensus of expert opinion.

Summary recommendations: TRT should be offered only to symptomatic older men with confirmed low testosterone concentrations after explaining the uncertainties regarding the long-term safety of this treatment. TRT may be offered to men with severe hypogonadism and erectile dysfunction to improve sexual desire, erectile, and orgasmic function. It should also be considered in hypogonadal men with severe insulin resistance or pre-diabetes mellitus. TRT may also be considered, in combination with proven treatment strategies, for osteoporosis, or for selected patients with persistent mild depressive symptoms and/or low self-perceived quality of life, combined with standard medical care for each condition. TRT is contraindicated in hypogonadal men actively seeking fertility treatment. Due to a lack of data, TRT should not be routinely used in older men to improve exercise capacity/physical function, improve cognitive function, or prevent cognitive decline. TRT must be avoided in older, frail men with known breast cancer or untreated prostate cancer and all men who have had myocardial infarction or stroke within the last four months, and those with severe or decompensated heart failure. The quality of evidence regarding patients with previous prostate cancer or cardiovascular disease is too low to draw definitive conclusions. Any limits on duration of use are arbitrary, and treatment should continue for as long as the man feels the benefits outweigh the risks for him, and decisions must be made on an individual basis. Withdrawal should be considered when hypogonadism is reversed after the resolution of underlying disorder. Short-acting transdermal preparations should be preferred for TRT initiation in older men, but injectable forms may be considered subsequently. Older men on TRT should be monitored at 3, 6, and 12 months after initiation and at least yearly thereafter, or earlier and more frequently if indicated. Evaluation should include assessment of the clinical response, and measurement of total testosterone, haematocrit, and prostate-specific antigen (PSA) concentrations. Bone density and/or quality should also be assessed. Obese and overweight patients should be encouraged to undergo lifestyle modifications, including exercise and weight loss, to increase endogenous testosterone.

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1. Introduction

People worldwide are living longer. The population aged over 60 years now surpasses 1 billion and is expected to double by 2050 [1]. Several population-based studies have documented an age-dependent, modest reduction of serum testosterone (T) concentrations in men after the fourth decade, with a decrease of about 1 % per year [2], and the T concentrations of some men will eventually drop below 8 nmol/L (250 ng/dL), the threshold agreed by most scientific societies to correspond to clinically meaningful testosterone deficiency (TD). Late-onset hypogonadism (LOH) is the clinical entity in which TD in older men is associated with clinical symptoms in the absence of organic diseases that permanently disrupt the hypothalamic-pituitary-testis (HPT) axis. Its reported prevalence varies from 2.1 % to 12.3 % [3,4]. LOH is associated with symptoms that may negatively impact the quality of life of older men, such as sexual dysfunction, and decreased energy and mobility. It has also been associated with metabolic syndrome, reduced bone mineral density, and an increased risk of cardiovascular (CV) morbidity and mortality [5,6] (Fig. 1). T replacement therapy (TRT) has been demonstrated to reverse most of these conditions in hypogonadal men of all ages, but while the risk/benefit ratio of TRT is clear for younger men, for ageing men it is uncertain [7,8].

In 2015 EMAS published a position statement on TRT in the ageing male [9]. This 2023 document takes into account new research, new T formulations and recently published clinical guidance [10–14]. It discusses the evidence on TRT in ageing men regarding the diagnosis of hypogonadism, the indications and contraindications of therapy, and the application and monitoring of TRT. There is a specific focus on controversial areas, especially safety.

2. Methodology

A literature search was performed by two investigators (GAK and RP) and included all randomised controlled trials (RCTs) and meta-analyses available in PubMed, in the English language and published between 2013 and 2023. The search string was: [disease/condition of interest] AND testosterone therapy. The title and abstract of the articles retrieved were reviewed and evaluated for their relevance. Only those studies including male patients with LOH and treated with TRT were eligible for further evaluation. Management of transgender and gender-nonconforming people is not covered in this statement.

2.1. Diagnosis of hypogonadism

2.1.1. When the diagnosis is established

The diagnosis of hypogonadism in the elderly (defined as aged over 65 years) should be made on biochemical and clinical grounds. The chances of detecting TD among asymptomatic men increases with age; however, the long-term effects and safety of TRT in asymptomatic men with isolated TD remain unclear [15,16]. Hypogonadism is a clinical syndrome characterised by T deficiency and a constellation of specific and non-specific symptoms and signs, categorised according to their response to TRT [17]. Sexual dysfunction (including reduced sexual desire and erectile dysfunction) and signs such as gynaecomastia and

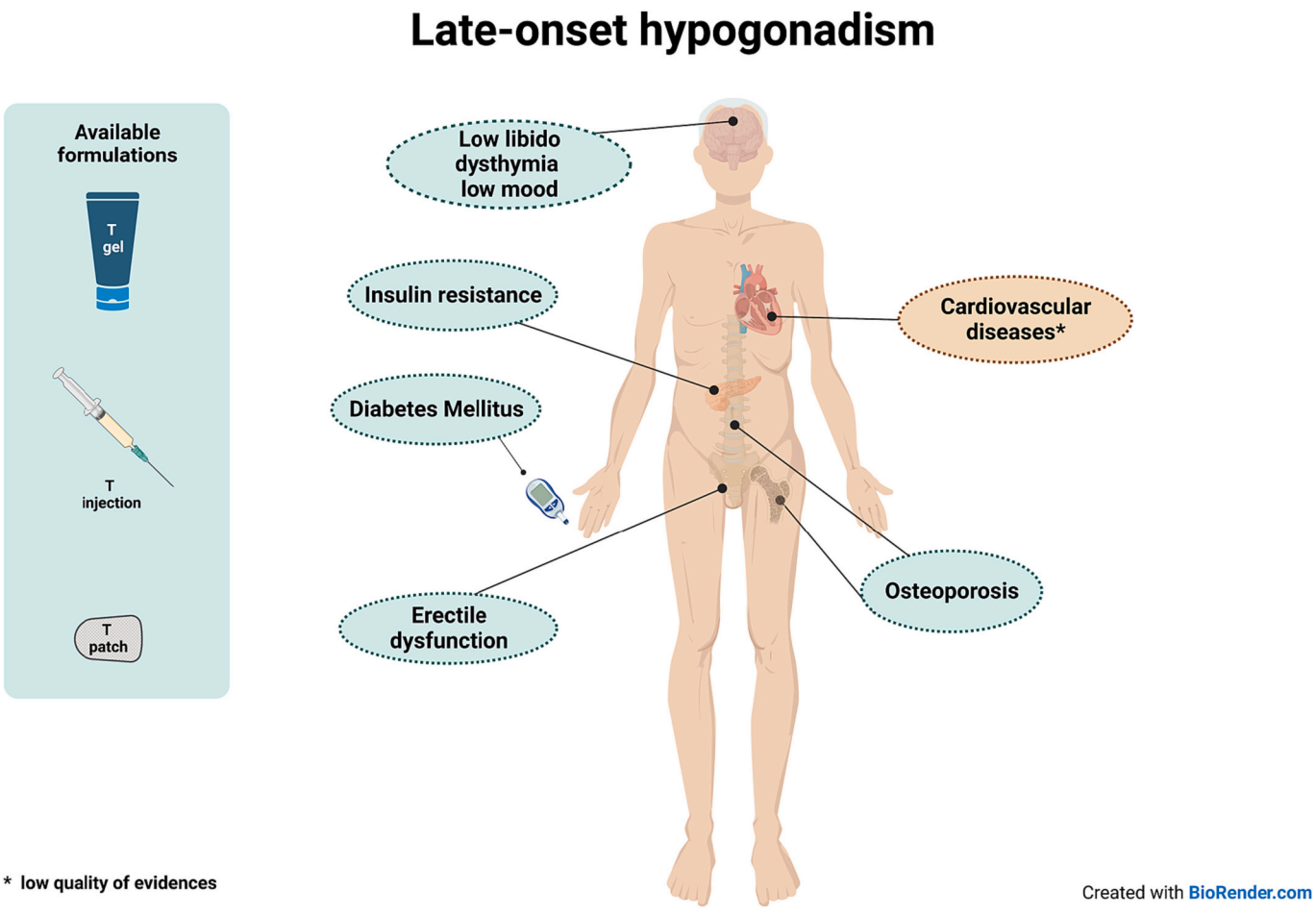

Fig. 1. Comorbidities associated with Late-onset hypogonadism. Green circles refer to complications in which testosterone therapy demonstrated beneficial effects. The orange circle refers to areas of uncertainty. T: testosterone. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

loss of sexual (axillary and pubic) body hair are considered specific. On the other hand, vague symptoms such as decreased energy, depressed mood, sleep disturbances, and conditions such as normochromic, normocytic anaemia, reduced bone mineral density, and increased fat/reduced lean body mass are suggestive but not specific since they can be the result of various pathologies. Among hypogonadal older men, non-specific symptoms usually prevail, overlapping with those arising from comorbidities and the effects of ageing; however, according to the European Male Ageing Study, a multicentre prospective cohort of 3369 community-dwelling middle-aged and elderly European men, only the triad of sexual symptoms (low libido, reduced spontaneous erections, and erectile dysfunction) were associated with low T concentrations [4].

The uncertainties accompanying the risk/benefit ratio of TRT in ageing men mean that a screening programme measuring T in the general population cannot be justified. Furthermore, the available clinical questionnaires for the diagnosis of hypogonadism are unsuitable for screening hypogonadal men due to their low specificity in relation to clinical outcomes [17]. Nevertheless, there are certain conditions associated with a higher risk of hypogonadism, such as lesions of the sellar region, osteoporotic fractures, and use of medications that affect T secretion and metabolism, that warrant T measurement. A systematic review showed that (aside from advanced age) obesity, metabolic syndrome, and poor general health status are the most important risk factors for hypogonadism [18].

Summary recommendation. The diagnosis of hypogonadism in ageing men should be based on low T concentrations when accompanied by relevant symptoms, especially sexual ones (low sexual desire, reduced spontaneous erections, and erectile dysfunction). Universal screening of ageing men for low T concentrations is not justified. The use of clinical questionnaires for diagnosing hypogonadism is not recommended.

2.2. Biochemical diagnosis and T measurement

Until recently, substantial variability existed in total T (tT) measurement within and across laboratories, impeding reliable interpretation of results [19]. Liquid chromatography-mass spectrometry (LC-MS/MS) is the gold standard method, albeit expensive and laborious. To improve the accuracy of immunoassays, a hormone standardisation programme has been implemented to develop a reference immunoassay and set the standards for certification of laboratories that measure T. Current T immunoassays show a good correlation with LC-MS/MS, provided that they are validated against an internationally harmonised reference range [20].

In conditions that alter concentrations of sex hormone-binding globulin (SHBG), confirmation of the results with assessment of free T (fT) is recommended (see Table 1). The preferable method for fT assessment is equilibrium dialysis (EqD), which, however, is laborious and not readily available [21]. On the other hand, measurement of fT with immunoassays is unreliable and should be discouraged [22,23]. In clinical practice, fT may be calculated using formulas based on the equilibrium dissociation constants of T with serum SHBG and albumin. The formula proposed by Vermeulen et al. shows a substantial correlation with EqD and is available online (http://www.issam.ch/freetesto.htm) [24].

Pitfalls in T measurement may arise due to pre-analytical errors. There is a considerable circadian variation in T secretion, with morning concentrations being 20–25 % higher than evening levels. This variation is preserved among older men but to a lesser degree [25]. Food intake, especially carbohydrates, may also suppress T secretion [26]. Consequently, T concentrations should be assessed in morning samples (ideally drawn between 7.00 and 11.00 am) after overnight fasting. Moreover, men present a considerable intra-individual daily variability in T concentrations: in 30 % of cases with an initial low T value, a repeat measurement may be within normal levels. Consequently, confirmation of a low T measurement on a different day is advised [27]. Finally, physical and psychological stressors may significantly impact T concentrations; therefore, T evaluation should be avoided during the acute phase of an illness [28]. Account should also be taken of medications known to affect T secretion, metabolism or action, such as antiandrogens and glucocorticoids [29].

Table 1
SHBG variation in physiological states and diseases.

Increased SHBG concentrations	Ageing
	Anorexia
	Hyperthyroidism
	Growth hormone deficiency
	Liver disease
	HIV
	High estrogen concentrations
	Anti-seizure medications
Decreased SHBG concentrations	Obesity
	Insulin resistance/type 2 diabetes
	Hypothyroidism
	Growth hormone excess
	Nephrotic syndrome
	Exogenous androgens/anabolic steroids
	Progestins
	Glucocorticoids

HIV: human immunodeficiency virus; SHBG: sex hormone-binding globulin.

Recent data from population cohorts of US and European ethnicity, based on a reference LC-MS/MS assay, demonstrated that the lower limit of the normal reference range for tT in healthy, non-obese young men (aged 19–39 years) was 9.2 nmol/L (264 ng/dL) [20]. However, it has been difficult to link a threshold tT concentration with symptomatic hypogonadism. The results of the European Male Ageing Study (with participants aged 40–79 years) showed that sexual symptoms can result from tT concentrations below a higher threshold (11 nmol/L, 320 ng/dL) [4]. Data from the US assessing physical and sexual function, as well as diabetes mellitus, raised this threshold even higher, to 12.1 nmol/L [30]. On the other hand, while positive effects of TRT have been unequivocally demonstrated for men with tT concentrations <8 nmol/L (231 ng/dL), it is less effective in men with tT >12 nmol/L (345 ng/dL) [31]. When tT concentrations fall in the grey zone of 8–12 nmol/L, assessment of fT may be helpful, since fT concentrations <225 pmol/L (<6.5 ng/dL) have been correlated with symptomatic hypogonadism [4].

Summary recommendation

Biochemical diagnosis of hypogonadism should rely on standardised tT assays with morning (7.00–11.00 am) fasting samples. Sampling should be avoided in the presence of acute stressors, and abnormal results should be confirmed on a different day. Hypogonadism is highly probable when tT concentrations are below 8 nmol/L (231 ng/dL), whereas tT concentrations above 12 nmol/L (345 ng/dL) typically exclude the diagnosis. For values between 8 and 12 nmol/L, the assessment of fT should be employed (either using EqD or calculated fT). Free T should also be used for patients with conditions that disrupt SHBG secretion.

2.3. Differential diagnosis of hypogonadism

The detection of low T concentrations warrants further investigations to identify possible organic causes of hypogonadism and localise the level of the disorder in the HPT axis. Determining the level of luteinising hormone (LH) is crucial, as it can distinguish testicular dysfunction (primary hypogonadism - elevated LH) from hypothalamic/pituitary disorders (secondary hypogonadism - low or inappropriately low-normal LH). In the case of primary hypogonadism, karyotyping may reveal abnormalities of sex chromosomes (e.g., Klinefelter syndrome), especially when accompanied by distinct phenotypic features (small firm testes, long-leggedness). If secondary hypogonadism is suspected,

the assessment of prolactin (PRL) and other hormones of the pituitary reserve is indicated. Magnetic resonance imaging (MRI) of the sellar region is justified in cases of very low T concentrations (<6 nmol/L, <175 ng/dL), particularly when accompanied by clinical signs and symptoms suggestive of a sellar mass (visual disturbances, headache, cerebrospinal fluid leakage), hyperprolactinaemia (>35 ng/mL) and evidence of alteration of the other pituitary axes [32,33]. A diagnosis of secondary hypogonadism also requires the exclusion of iron overload disorders [34]. The differential workup will not reveal an organic disorder in most patients, particularly those with low-normal tT and normal LH concentrations. Spontaneous remission is occasionally seen in such cases [35]. There is also a subpopulation of older men with low normal tT and elevated LH, described as subclinical or "compensated secondary hypogonadism", a clinical entity of debated clinical significance [36]. However, in general, inclusion of the measurement of gonadotropins is considered of some value for tailoring the management of patient follow-up [37].

Summary recommendation

The assessment of LH should follow the diagnosis of hypogonadism to differentiate between primary and secondary hypogonadism. In primary hypogonadism, karyotyping to exclude Klinefelter syndrome may

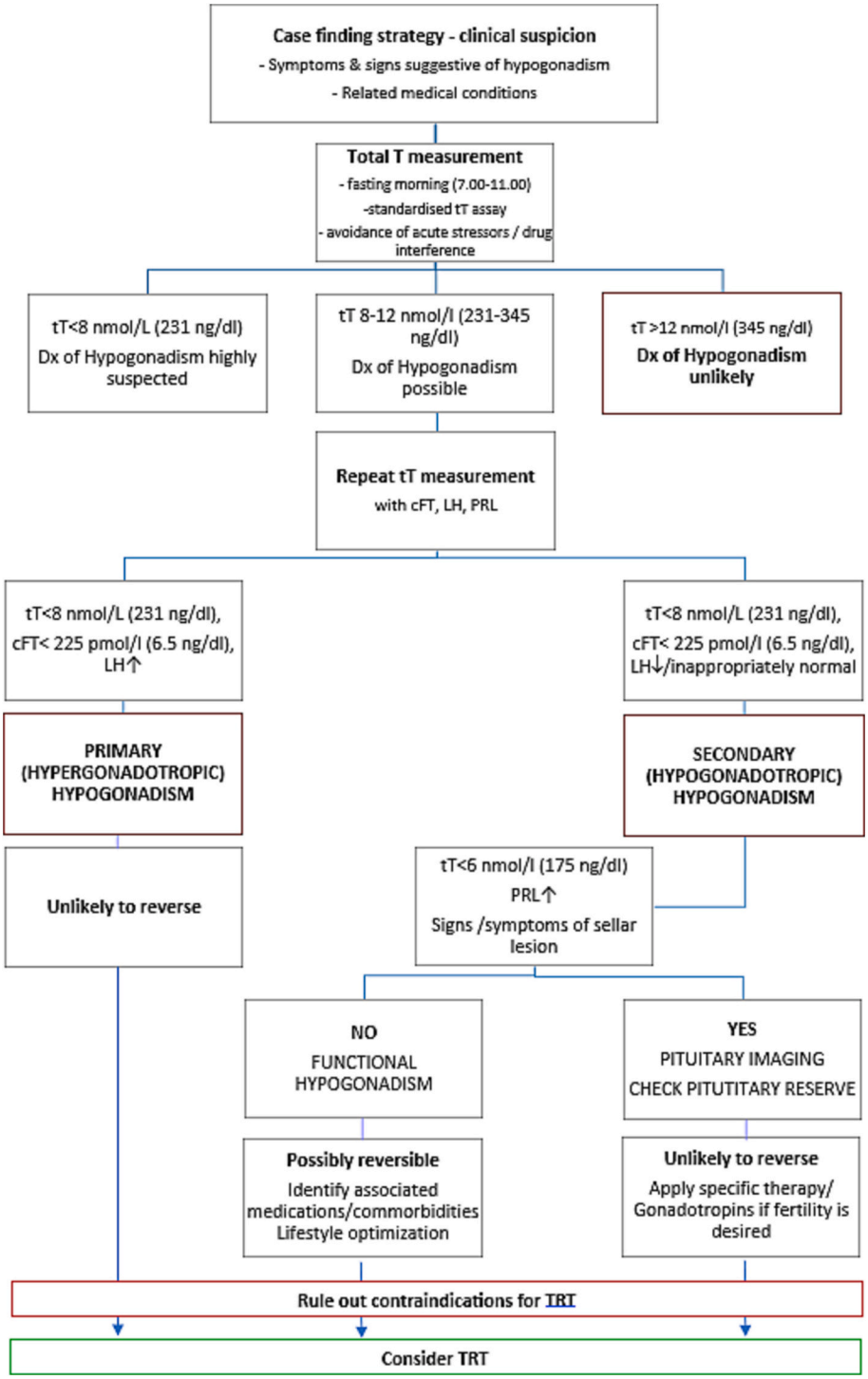

Fig. 2. Proposed flow chart for the diagnosis and decision to treat hypogonadism in older men.

be considered. In secondary hypogonadism, particularly in the presence of very low tT concentrations (<6 nmol/L, <175 ng/dL) and concomitant signs and symptoms of a sellar mass and/or other pituitary hormone deficiencies, the investigation should be completed with MRI of the sellar region. If an organic disorder is not established, the condition should be diagnosed and managed as functional hypogonadism. An overview is given in Fig. 2.

2.4. Testosterone replacement therapy

2.4.1. When to treat – indications

Treating hypogonadal older men, particularly those older than 65 years, remains highly controversial and depends on symptoms and comorbidities [7]. Most randomised controlled trials (RCTs) have demonstrated beneficial effects, mainly on sexual function, and promising results regarding metabolic syndrome and pre-diabetes or early diabetes. The effects on QoL and bone health are less prominent. Finally, there is little to no evidence of benefit in relation to cognitive decline and frailty [38].

Summary recommendation. TRT in older men should be offered after setting realistic goals depending on the presenting symptoms, after a thorough evaluation of the patient's comorbidities, and after explaining the uncertain long-term safety of this approach.

2.4.2. Sexual function

The positive effects of TRT on different aspects of sexual function have been demonstrated in recent RCTs and meta-analyses. The Sexual Function (SF) Trial of the T-Trials showed that TRT for hypogonadal (tT < 9.4 nmol/L, 275 ng/dl) men older than 65 years resulted in a modest improvement in self-reported sexual activity [effect size 0.45, 95 % confidence interval (CI) 0.30 to 0.60; $p < 0.001$], including sexual desire (0.44, 95 % CI 0.32 to 0.56; $p < 0.001$) and erectile function (0.32, 95 % CI 0.20 to 0.44; $p < 0.001$). Interestingly, the effect size was more prominent among men with lower baseline T concentrations and was proportional to the increase in T concentrations observed during the study period. The tools used for this assessment were the Psychosexual Daily Questionnaire, the sexual-desire domain of the DISF-M-II, and the International Index of Erectile Function (IIEF) [8].

Other studies have demonstrated that TRT improves sexual desire, particularly for men with severe hypogonadism (tT < 8 nmol/L). This improvement is more consistent than for erectile function [39–42]. The most recent meta-analysis endorsed by the American College of Physicians included 38 studies enrolling mostly older men (mean age 66 years). It confirmed these results by demonstrating a small improvement in global SF [standardised mean difference (SMD) 0.35, 95 % CI 0.23 to 0.46; $I^2 = 0$ %; moderate-certainty evidence] and an even smaller positive impact on erectile function (SMD 0.27, 95 % CI 0.09 to 0.44; $I^2 =$ 13 %; low-certainty evidence) [38].

The effects of TRT on erectile function were assessed in a meta-analysis of 14 studies that enrolled a total of 2298 men of mean age 60 years, in which the IIEF's erectile function domain (IIEF-EFD) was used as the outcome measure. TRT resulted in a significant increase in the EFD score compared with placebo (mean difference 2.31, 95 % CI 1.41 to 3.22), and this effect was greater in men with severe (tT <8 nmol/L) vs. mild (tT <12 nmol/L) hypogonadism (mean difference 2.95, 95 % CI 1.86 to 4.03 and 1.47, 95 % CI 0.90 to 2.03, respectively) [29]. This study also demonstrated that TRT's beneficial effects on erectile function were blunted by metabolic derangements, such as diabetes mellitus and obesity. The increase in EFD score produced by TRT is considered modest compared with the 5.7 points produced by phosphodiesterase (PDE)-5 inhibitors and has been shown to be of clinical significance only among men with mild erectile dysfunction [43]. On the other hand, some studies have shown no benefit from TRT on erectile dysfunction [44].

The above evidence, combined with the fact that only one-third of patients with erectile dysfunction are hypogonadal, suggests that, despite the proven dependency of erectile function on the actions of T, the T threshold associated with erectile dysfunction might be lower than it is for other symptoms of hypogonadism, bearing in mind that erectile dysfunction has a multifactorial pathogenesis, including metabolic and vascular factors [45]. A recent network meta-analysis showed no benefit of a particular T formulation over the others in improving erectile function [40].

Evidence on the impact of TRT on orgasmic function is mainly based on the orgasmic domain of the IEEF. Available data show a benefit of TRT over placebo, with an effect size of 0.68 (95 % CI 0.34 to 1.02), which is inversely correlated to baseline mean tT concentrations [31]. A recent RCT using the three-item Male Sexual Health Questionnaire-Ejaculatory Dysfunction-Short Form disputes the beneficial effect of TRT in ejaculation disorders; however, it has been criticised for including a population with premature ejaculation [46].

Summary recommendation. TRT should be offered to older men with sexual complaints to improve sexual desire and orgasmic function. TRT is expected to improve erectile dysfunction in men with severe hypogonadism (tT <8 nmol/L) and mild erectile dysfunction (IEEF ED score ≥22). In men with mild hypogonadism (tT 8–12 nmol/L) and/or severe erectile dysfunction (IEEF ED score <22), established treatment options for erectile dysfunction, such as PDE5-inhibitors, should be tried before TRT.

2.4.3. Obesity, metabolic syndrome, and testosterone treatment

Other factors may impact general health and contribute to the decline of T concentrations, such as obesity and type 2 diabetes mellitus (T2DM) [2,47–49]. On the other hand, lower T concentrations can promote fat accumulation and insulin resistance, suggesting a bidirectional relationship between obesity and low T. The latter is common in men who are overweight and is associated with an increased risk of T2DM [50–52]. Albeit diet-induced weight loss can reverse the reduction in serum T in obese men without primary (gonadal) disease, adherence to community-based lifestyle programmes can be poor, efficacy diminishes over time, and the effects (typically, weight loss of 2–4 kg) are too small to convey much clinical benefit [53].

Since optimal androgen status in men is associated with metabolic health [54], TRT has become an attractive option for hypogonadal men with obesity and/or metabolic syndrome. Several observational studies have documented that TRT can improve body composition and metabolic profile in T2DM [55,56]. However, data derived from placebo-controlled trials are conflicting. In an RCT enrolling 88 men with obesity, T2DM, and low (<12 nmol/L) T concentrations, treatment with T undecanoate for 40 weeks reduced fat mass and increased lean mass without changes in total body weight, body mass index (BMI), and waist circumference (WC). However, it did not affect insulin resistance (as measured with the oral glucose tolerance test) or glycated haemoglobin (HbA_{1c}) [57]. In contrast, a more recent trial demonstrated that one year of treatment with T undecanoate in a cohort of 55 men did improve insulin resistance (as measured with HOMA-IR) and fasting glucose/insulin concentrations, as well as HbA_{1c} compared with placebo. Moreover, improvement of endothelial function (as measured with flow-mediated dilation and intima-media thickness) was found in the T group, but no differences in anthropometric measures, BMI, blood pressure, and cholesterol concentrations [58]. These results (reduced WC, improved HOMA-IR, HbA_{1c}, and markers of endothelial dysfunction) were confirmed in 80 patients with T2DM treated with 50 mg/day of T gel. In this study, the effects were larger in younger patients and those reaching higher T concentrations during treatment [49]. Similarly, in an RCT that included 94 patients with T2DM treated for 24 weeks with T cypionate, T treatment improved insulin resistance (evaluated through the gold standard hyperinsulinaemic-euglycaemic clamp) and

body composition (reduced fat mass and increased lean mass) [59].

A recent RCT conducted in Australia (the T4DM study) with >1000 patients with a waist circumference >95 cm, impaired glucose tolerance or newly diagnosed T2DM, and T concentrations <14 nmol/L provided promising results. In this trial, two years of T undecanoate (and lifestyle changes) almost halved the risk of developing T2DM beyond the effects of lifestyle changes. Treatment also reduced serum glucose concentrations (both fasting and after a 2-h oral glucose tolerance test) but not HbA_{1c}. Despite no change in total body weight, a greater reduction in WC, total and abdominal fat mass, and increased lean body mass after treatment was measured in patients treated with T compared with placebo [53].

Our PubMed search retrieved five meta-analyses of RCTs [60–64] and one of observational studies [65] concerning the effects of TRT on glucose metabolism and lipid profile. Improvement in insulin resistance was seen in studies using HOMA-IR [61,63] but, interestingly, not when a more stringent, computer-based equation (HOMA2) was used [63]. Moreover, TRT reduced HbA_{1c}, fasting plasma glucose, and insulin concentrations in most [60–62] but not all [63] of the included studies.

Compared with controls, TRT decreased total cholesterol (TC) and triglyceride (TG) concentrations in most of the studies [60–62,64], but a detrimental effect on HDL-cholesterol was also described [60]. Most meta-analyses found no effects on blood pressure or BMI [60–63].

Regarding the effects of TRT on body composition in patients with obesity, two RCTs, that each included >80 patients with hypogonadism (T < 12 nmol/L), demonstrated that 3 and 6 months of TRT (undecanoate in one study, gel in the other) reduced fat mass and increased lean body mass, compared with controls, but again without an effect on body weight [66,67]. Interestingly, the beneficial effects of TRT on the body composition of patients with obesity seem not to persist after treatment withdrawal [68]. A meta-analysis of 16 studies involving >1000 men with obesity found that TRT (in various formulations, including intramuscular, buccal, transdermal, gels, and liquids) slightly improved lean body mass and LDL-cholesterol concentrations and did not affect blood pressure, and these effects were greater in younger patients [69].

Summary recommendation. Data suggest favourable effects of TRT on insulin resistance and body composition in patients with T2DM and obesity, but the discrepancies regarding its efficacy on HbA_{1c} do not support its widespread use as monotherapy for diabetes treatment. TRT should be considered in those patients with hypogonadism (T < 12 nmol/L) and severe insulin resistance or T2DM, alongside a concomitant lifestyle programme and standard medical care.

2.4.4. Bone health

T is essential for bone health at all ages [70] and contributes directly and indirectly to the maintenance of correct bone homeostasis [71–73], governing the balance between bone resorption and formation [70,74]. Reduced T concentrations can affect bone health in terms of mass and strength [74] as well as bone mineral density (BMD), and represent a major risk factor for osteoporosis [71,72,74,75]; nevertheless, the effects of TRT on bone homeostasis in ageing men with LOH are conflicting [73,76].

One of the first RCTs, performed in 60 men with LOH (T < 11 nmol/L) treated with 36 weeks of T undecanoate, demonstrated that treatment increases lumbar as well as femoral BMD at a rate of about 5 % per year, and effects were related to serum T concentrations [77]. The results were confirmed in a similar trial on 74 patients diagnosed with osteopenia/osteoporosis and hypogonadism treated with 12 months of T enanthate [78].

However, in 2020, a large meta-analysis of RCTs, which included 52 studies with >5000 participants in total, treated with different T formulations, showed no effects of TRT on BMD over either the short-term (less than two years) or the long-term studies nor in the incidence rate of fracture or falling. However, among the limitations of that meta-analysis are the inclusion of studies with low-quality evidence, underpowered for this specific outcome, and significant heterogeneity [79].

In 2022, a meta-analysis of 36 studies (25 RCTs and 11 observational trials) aimed to clarify the effects of TRT on bone parameters [80]. More than 3000 patients (mostly with T < 12 nmol/L) were treated with different T formulations for a median of 66 weeks. TRT resulted in an improvement of lumbar and femoral neck BMD, with an effect size comparable to that seen with antiresorptive drugs [81–84]. However, TRT was seen to improve lumbar spine BMD and not femoral neck BMD when only RCTs were considered. Notably, the effects on BMD were larger in those patients with lower T concentrations before treatment and increased as a function of treatment duration. Interestingly, this response was more prominent in studies which enrolled more patients with T2DM [80]. Similar results were demonstrated by an open-label trial on 105 patients with hypogonadism (T < 10.4 nmol/L) treated with T cypionate for 18 months, in which lumbar spine BMD improved more in T2DM patients than in those without T2DM [85].

These results were supported by a recent sub-analysis of a large, placebo-controlled trial (T4DM) [53] using dual-energy x-ray absorptiometry (DXA) to assess areal BMD (aBMD) and quantitative computed tomography (qCT) to assess the volumetric BMD (vBMD). This study included 177 patients with WC ≥95 cm, impaired glucose tolerance or newly diagnosed T2DM, and a fasting morning serum T level of ≤14 nmol/L. It showed that two years of T undecanoate significantly increased aBMD at the lumbar spine and the total hip, as well as vBMD, particularly in the cortical bone at both tibia and radius [86]. This result confirmed the previously published bone sub-trial of the T-Trials on 211 men with low T concentrations (<8 nmol/L) treated for one year with T gel [87].

Most studies last less than two years, whereas conventional osteoporosis monitoring and evaluation of fracture risk need longer follow-up for reliable estimation. Therefore, whether the beneficial effect of T on bone metabolism translates into a real clinical benefit is still unknown.

Summary recommendation. Men with hypogonadism should be screened for osteoporosis. TRT is recommended to prevent bone loss and help maintain peak bone mass as it can improve BMD and bone structure. This effect is more prominent in the lumbar spine, in men with lower pre-treatment T concentrations, and, notably, in the presence of osteopenia/osteoporosis at baseline. However, available evidence does not support the beneficial effect of TRT in decreasing the incidence of fractures; therefore, in patients with hypogonadism and high fracture risk, TRT should be adjunctive to standard anti-osteoporotic medical care.

2.4.5. Quality of life - mood

The association between hypogonadism and reduced quality of life (QoL), depression, and reduced physical activity has been demonstrated in several observation studies [42]. A recent meta-analysis of 7 RCTs with a total of over 1000 patients, based on the evaluation of the Aging Males' Symptoms (AMS) scale, demonstrated that TRT can improve QoL in hypogonadal men. The weighted mean total score on the AMS scale before the initiation of TRT was 43 points (scale, 17 to 85 points), indicating moderate severity of symptoms, while TRT resulted in a weighted reduction in score by 7.0 points, compared with 3.6 points in the placebo group (weighted mean difference, −3.3 [CI, −5.2 to −1.3]). This change can be of clinical significance, as it is sufficient to move an individual patient from the moderate to mild symptom severity category [38]. This improvement seems to affect all three subscales of the AMS (psychological, somatic, sexual); however, the sexual function subscale is particularly benefited by TRT [88]. Similar results were reported by a network meta-analysis of 23 RCTs involving 3090 men (SMD –0.26, 95 % CI –0.41 to −0.11), regardless of T formulations or major comorbidities [40].

Although hypogonadism has been associated with depressive mood,

it is unclear if it contributes to major depressive disorder [89]. Older meta-analyses have shown a positive impact of TRT on mood, but this was not significant in men aged over 60 years [90]. The Vitality Trial of the T-Trials demonstrated a significant reduction in the PHQ-9 depression score; however, the effect size was small (−0.18, 95%CI −0.30 to −0.06), and men with major depression were excluded [8]. A network meta-analysis by Elliott et al. showed that TRT significantly improves depression irrespective of the T formulation used; however, the effect size was again small (SMD –0.23, 95 % CI –0.44 to −0.01) and became non-significant when patients with major comorbidities were excluded [40]. According to recent meta-analyses, TRT may reduce depressive symptoms in hypogonadal men (tT <12 nmol/L or fT <225 pmol/L) with mild depressive symptoms, but not in men with major depressive disorder [91]. This effect is positively correlated with T dosage [92].

Summary recommendation. TRT may be offered as monotherapy to hypogonadal men with persistent mild depressive symptoms and/or low self-perceived QoL; however, when a major depressive disorder is diagnosed, TRT should be used only as adjunctive treatment to antidepressants.

2.5. When not to treat – lack of efficacy

2.5.1. Physical function

The role of TRT in increasing skeletal muscle mass and strength is well established [93]. The Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) trial showed that TRT in older men (>60 years) attenuates the age-related decline in aerobic capacity [94]. On the other hand, the role of TRT in improving physical function in older men with mobility problems remains unclear. The National Health and Nutrition Examination Survey 1999–2004 did not find a correlation between physical activity status and serum tT concentrations [95]. The Physical Function Trial of the T-Trials did not show any improvement in gait speed as measured by the 6-min walk test vs. placebo (adjusted OR 1.42, 95 % CI 0.83 to 2.45); however, the participants of this trial had mobility limitations (baseline gait speed < 1.2 m/s). Nevertheless, assessment of gait speed among all the participants of the T-Trials, regardless of baseline, demonstrated a small advantage of TRT over placebo (adjusted OR 1.76, 95 % CI 1.21 to 2.57) [8]. A recent meta-analysis also failed to show a positive impact of TRT on physical function either by subjective or by objective measures [38].

2.5.2. Cognitive function

An association between hypogonadism and impaired cognitive function in older men has been suggested. Free T can cross the blood–brain barrier and act on neuronal cells, while a reduction in cognition and the T decline are temporally related [96]. A meta-analysis of studies of men taking androgen deprivation therapy (ADT) demonstrated deterioration specifically in the visuomotor domain of cognition compared with controls or their pre-therapeutic status. However, this decline was not significant when non-prospective studies were excluded or when only studies assessing tT with a reliable method (mass-spectrometry) were considered [97]. Moreover, the Cognitive Function Trial of the T-Trials demonstrated that one year of TRT in older men with age-related memory impairment did not improve the evaluated cognitive functions (visual memory, spatial ability, and executive function) [98]. When assessing the cognitive function in men of the T-Trials without memory impairment, there was a significant but small improvement in executive function only [99]. These results were confirmed by a meta-analysis that reported a small (though clinically relevant) improvement in psychomotor speed and executive function [100]. Nevertheless, the results of the most recent meta-analyses of RCTs in older men (mean age of 70 years) with various degrees of cognitive function found no beneficial effects of TRT [99,101]. A limitation of the above meta-analyses is that most RCTs included both hypogonadal and eugonadal men.

Summary recommendation. Due to a lack of robust data supporting its efficacy, TRT should not be routinely used in older hypogonadal men to improve exercise capacity/physical function or cognitive function, or to prevent cognitive decline.

2.6. When not to treat – contraindications

Diseases known, or believed to be, aggravated by TRT, such as breast cancer (BrCa), prostate cancer (CaP) or severe lower urinary tract symptoms, and recent CV disease (including stroke), raise concern and preclude affected men from participating in trials evaluating TRT. Moreover, most RCTs lack adequate statistical power and duration to determine whether TRT has a causative role in the development of these conditions; therefore, the long-term safety of TRT in this context is unknown [102].

2.6.1. Hormone-sensitive cancers

BrCa and CaP are well known to be sensitive to sex steroids. The detrimental effects of TRT on male BrCa are thought to be mediated by the peripheral aromatisation of T to estrogens, which in turn induce the proliferation of the mammary gland tissue; however, data on this issue are scarce due to the rareness of male BrCa [103]. CaP, on the other hand, has been traditionally considered a T-dependent neoplasia, which is worsened in the presence of T and hampered by androgen deprivation therapy [104]. Older studies have shown a trend for higher rates of 'prostate events' among men on TRT, including CaP, prostate-specific antigen (PSA) concentrations >4 ng/mL, and a higher rate of prostate biopsies [105]. The evidence from RCTs does not support an increased risk of de novo appearance of CaP during short-term TRT (up to 3 years); however, long-term data are lacking, and it is unknown whether TRT can induce the growth of subclinical pre-existing prostate cancer. Consequently, men with known CaP or a PSA value exceeding a predetermined level (typically >4.0 ng/mL) have been typically excluded from RCTs [106].

2.6.2. Elevated haematocrit, cardiovascular disease, and thrombosis

TRT is known to stimulate erythropoiesis due to increased iron mobilisation [107], and haematocrit elevation may be evident within one month of therapy, but it is reversible after the discontinuation of TRT. Elevation of haematocrit above the upper limit of normal (polycythaemia) is the most common adverse effect of TRT and has been associated with CV events and/or venous thromboembolism due to blood hyperviscosity, particularly when haematocrit levels exceed 54 % [108].

Due to TRT's possible atherogenic and thrombogenic effects, most RCTs excluded men with a recent history (less than six months) of myocardial infarction or stroke. Recently, the Testosterone Replacement therapy Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) study was published; this was a phase-4, randomised, double-blind, placebo-controlled, parallel-group, non-inferiority, multicentre study with 5204 symptomatic hypogonadal (tT < 300 ng/dL) men of middle to older age (45 to 80 years). These men had pre-existing CV disease or increased risk of CV disease and may had had an acute coronary syndrome or stroke in the four months before their randomisation [109]. A recent Mendelian randomisation study from the UK Biobank has confirmed an association between endogenous T and myocardial infarction and heart failure in men [110]. Moreover, due to the ability of T to cause fluid retention and aggravate oedematous conditions such as heart failure, patients with severe [New York Heart Association (NYHA) Class III or IV] or decompensated heart failure have normally been excluded from RCTs on TRT. Consequently, most guidelines deter clinicians from using TRT in these groups of patients.

Epidemiological data show that the prevalence of a first episode of recurrent venous thromboembolism (VTE) is higher in men than women. Pathophysiological data suggest a prothrombotic action of T mediated by polycythaemia and ensuing blood hyperviscosity, as well as increased platelet aggregation, due to increased expression of the thromboxane A2 receptor. Moreover, exogenous T may indirectly activate the thrombotic mechanism by its aromatisation to E2 [111]. Accordingly, the study mentioned above from the UK Biobank demonstrated a positive association between endogenous T and VTE in men [110]. On the other hand, large population-based studies failed to confirm this association [112]. Data from case reports and post-marketing surveillance reports have also associated TRT with VTE, while a meta-analysis of three RCTs reporting VTE in the context of TRT (283 participants taking TRT and 233 controls) showed more than a five-fold increase in the risk of VTE compared with placebo (odds ratio 5.94, 95 % CI 1.00 to 35.3) [113]. This, and similar evidence, led the US Food and Drug Administration to require a label on T products warning about the risk of VTE. A subsequent population-based case-control study from the UK showed an increased risk of VTE among men on TRT, particularly in the first six months (adjusted OR 1.63, 95 % CI 1.12 to 2.37), which was similar across the various routes of administration (intramuscular vs. transdermal vs. oral testosterone), but this declined over time [114]. A retrospective chart review of patients hospitalised for pulmonary embolism also demonstrated an elevated risk for VTE that peaked during the first six months of TRT [115]. This study also showed that most TRT-related cases of VTE may have been related to undiagnosed inherited thrombophilia. The TRAVERSE study showed a higher incidence of thromboembolic events in the T than in the placebo group (44 vs. 30, or 1.7 % vs. 1.2 %), ranging from venous thrombosis to pulmonary embolism, although this difference was not statistically significant (hazard ratio 1.46, 95 % CI 0.92–2.32) [109].

2.6.3. Fertility

The ability of exogenous TRT to suppress the output of the HPT axis and, subsequently, spermatogenesis is well established and used in proof-of-concept studies for male hormonal contraception [116]. Therefore, TRT is expected to hamper the efforts of men actively seeking fertility. However, the negative impact of T on fertility is transient and recovery to baseline is anticipated, reaching 90 % in 12 months and almost 100 % within 24 months [117].

Summary recommendation. TRT should not be attempted in older men with BrCa and untreated CaP and should be preceded by digital rectal examination (DRE) and PSA measurement to identify pre-existing CaP. Those with abnormal DRE and PSA >4 ng/mL should undergo further urological evaluation. Men with a recent history (<4 months) of myocardial infarction or stroke and severe (NYHA Class III or IV) or decompensated heart failure should also be precluded from TRT. Haematocrit should be measured before initiating TRT, and if it exceeds the normal range therapy has to be postponed until it has normalised. A personal history of VTE is a contraindication for TRT; for men with a family history of VTE, inherited thrombophilia should be excluded before the initiation of TRT. TRT is contraindicated in hypogonadal men actively seeking fertility.

2.7. Areas of uncertainty

2.7.1. Cardiovascular risk and testosterone treatment

A large amount of data endorse the association between hypogonadism and increased risk for CV events [118,119]. It would therefore seem reasonable that normalising T concentrations will reduce the incidence of CV events. However, there has been concern, based mainly on older studies, that TRT might instead increase CV risk in men [120–122]. Pharmaco-epidemiological studies [120,121], along with one RCT [123] and one meta-analysis [124] published in prestigious international journals, have highlighted possible TRT-related CV effects. However, these papers had major flaws, precluding meaningful conclusions. The two retrospective observational studies [120,121] have been strongly criticised [125,126] regarding the short follow-up and the retrospective design (i.e., prescription does not mean consumption), while some authors even asked for retraction [127]. The interpretation of epidemiological data is biased by the effect of many parameters (including selection, information, and confounding biases), and observational studies should not be interpreted to infer causal relationships, which are more properly addressed by RCTs.

The meta-analysis by Xu et al. [124] evaluated 27 RCTs and concluded that TRT increased by 54 % the risk of a very broad set of "CV-related events". However, in this study, "events" included clinically questionable anecdotal conditions not normally considered in the assessment of CV risk (including peripheral oedema, hypertension, and self-reported syncope), leading to an artificial increase in the overall number of events. The Testosterone in Older Men with Mobility Limitations (TOM) trial [123] examined the effects of doses of T which produced supraphysiological T levels in frail older men with limitations in motility and also used a very broad definition of CV events. The trial was prematurely terminated for concern over CV safety, but its results are difficult to generalise for the reasons mentioned.

On the other hand, several epidemiological studies strongly support the association of low serum T/hypogonadism with CV events, especially in older men [128,129]. Many retrospective cohort studies demonstrated no effect [130–132] or beneficial effects [119] of TRT (various formulations prescribed to an extremely heterogeneous cohort of patients) on CV risk, but these studies are affected by all the limitations intrinsic to the retrospective design.

As mentioned above, TRT favourably changes many CV risk factors since it decreases fat mass and insulin resistance, increases muscle mass, and can reverse metabolic syndrome in some men. No RCTs have had sufficient statistical power to evaluate the CV risk related to TRT in men. Available evidence comes from short-term studies (mostly less than a year) or RCTs designed for other outcomes.

An RCT with 156 patients older than 60 years and low-normal T concentrations (3–14 nmol/L) demonstrated that testosterone (7.5 g of 1 % gel) administration for three years did not result in a significant difference in the rates of change in either common carotid artery intima-media thickness or coronary artery calcium (TEAAM study) [133]. On the other hand, a similar multicentre RCT with 138 patients aged over 65 years with low T concentrations (<10 nmol/L), who were treated with testosterone 1 % gel 5 g/day for one year, showed a greater increase in coronary artery non-calcified plaque volume (as assessed by coronary computed tomographic angiography) compared with placebo. Whether these alterations translate into increased CV risk is unknown [134].

Finally, a multicentre trial with 788 men older than 65 years with low T concentrations (<10 nmol/L) evaluated the effects of testosterone gel 1 %, 5 g a day for 12 months on serum markers of CV risk (lipids, glucose metabolism, fibrinolysis, inflammation, and myocardial damage). TRT was associated with small reductions in cholesterol (total, LDL- cholesterol, and HDL-cholesterol) and insulin, but not with other glucose markers (HbA_{1c}), markers of inflammation, fibrinolysis, or troponin levels [135].

Six meta-analyses (that included both RCTs and observational studies) have evaluated the effect of TRT on CV risk in men with low-normal T concentrations (<15 nmol/L). It should be emphasised that none of the trials included was designed to assess CV events as a primary outcome; moreover, the studies evaluated various T formulations and treatment duration ranging from 6 weeks to 3 years.

T did not increase major adverse cardiovascular events (MACE), CV risk, or mortality in most of the studies [136–138], even after adjusting for baseline age, BMI, T concentrations [14,136,138], or formulation [14]. Subgroup analysis confirmed a protective effect of TRT in men with metabolic derangements [136] and obesity [14], but showed

increased CV events in frail patients [14], those older than 65 years, and those treated for <12 months [138] or at doses above the current recommendations [14]. Finally, two large independent meta-analyses of RCTs [139] and observational studies [140,141] found that TRT was not associated with an increased risk of VTE, but the quality of evidence was low.

The TRAVERSE study was designed and powered to determine CV safety of TRT in middle-aged and older men (half of them over the age of 65), with either pre-existing or a high risk of CV disease [109]. CV disease was defined as clinical or angiographic evidence of coronary artery disease, cerebrovascular disease, or peripheral arterial disease. Increased CV risk was defined as the presence of three or more risk factors (hypertension, dyslipidaemia, current smoking, stage-3 chronic kidney disease, diabetes, elevated high-sensitivity C-reactive protein level, age of 65 years or more, increased Agatston coronary calcium score). Patients were randomised in a 1:1 ratio to either daily transdermal testosterone gel (1.62 %) or a matching placebo for a mean duration of approximately 22 months. Men with a history of thrombophilia or recent (within 4 months) acute coronary syndrome, stroke or coronary/peripheral revascularisation were excluded from the study.

The primary end point of the study was the first occurrence of any component of MACE, a composite of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke in a time-to-event analysis. The secondary end point included the previous components with the addition of coronary revascularisation in a time-to-event analysis. Tertiary end points included death from any cause, hospitalisation or an urgent visit for heart failure, peripheral arterial revascularisation, and venous thromboembolic events.

The results showed that TRT was safe and did not increase the incidence of major adverse cardiac events over placebo (7.0 % vs. 7.3 %; HR 0.96, 95 % CI 0.78–1.17). Accordingly, the incidence of secondary end points or of each of the events of the composite primary cardiovascular end point appeared to be similar in the two groups. Among the tertiary end points, a slightly higher incidence was demonstrated only for venous thromboembolism in the testosterone group over placebo, confirming that T should be used with caution in men who have had thromboembolic events. The testosterone group also had higher rates of non-fatal arrhythmias (5.3 % vs. 3.3 %) and atrial fibrillation (3.2 % vs. 2.4 %) than the placebo group; additionally, a small increase in blood pressure was observed, similar to that reported previously with other testosterone formulations.

Summary recommendation. The quality of evidence regarding the cardiovascular safety of TRT in LOH has been low. However, the most recent data have shown that testosterone treatment in older men with hypogonadism and at increased cardiovascular risk is safe, at least in terms of major adverse cardiac events. Nevertheless, a thorough evaluation of the patient's CV risk prior to TRT is mandatory, as is strict compliance to prescription guidelines regarding dose and treatment monitoring. CV risk must be re-evaluated during TRT, and patients should be informed about the lack of definitive studies on TRT's long-term effects (>3 years). TRT must not be offered as a cardioprevention therapy to frail older men until better outcome data are available.

2.8. Prostate health and testosterone treatment

Recent data cast doubt on the dogma of Huggins and Hodges [142] regarding the dependence of CaP on androgens [143]. According to older population studies and a more recent meta-analysis, the incidence of CaP appears to be unrelated to endogenous T concentrations [144,145]. Men with CaP do not seem to have higher T concentrations than those without cancer; on the contrary, low T concentrations may predict more aggressive forms of CaP [146]. Moreover, CaP is more prevalent in older men, at ages when T concentrations decline. Similar conclusions may be drawn regarding TRT in men with hypogonadism, which does not appear to increase the incidence of CaP compared either to the general population (incidence <1 %) or to controls [odds ratio (OR) 0.97, 95 % CI 0.35 to 2.69] [38,109,144]. These findings align with the "prostate saturation" hypothesis, according to which when all androgen receptors of the prostate are saturated, a further increase in circulating T cannot affect the prostate gland [147].

Questions have been raised about whether CaP survivors with symptomatic hypogonadism can safely undergo TRT. Meta-analysing observational data from retrospective studies shows that TRT does not increase the risk of biochemical recurrence or progression of CaP after radical prostatectomy [148]. Similar results were obtained for patients treated with external beam radiation therapy, brachytherapy, cryotherapy, or high-intensity focused ultrasound, though the recurrence rate was higher compared with radical prostatectomy [149]. Patients whose initial assessment demonstrated a low-risk localised CaP (Gleason score <7, pT1–2, preoperative PSA <10 ng/ml) and who have constantly undetectable PSA concentrations after radical prostatectomy seem to have a lower risk of recurrence [143]. Nevertheless, it should be stressed that no RCTs have been conducted on this issue, rendering the level of evidence low and, thus, patients should be informed accordingly, give informed consent before TRT, and undergo close monitoring.

Concerns have also been expressed about the ability of TRT to augment prostate volume and to worsen lower urinary tract symptoms (LUTS); thus, men with severe LUTS, as defined by an International Prostate Symptom Score (IPPS) >19, are usually excluded from trials on TRT. Accordingly, TRT in this population is contraindicated in most guidelines. However, this recommendation is not based on high-quality evidence [150]. Meta-analysis of studies of TRT in men with pretherapeutic mild LUTS did not show either a worsening of symptoms or an increase in prostate volume after treatment [151]. A recent trial that included hypogonadal men with metabolic syndrome and benign prostate hyperplasia showed that TRT can improve indices of prostate inflammation [152].

Summary recommendation

TRT may be considered in hypogonadal men with a history of previous low-risk, localised CaP (Gleason score <7, pT1–2, preoperative PSA <10 ng/mL) who have constantly undetectable PSA concentrations after a radical prostatectomy; however, close monitoring is mandatory. TRT should not be avoided in men with hypogonadism and benign prostate hyperplasia/LUTS; however, caution should be paid to those with severe LUTS (IPSS >19).

2.9. How to treat

A common question is whether TRT should be lifelong. Studies investigating the effects of TRT withdrawal on patients with hypogonadism showed that such a strategy resulted in a prompt reduction of tT to hypogonadal levels. Moreover, substantial outcomes of TRT, such as changes in body composition, sexual function, and IPSS scores that improved during TRT, worsened after therapy discontinuation [153]. According to these results, therefore, TRT is effective only as long as it is applied [106].

Oral, transdermal (gel or patch), transmucosal (trans-buccal or nasal), and intramuscular T formulations are available. Regarding TRT efficacy, recent systematic reviews and network meta-analyses have not shown a clear advantage of any individual product, apart from the inferiority of oral formulations in improving libido compared with the injectable ones [38,40]. Older oral methylated compounds have been associated with liver toxicity. Oral esterified preparations, although lacking these adverse properties, are impractical since they must be administered several times daily and accompanied by food ingestion due to their lipophilic nature [154]. Recently, a new oral T undecanoate formulation was evaluated in a phase-3 clinical trial and proved to restore T concentrations in men with hypogonadism, when administered

every 12 h concomitantly with a meal [102]. Nevertheless, this study demonstrated an increase in systolic blood pressure of 3–5 mm Hg during TRT, which led the FDA to publish a statement deferring approval of this new oral T undecanoate in older men with LOH.

Mid-range and long-acting injectable T esters (T enanthate and T undecanoate, respectively) are among the most popular options for TRT due to their practicality; however, they have been associated with more frequent erythrocytosis (T enanthate in particular), which may carry elevated CV risks among older men [155]. Long-acting T is also available in the form of pellets, which are implanted in the subcutaneous adipose tissue and may last up to 6 months. However, their application requires a minor surgical incision, and they are currently not available in Europe apart from the UK [156]. Transdermal preparations, particularly short-acting gels, are associated with less serious adverse events and may rapidly be cleared from circulation if necessary. On the other hand, TRT with gel preparations is associated with high intra-individual variability in serum T levels, which hampers accurate biochemical follow-up [157]. Nasal and buccal preparations are associated with local irritation and are not currently available in Europe [158].

In men with functional hypogonadism, remission is anticipated after the withdrawal/substitution of factors or medications known to disrupt the HPT axis and appropriate lifestyle modifications [10]. Data from the European Male Ageing Study and recent meta-analyses consistently show that weight reduction increases T concentrations, independently of how it is achieved (diet, pharmaceutical, or surgical intervention), in overweight or obese men with functional hypogonadism [159,160]. This correlation is linear and meta-regression analysis has calculated that each 5 kg of weight reduction results in a 1 nmol/L increase in tT. Similar results are achieved by moderate aerobic exercise, particularly when combined with weight loss [161]. However, in a recent RCT of obese hypogonadal men with erectile dysfunction, TRT combined with weight loss was superior to weight loss alone in improving ED [162].

Summary recommendation. There is no clear maximum duration for TRT. Short-acting transdermal preparations should be the preferred method of administration for older men, due to the avoidance of liver metabolism, a lower complication rate, in particular regarding polycythaemia, and the possibility of prompt withdrawal if required. Injectable forms of T may be considered if transdermal TRT has proven beneficial and safe in a given patient. In cases suggestive of functional hypogonadism, withdrawal or substitution of detrimental factors should be advised when possible, and in overweight or obese patients, weight loss by any means combined with exercise should be the first-line recommendation, possibly supported with TRT to augment the effects and reinforce the patient's commitment to lifestyle modifications.

2.10. Monitoring schedule

Monitoring of TRT should take into consideration efficacy and safety. Improvements in sexual desire, mood, and quality of life usually occur in the first weeks of treatment. During the same period, it is possible to detect behavioural disturbances, since exogenous T has been shown to potentiate aggressive behaviour, in particular among men with a dominant or impulsive personality [163]. The effects on erythropoiesis and metabolic parameters such as glycaemic control and lipid profile may take up to three months. The impact of TRT on body composition and bone health is expected to appear later, usually between 6 and 12 months of treatment, and may continue further during TRT. PSA concentrations may rise after three months of TRT but after 12 months tend to stabilise at around the levels of eugonadal men [164].

The optimal concentrations of tT during TRT in older men have not been assessed; however, it would be prudent not to exceed the upper limit of normal for young, healthy men, as supraphysiological tT concentrations are associated with erythrocytosis. The clinical significance of erythrocytosis and its association with thromboembolism is ill-defined; however, in a population study, haematocrit in men exceeding 54 % was associated with CV disease [73,108,165]. If this is the case, TRT dosing should be decreased, while T withdrawal and phlebocentesis may assist in refractory cases. Regarding PSA, elevations >1 ng/mL are not common during TRT, while <5 % of men on TRT experience elevations >1.4 ng/dL [8]. Accordingly, PSA elevation >1.4 ng/dL within 3–12 months of TRT should warrant urological evaluation.

The effects of TRT and/or anti-resorptive therapy on BMD may be assessed using dual-energy X-ray absorptiometry (DXA) at the spine and hip according to the relevant guidelines [73], even though evidence supporting follow-up with DXA as a means of treatment monitoring is weak [166]. Moreover, the appropriate frequency of follow-up with DXA is ill-defined, ranging from annual to 5-year intervals, and depends greatly on the fracture risk of each individual.

Summary recommendation

Older men on TRT should be monitored at 3, 6, and 12 months after initiation and yearly after that. Evaluation should include the assessment of clinical response, and measurement of tT concentrations, haematocrit, and PSA. BMD should be assessed using DXA and follow-up may be at one year or up to 5 years according to the patient's fracture risk. The monitoring schedule is summarised in Fig. 3.

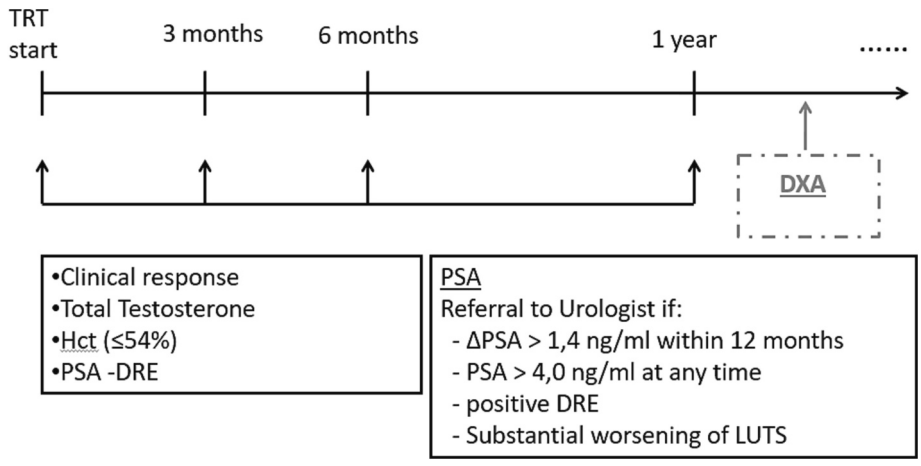

Fig. 3. Monitoring schedule for testosterone replacement therapy (TRT) in older men.
Hct: haematocrit; PSA: prostatic specific antigen; DRE: digital rectal examination; LUTS: lower urinary tract symptoms.

3. Conclusions

The identification of clear, evidence-based indications for treating LOH remains an unmet need. An individualised, tailored approach is strongly recommended when considering hormone replacement therapy. TRT has shown the potential to reduce age-related comorbidities and improve quality of life. However, there are multiple areas of uncertainty and a need for large-scale, prospective, adequately powered RCTs specifically designed to examine the efficacy of TRT and its safety particularly in relation to metabolic and bone health, and prostate disease.

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