CONSENSUS STATEMENT

Adult- and late-onset male hypogonadism: the clinical practice guidelines of the Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE)

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Abstract

Purpose To provide the evidence-based recommendations on the role of testosterone (T) on age-related symptoms and signs remains.

Methods The Italian Society of Andrology and Sexual Medicine (SIAMS) and the and the Italian Society of Endocrinology (SIE) commissioned an expert task force to provide an updated guideline on adult-onset male hypogonadism. Derived recommendations were based on Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.

Results Clinical diagnosis of adult-onset hypogonadism should be based on a combination of clinical and biochemical parameters. Testosterone replacement therapy (TRT) should be offered to all symptomatic subjects with hypogonadism after the exclusion of possible contraindications. T gels and the long-acting injectable T are currently available preparations showing the best efficacy/safety profile. TRT can improve all aspects of sexual function, although its effect is limited in more complicated patients. Body composition (reducing fat mass and increasing lean mass) is improved after TRT, either in subjects with or without metabolic syndrome or type 2 diabetes. Conversely, the role of TRT in improving glycometabolic control is more conflicting. TRT can result in increasing bone mineral density, particularly at lumbar site, but no information on fracture risk is available. Limited data support the use of TRT for improving other outcomes, including mood frailty and mobility.

Conclusions TRT can improve sexual function and body composition particularly in less complicated adult and in aging subjects with hypogonadism. When hypogonadism is adequately diagnosed, T appropriately prescribed and subjects correctly followed up, no short-term increased risk of adverse events is observed. Longer and larger studies are advisable to better clarify TRT long-term efficacy/safety profile.

Keywords Late-onset hypogonadism · Testosterone · Hypogonadism · Erectile dysfunction · Obesity · Metabolic syndrome · Bone mineral density

Introduction

During the last 2 decades, there was a growing awareness concerning male hypogonadism and its potential treatment. To the classical forms of hypogonadism, the description of an “age-associated testosterone decline”, supported by several epidemiological studies [1–4], widely broadened the number of potentially treatable men. To what extent the decline in testosterone (T) concentrations observed in the aging male contributes to age-related morbidities and symptoms remains under scrutiny [5]. Interestingly, the sales of T-containing medications dramatically increased worldwide [6]. While the global trend reflected an increased awareness toward male hypogonadism, often an underdiagnosed and undertreated condition with a worldwide evenly distributed prevalence in North America reflected the effect of direct-to-consumer advertising (DTCPA). T treatment was inappropriately promoted as a fountain of youth, and exposure to televised DTCPA was associated with greater T testing, new initiation of therapy and, especially, initiation of therapy without prior T testing [7]. To halt T overuse, the US Food and Drug Administration (FDA) cautioned that the benefits of T treatment were not clearly established when T
concentrations were low due to aging [8]. The FDA warned that T replacement therapy (TRT) should be considered only for men with “classical hypogonadism”, i.e. due to primary or secondary T deficiency resulting from known problems within the testis, pituitary, or hypothalamus [8]. Later on, this concept was partially introduced into the clinical practice guidelines of the US Endocrine Society [9] as well as in the Australian one [10] advocating a theoretical dichotomic distinction between organic (classic) and functional hypogonadism, the latter including the age-associated T deficiency.

In Southern Europe, however, the picture is different and DTCPA more often prohibited. The first Italian guidelines covering the issue of male hypogonadism, including age-associated deficiency, were issued in 2015 by the Italian Society of Endocrinology [11]. Important multicenter trials have been published since then, disclosing novel data on the effectiveness of TRT on various outcomes. Considering the different background between the European and North American situation, aim of these guidelines is to provide an evidence-based updated support to clinician operating on male hypogonadism on behalf of the Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE).

Methods

The SIAMS and SIE are large national multidisciplinary non-profit scientific societies leading research in this field. The SIAMS and SIE have commissioned an expert task force to provide an updated guideline on male hypogonadism. Following scrutiny and discussion of the best evidence from published literature available in PubMed, the Authors generated a series of consensus recommendations according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [12]. The GRADE system allows to rate the quality of evidence and the strength of recommendations and to enhance the value of the clinical advices here provided [12] with a consistent language and graphical descriptions for standardizing the grading of both the strength of recommendation and the quality of evidence [12]. Concerning the strength of recommendation, the number 1 indicates a strong recommendation and is associated with the terminology “we recommend”; the number 2 denotes a weak recommendation and is associated with the wording “we suggest”. The four levels grading of the quality of evidence employs the following graphical descriptions: ○○○○○ denotes “very low-quality evidence”, ○○○○ “low quality”, ○○○○ “moderate quality”, and ○○○○○ “high quality”.

According to SIAMS rulings, these Guidelines have been arranged by a team of experts on the topic coordinated by the senior author and two members of the SIAMS Guideline Committee, then sent to the SIAMS and SIE Executive Committee and to the Directors of all SIAMS Excellence Centers for revisions and/or approval. Guidelines have then been announced by mail and published for two weeks on the SIAMS and SIE Society’s website, siams.info, so that all SIAMS Members could provide further comments and suggest additional minor revisions. Following this last step, the present manuscript has been submitted to the Journal of Endocrinological Investigation for international peer reviewing.

Definitions

Hypogonadism refers to a clinical and biochemical syndrome characterized by the inability of the testes to produce physiological concentrations of T and/or number of normal sperm cells [13–16]. Male hypogonadism can be due to a testicular dysfunction (primary hypogonadism), a pituitary/hypothalamic failure (secondary hypogonadism) or a combination of both (mixed hypogonadism) [13, 14, 16]. Some classifications also consider the onset of symptoms (e.g., late-onset hypogonadism—LOH) or the potential reversibility of the condition. In this respect, “organic hypogonadism” refers to an irreversible form of hypogonadism caused by congenital or acquired (destructive or structural) impairment occurring at any level of the hypothalamic–pituitary–testis axis [17–19], while “functional hypogonadism” refers to a potentially reversible impairment of the hypothalamic–pituitary–testis feedback loop. Functional hypogonadism more often occurs in middle aged or older men (> 40–50 years), is associated to comorbid illnesses (e.g. poor health or obesity), and is associated with a less marked lowering of T concentrations [17–19]. The latter classification is not universally accepted and still a matter of vivid debate.

Clinical presentation

Signs and symptoms of hypogonadism vary according to the age of onset, etiology and severity of T reduction [20, 21]. In adults, the predominant symptoms include sexual dysfunctions (e.g., erectile dysfunction, decreased libido, reduced nocturnal/morning erections), fatigue, impaired concentration, sweating, low wellbeing and depressive mood [13, 14, 20, 21]. Increased body fat, decreased muscle mass and body hair, gynecomastia and reduced testicular volume are common findings at physical examination. Hypogonadism is also associated with anemia, lower prostatic-specific antigen (PSA) concentrations for age, and reduced bone mineral density [13, 14, 20, 21] (Fig. 1).
Diagnosis

We recommend measuring total testosterone (tT) and luteinizing hormone (LH) in all men with clinical manifestations consistent with hypogonadism and to adopt a threshold of $\leq 12.0 \text{ nmol/L}$ to define low total testosterone ($1000\text{O}$).

We suggest measuring sex hormone-binding globulin (SHBG) during diagnostic workup to calculate free testosterone in all men with clinical manifestations consistent with hypogonadism and to adopt a threshold $< 220 \text{ pmol/L}$ to define low calculated free testosterone ($fT$) ($2000\text{O}$).

A value of LH $\geq 9.4 \text{ IU/L}$, in the presence of low total or calculated free testosterone, suggests primary hypogonadism. For LH concentrations $< 9.4 \text{ IU/L}$, measuring follicular stimulating hormone (FSH) is helpful in the differential diagnosis between primary and secondary hypogonadism ($2000\text{O}$).

We suggest a diagnosis of compensated hypogonadism in presence of LH $\geq 9.4 \text{ IU/L}$ and normal testosterone or calculated free testosterone concentrations (Expert Opinion).

Evidence

The diagnosis of hypogonadism relies on the concomitant presence of low T concentrations and clinical symptoms and signs of T deficiency [13, 14, 16, 20–22]. Sexual symptoms (erectile dysfunction, low libido, reduced nocturnal erections) are the most frequently complained in adult men with reduced T concentrations [22, 23].

The diagnosis requires the detection of a low T on two separate occasions with blood taken in the morning in standardized conditions, i.e., before 10:00 am and fasting. Liquid chromatography–tandem mass spectrometry (LC–MS/MS) is considered the gold standard for T measurement; however, good-quality immunoassays still provide reliable results in the clinical settings [24]. Conversely, the available immunoassays cannot guarantee accurate values of fT. Hence, fT evaluation by immunoassay is discouraged [25].

To date, there is no agreement on what should be the T threshold value defining hypogonadism or the lower limit of normal for T distribution in the population, whose values (harmonized to the 2.5th percentile) ranges from 264 ng/ml (9.2 nmol/L) to 348 ng/ml (12 nmol/L), according to large cohort studies on healthy, non-obese, young adult males [26]. However, different thresholds, ranging from 220 (7.6 nmol/L) to 350 ng/dl (12.1 nmol/L), have also been proposed [15]. Data derived from available meta-analyses suggest that TRT is without effects in subjects with baseline T concentrations $> 12 \text{ nmol/L}$ (3.5 ng/mL) (Fig. 2) [20, 27]. Since some beneficial effects on various outcomes have been
documented when T concentrations are below 12 nmol/l [20, 27], the panel reached consensus on adopting the 12 nmol/L as a threshold for considering TRT in symptomatic hypogonadal men.

The EMAS study showed that fT improved the possibility to correctly identify LOH. According to that study, reduced fT (< 220 pmol/L) increased the odds ratio for hypogonadism as compared with the total T level alone, especially for thresholds between 8.0 and 11 nmol per liter [22, 28]. Similar data have been observed in the longitudinal evaluation of the same study [29].

fT can be determined after physical separation from the protein-bound forms, which is achieved through equilibrium dialysis or ultracentrifugation. Equilibrium dialysis is the most accurate method [30]. However, the latter is expensive, time-consuming, and unfeasible in a clinical setting. Several SHBG and albumin level-based calculations have been proposed to estimate fT (cfT). The Vermeulen method [31] is still the most accurate, albeit slightly overestimating fT value [30].

The classification into primary vs. secondary hypogonadism has important clinical and therapeutic implications [13, 14]. According to the baseline data of European Male Aging Study (EMAS), LH concentrations ≥ 9.4 IU/L define primary hypogonadism, whereas low or low-normal LH concentrations, in the presence of reduced T concentrations, define secondary hypogonadism. LH concentrations failing to rise when T is low, suggest they are inappropriately normal [32]. When LH concentrations are close to the 9.4 IU/L threshold value, FSH determination, a marker of Sertoli function [33], may help to identify primary testicular failure, despite there is no consensus on a specific FSH threshold value [13, 14].

Conversely, a suspect of organic secondary hypogonadism requires additional investigations including magnetic resonance imaging (MRI) scanning of the pituitary-hypothalamus, iron saturation as well as prolactin and other anterior pituitary function. To adopt cost-effective strategy, the aforementioned examinations are indicated when a greater suspicion is driven by specific features including—but not limited to—pituitary mass effects symptoms, visual disturbances, headache or significant hyperprolactinemia or severely reduced T concentrations (i.e. < 6 nmol/L or < 175 ng/dL) are detected ([34–36]; see also Fig. 2).

According to EMAS data, LOH is more frequently characterized by a secondary or mixed, rather than primary or ‘compensated’ hypogonadism [32]. The EMAS consortium proposed to categorize men with a ‘compensated hypogonadism’ those having normal T and elevated LH (≥ 9.4 IU/L) [32]. These subjects report mainly physical symptoms, and they had 16-fold increased risk to progress to genuine primary hypogonadism over time, when compared to eugonadal individuals [37]. For this reason, as for thyroid

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**Fig. 2** Proposed flowchart to diagnose and manage adult-onset hypogonadism: cFT calculated free, testosterone; FSH follicular-stimulating hormone, LH luteinizing hormone, SHBG sex hormone binding globulin, T testosterone. The dashed lines reflects a lower level of evidence
disorders, it could be named ‘subclinical hypogonadism’ in which ‘decompensation’ occurs when T fell into the hypogonadal range. However, current data on long-term clinical significance of compensated hypogonadism and the impact of TRT in affected subjects are scanty, making advisable a watchful follow-up (Fig. 2) [37–39].

Remarks

Clinical manifestations of hypogonadism can occur at different T thresholds and, owing to inter-individual variability, some patients may experience symptoms having serum T in the range of, rather than at, the punctual, threshold values [22]. For this reason, information coming from LH, SHBG and cfT is much needed. Available data suggest that immunoassays for SHBG evaluation correlate closely with data obtained from LC–MS/MS. However, comparisons of different SHBG immunoassays showed a weaker inconsistent correlation of free T and bioavailable T [40]. On the other hand, several clinical conditions can influence SHBG concentrations (Table 1) limiting the validity of only total T evaluation for a correct clinical diagnosis of hypogonadism.

TRT options

We recommend starting TRT in all symptomatic hypogonadal men, after contraindications are excluded, in whom a reversal of the condition cannot be expected in a reasonable time-frame (1 Ø000).

We suggest using testosterone gels in older hypogonadal men, in particular in case of potentially reversible conditions (Expert Opinion).

We suggest using long-acting injectable T preparations to treat younger hypogonadal men, in particular in case of irreversible conditions (Expert Opinion).

| Evidence |

T delivered at any age with several preparations, including oral, parental and transdermal T formulations (Table 2), once patients are adequately informed on the advantages and disadvantages of TRT and available formulations. Absolute contraindications should be ruled out and the final decision should be made balancing the clinical situation, available formulations and patient preferences.

Compared to primary hypogonadism, LOH can be a reversible condition associated with co-morbidities and medications interfering with T production or activity. Lifestyle modifications and weight loss should be strongly encouraged in all overweight and obese men with hypogonadism since able to increase T levels per se [19]. Similarly, when possible, interfering drugs should be withdrawn [41].

Old oral T undecanoate formulations, although still available in Europe and in Italy are no longer recommended, due to the poor bioavailability [42]. The US FDA approved a new formulation of oral T undecanoate incorporating a liquid-filled hard capsule drug delivery system improving oral availability (https://www.fda.gov/media/110187/download). However, the latter compound is not yet available in several European countries. Very short- or short-acting parental T formulations such as propionate, cypionate and enanthate have been associated with wider fluctuations of T concentrations, often resulting in patient discomfort and more adverse effects, such as polycythemia [42]. At present time, long-acting injectable T undecanoate and T gels appear the most suitable formulations to restore serum T concentrations in the normal range with good safety profile [42, 43].

The implantation of T pellets represents the longest available T formulations lasting from 4 to 7 months. Implants have a good safety profile, but the procedure is invasive, limiting its widespread use [42]. In addition, the latter, like the trans-nasal and trans-buccal formulations, are not available in Italy. Although face-to-face comparisons among different T formulation are lacking, T gels should be preferred in older subjects with a higher risk profile or when a potential reversible condition is suggested. The T gel formulations

| Table 1 Main factors associated with an increase or with a reduction of Sex hormone binding globulin (SHBG) circulating levels |
| SHBG increase | SHBG decrease |
| Drugs: anticonvulsant, estrogens, thyroid hormone, antiretroviral drugs | Drugs: GH, glucocorticoids, testosterone, Anabolic androgenic steroids |
| Hyperthyroidism | Hypothyroidism |
| HIV disease | Obesity |
| Cirrhosis and hepatitis | Acromegaly |
| Aging | Cushing Disease |
| | Insulin resistance |
| | Nephrotic syndrome |
may also better mimic the circadian variation in T secretion, higher in the morning and lower at bedtime [42]. Conversely, when hypogonadism is irreversible, especially in younger patients, long-acting parental injectable formulation should be considered, as the first option. Accordingly, the daily application of rub-on gel is often considered a time-consuming procedure, reinforcing the suffering from a chronic condition, with possible consequences on long-term compliance. In contrast, long-lasting injectable T preparations, requiring between three to five deliveries per year, can relieve the patient from being remembered daily to suffer from a chronic, irreversible condition [43].

**Remarks**

Data on the role of TRT in patients with compensated hypogonadism are lacking. This condition represents only a preclinical form of an overt hypogonadism, which might deserve an adequate follow-up. TRT should be started only when overt hypogonadism occurs.

Anti-estrogens or aromatase inhibitors have been frequently used for the treatment of secondary hypogonadism, especially in patients with obesity or with metabolic derangements [44]. However, up to now, the available data are limited and more studies are advisable to better clarify the use of these compounds in patients with LOH.

### Contraindications

#### Prostate and breast contraindications

*We recommend against starting TRT in patients with active breast and prostate cancers (Good clinical practice).*

*We suggest not considering a treated low-risk prostate cancer as an absolute contraindication to TRT (2, ØOOOO).*

*We suggest not considering a mild-to-moderate lower urinary tract symptoms (LUTS) as absolute contraindication to TRT (2, ØØØØ).*

### Evidence

Prostate cancer (PC) growth and development occur in a T-sensitive manner [45]. As a result, hormonal castration is included among the available therapeutic options.
for advanced and metastatic PC [46]. This justifies the absolute contraindication of TRT in patients with PC. Similarly, patients with a suspicion of PC (e.g., increased/raising PSA concentrations and/or relevant findings at digital rectal examination) deserve further evaluation before commencing TRT. Some meta-analyses reported a very low risk of PC recurrence in patients on TRT after local therapy completion (radical prostatectomy, external beam radiation therapy, brachytherapy, cryotherapy) [47, 48]. However, it should be recognized that the available data are insufficient to address this issue, due to the high heterogeneity and limited follow-up. Hence, risks and benefits of starting TRT in symptomatic hypogonadal men with a treated low-risk PC should be extensively discussed and tailored to the individual condition.

Male breast cancer (MBC) is a rare tumor. Even in men, breast cancer can be hormone sensitive. Considering that breast cancer tissue expresses high levels of P450 aromatase [49], it is conceivable that T administration to an otherwise hypogonadal man with a history of treated mammary cancer could increase the risk of recurrence, although evidence on this topic are very limited [50].

The effects of TRT on benign prostatic hyperplasia (BPH) and low LUTS are a matter of debate. Although some concerns have been raised in patients with BPH-LUTS on TRT, a meta-analysis of 14 RCTs (2029 participants, mean follow-up 34.4 months) reported that TRT does not change the International Prostatic Symptoms Score (IPSS) in patients with LOH [51]. Similarly, another meta-analysis on RCTs (1779 patients) reported no effect of TRT on LUTS [52]. A single study carried out in 52 patients with hypogonadism, mild BPH and LUTS showed an improvement of IPSS, maximum flow rate, and voiding volume and no change in post-voiding residual volume after 12 months compared with an untreated control group [53]. It is important to note that these data refer to patients with mild-to-moderate LUTS since patients with severe LUTS (IPSS > 19) were systematically excluded from RCTs [27].

Values

The evidence places a high value on the unsafe use of TRT in patients with active breast and prostate cancers. The evidence against considering mild-to-moderate LUTS as an absolute contraindication for TRT in patients with hypogonadism is of moderate quality.

Remarks

Limited evidence is available on the effects of TRT in patients with severe LUTS (IPSS > 19), mainly because they are not included in RCTs. Moreover, BPH has not been clearly specified as an inclusion criterion in meta-analytical studies exploring the effects of TRT on LUTS [51, 52, 54].

Cardiovascular contraindications

We suggest not considering mild-to-moderate heart failure as an absolute contraindication for TRT (2, ØØOO).

We suggest not prescribing TRT to patients with a recent major adverse cardiovascular event (2, ØØOO).

We suggest considering the global cardiovascular risk and associated morbidities, including hematocrit level, before prescribing TRT (2, ØØOO).

We suggest collecting a detailed family, personal and clinical history of venous thromboembolism before prescribing TRT (2, ØØOO).

Evidence

In prospective RCTs, analysis of the effects of TRT in patients with mild-to-moderate heart failure (HF) and reduced ejection fraction (rEF) including classes New York Heart Association (NYHA) II and III and left ventricular ejection fraction (LVEF) < 40%,—showed no [55, 56] or positive effects [57] on heart function and no TRT-related major events [56–60]. Accordingly, a meta-analysis of RCTs including 198 patients with heart failure (LVEF < 40%, NYHA II and III) with a duration up to 52 weeks described a significant amelioration of the six-minute-walking test and no adverse cardiovascular events [61]. Conversely, no data are available on the effects of TRT in patients with severe HF and rEF (class NYHA IV), nor in those with recent major adverse cardiovascular events (MACE).

The association between TRT and cardiovascular (CV) risk remains one of the most conflicting issues of the topic. Limited data, mainly derived from pharmaco-epidemiological studies published in the last 10 years, have suggested a possible increased risk of CV mortality and morbidity during TRT, especially in aging and complicated patients (see above; [62, 63]).

However, it is important to recognize that several double-blind, placebo-controlled randomized clinical trials (RCTs) have shown that T can delay time to ischemia in patients with coronary artery disease and stable angina followed up from four weeks to 12 months (see for review [62]). In addition, a meta-analysis including 37 observational studies and 43,041 subjects, showed that reduced T concentrations at baseline was associated with an increased CV mortality and morbidity [64]. Data were confirmed when only population-based studies were considered [64]. Similarly, a large epidemiological study including 154,965 men from United Kingdom (UK) Biobank showed that tT and fT concentrations were inversely associated with all-cause
and cancer mortality [65]. In line with these data, the largest meta-analysis published so far on CV effect of TRT, including 15 pharmaco-epidemiological and 93 RCTs, documented that TRT reduces overall mortality and CV morbidity in pharmaco-epidemiological studies and had no clear effect, either beneficial or detrimental, on the incidence of CV events when RCTs were considered [66]. The latter study also documented that an increased risk of CV diseases was observed in RCTs when T preparations were prescribed at dosages above those normally recommended, or when frail men were considered [66]. In line with this evidence a more recent individual patient and aggregate data meta-analysis, including 35 primary studies (5601 participants, mean age 65 years) found no evidence that TRT increased short-term to medium-term CV risks in men with hypogonadism [67]. Accordingly, the conclusion of the European Medicine Agency (EMA) did not align with the FDA opinion and stated the safety of TRT on the cardiovascular profile [68].

Values

Evidence on the safety of TRT on the cardiovascular profile is of moderate quality and place a high value when TRT is given to restore physiological concentrations. An accurate family history evaluation to rule out thrombophilia-hypofibrinolysis is crucial before initiating TRT.

Remarks

Available data on CV risk of TRT are mainly derived from studies with non-CV primary endpoints and whose design was inadequate to exclude such a risk (limited duration of exposure and insufficient numbers of participants). An industry-supported multicenter RCT is underway to better clarify the CV risk of TRT (clinicaltrials.gov: NCT03518034).

Other contraindications

We recommend against TRT in men desiring fatherhood in the near future (1, ØØØØ).

We suggest not considering a treated obstructive sleep apnea syndrome (OSAS) as an absolute contraindication for testosterone replacement therapy (2, ØØØØ).

Evidence

Male hormonal contraceptive trials have clearly shown that T administration suppresses sperm production and sperm cell concentration to various degrees and in 100% of subjects within 24 months [72]. The recovery period from T-induced spermatogenesis suppression is variable, being reported longer when it is consequence of anabolic–androgenic steroids (AAS) abuse [73]. Hence, TRT is contraindicated in all men who desire fatherhood. Specific SIAMS recommendations on this topic were provided elsewhere [74].

The impact of TRT on respiratory parameters in subjects with hypogonadism with OSAS, studied in RCTs, seems to be transient and time-dependent. TRT can worsen saturation index and nocturnal hypoxemia (sleep time with oxygen saturation < 90%) after seven weeks [75, 76], but the effects are neutral after 12–18 weeks [75–77], and eventually resulted in a significant improvement of sleep disturbances after 12 months [78]. Taken together these data suggest that short-term, high-dose TRT may worsen OSAS. However, these adverse effects seem to have disappeared with time, rather than worsen [79].

Remarks

The available evidence regarding the role of TRT in men with OSAS is poor. In addition, the possible role played by obesity in these patients remains unclear.

Outcomes

Sexual function

We recommend using TRT in subjects with hypogonadism with low sexual desire and/or erectile dysfunction (ED) (1 ØØØØ).

Since ED is a multifactorial disorder, we suggest promptly considering combination therapies, in subjects with hypogonadism, whenever needed to fully address the condition (2 ØØØØ).

Evidence

As previously reported, sexual dysfunctions are considered a hallmark of T deficiency [22, 23, 80]. Data derived from available meta-analyses documented that TRT can significantly improve all aspects of sexual function, being the magnitude of the outcomes more evident when sexual desire
and erectile function were considered ([52, 81–86]; Table 3 and Supplementary Table 1). The same studies [52, 81–86] also excluded beneficial effects of TRT when the mean T of the enrolled subjects exceeded 12 nmol/L. The first meta-analysis of studies reporting International Index of Erectile Function as main outcome suggested that TRT alone is only able to improve mild ED [87]. Similar results were reported by a comparable study [88]. The effect, small, is even attenuated by metabolic impairment, such in obesity and diabetes, most probably because of underlying neuro-vascular alterations [87]. Accordingly, lifestyle modifications and reduction of CV risk is advocated to improve ED [89, 90]. In subjects with hypogonadism with comorbid ED, T should be given prior to phosphodiesterase-5 inhibitors (PDE5i) but if it turns out insufficient to restore sexual function in comorbid vascular patients the add-on of PDE5i should be considered without delay. In this respect, the first meta-analysis of the very few studies on the combination of PDE5i and TRT (mixed enrollment) failed to reveal additive effects [83]. The re-analysis of the latter data, however, documented that the combination therapy (TRT and PDE5i) can produce better outcome in more complicated subjects such as those with type 2 diabetes mellitus [80]. A further meta-analysis including eight studies and 913 patients concluded that combination therapy (TTR plus PDE5-i) is superior to PDE5i monotherapy in restoring erectile function [86]. However, the analysis included also non-placebo-controlled RCTs and paper not published in English language, limiting its generalizability.

### Values

We place a high value for TRT in improving low sexual desire and erectile function in subjects with hypogonadism (tT < 12 nmol/L). We place a lower value on the less consistent effects of TRT on other sexual problems including ejaculatory dysfunctions.

### Remarks

At present, the place and timing of combination therapy T plus PDE5i in the management of ED remains unclear, requiring an individually tailored approach. The efficacy of the combined use of TRT and intracavernosal injection of prostaglandin E1 (PGE-1) and/other drugs is lacking.

### Bone

We recommend TRT to improve bone mineral density and prevent bone loss in subjects with hypogonadism (1 ØØØØ). We recommend against TRT as monotherapy to prevent bone fracture in subjects with hypogonadism with high fracture risk (1 ØØØØ).

### Evidence

T is essential for skeletal development during puberty and bone health maintenance (mass and strength) throughout adult life, by promoting periosteal apposition and endocortical bone resorption, and by slowing bone remodeling rate [91]. Hypogonadism, both in the young men and in aging, is associated with lower bone mineral density (BMD) and represents a major cause of osteoporosis [92, 93]. TRT can improve BMD, particularly at the vertebral level and when T concentrations are very low (Table 3 and Supplementary Table 2; [94–98]. The effect is more evident in younger men with organic hypogonadism, as a meta-analysis showed in men with Klinefelter syndrome [99]. The Bone Trial of the Testosterone Trials (T-Trials), showed that T treatment for one year in older men with low T significantly increased volumetric BMD and estimated bone strength, more in trabecular than peripheral bone and more in the spine than hip [100]. Similarly, the T4 Bone trial, a sub-study of the larger Testosterone for Diabetes Mellitus (T4DM), confirmed that

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**Table 3** Summary of testosterone replacement therapy (TRT) outcomes

| TRT outcomes | Outcome evaluation |
|--------------|--------------------|
| Sexual function |                      |
| Erectile dysfunction | ↑⊕⊕ |
| Libido | ↑⊕⊕ |
| Ejaculation | ↑⊕ |
| TRT + PDE5i | ↔ |
| Body composition |             |
| Fat mass | ↓⊕ |
| Lean mass | ↑⊕ |
| Body mass index | ↔ |
| Waist | ↔ |
| Metabolic control |         |
| Glucose metabolism | ↑⊕ |
| Lipid profile | ↑⊕ ↔ |
| Blood pressure | ↔ |
| Bone |             |
| Bone mass | ↑⊕ |
| Fracture risk | NA |
| Mood/cognition |       |
| Depressive symptoms | ↑⊕ |
| Cognition | NA |
| Mobility | ↑⊕ |

⊕ = arbitrary unit indicating: ⊕ = mild ⊕⊕ = moderate, ⊕⊕ ⊕⊕ = strong effect. ↑ = positive effect ↓ = negative effect ↔ = neutral effect. NA = not available; PDE5i, phosphodiesterase type 5 inhibitors
two years of T increased by 3% volumetric bone density over placebo, predominantly acting on cortical bone [101]. However, both trials investigated subjects with relatively normal BMD at baseline, whether similar, lower or higher finding could be expected in osteoporotic men remains to be established.

Values

Hypogonadism should always be considered during the clinical workup of male osteoporosis and, similarly, subjects with hypogonadism should be assessed for bone health [102]. There is growing evidence on the effects of TRT on BMD, although trials exploring its beneficial effect on osteoporosis are lacking. TRT is particularly recommended in young adult subjects with hypogonadism to prevent bone loss and help acquiring peak bone mass [102]. In the other groups of patients, mainly older men with LOH, the benefits and risks of TRT should be accurately discussed with the patients. To date, TRT cannot be recommended as monotherapy and should be associated with antiresorptive drugs when fracture risk is high [102, 103]. In general, we recommend following the European Academy of Andrology clinical guidelines on management of bone health in the andrological outpatient clinic [102].

Remarks

The effect of TRT alone on bone health in subjects with hypogonadism is still not completely defined [93, 102], specifically, no studies with fractures as primary endpoint are yet available. The combined treatment of TRT with drugs approved for the treatment of osteoporosis has not been investigated. To what extent the effects on TRT on bone density are a direct on bone metabolism, or rather an indirect effect through skeletal muscle is still unclear.

Mood

We recommend against TRT as monotherapy for improving major depressive symptoms in subjects with hypogonadism (1 ØØØØØ).

Evidence

Observational studies found depressive symptoms, including major depressive disorder, and hypogonadism associated [22, 23, 104–107]. A nine-year follow-up study found the risk of depression nearly double in men with low T at baseline [108], confirming previous results of an increased incidence of depression in men with low T concentrations during two-year observation [109]. However, very few placebo-controlled RCTs investigated the role of TRT on depressive symptoms as primary outcome. Overall, they found TRT beneficial, with effect size larger among those subjects with milder symptoms than those who met criteria for major depressive disorder [110]. Data from the Vitality Testosterone Trial [111] showed that TRT in subjects with hypogonadism, who self-reported low vitality and fatigue scores, slightly improved mood and depressive symptoms. A systematic review of six RCTs confirmed that TRT can reduce depressive symptoms in patients with mild depression and in the presence of hypogonadism but not in those with major depressive disorders (Table 3; and Supplementary Table 3; [112–115]).

Values

Although TRT may produce marginal improvement in mood and depressive symptoms in subjects with hypogonadism, we place a high value on the recommendation not to offer TRT with the sole purpose of improving these symptoms. Established anti-depressive treatments should be considered in combination to TRT in all hypogonadal subjects with hypogonadism with major depression.

Remarks

Depressive mood and other non-specific symptoms of hypogonadism are indistinguishable from true psychiatric conditions related to mood and major depressive disorders [110]. Low T can impact on mood in patients with hypogonadal-type depressive conditions [116]. However, the benefit of restoring T concentrations for depressive symptoms and for treatment of major depressive disorder is more controversial. Similarly, it is unclear whether low T is related to the development of major depressive disorders. Studies on the combination of TRT with established anti-depressive therapies have not been performed.

Cognition

We recommend against testosterone replacement therapy in subjects with hypogonadism to specifically improve cognitive function (1 ØØØØØ).

Evidence

Some studies suggest that T deficiency might be involved in the pathogenesis of both age-related and Alzheimer disease (AD)-related cognitive impairment [117, 118]. A meta-analysis including 27 studies and 18 599 subjects concluded that low T can predict all-cause dementia or AD [119]. However, that latter study used a fixed model for the analysis which strongly limits the results obtained [119]. The association between LOH and cognitive decline are partially supported
by studies on patients undergoing androgen deprivation therapy (ADT), in whom a worse performance in visuomotor tasks, but not in visuospatial tasks not comprising motor components, has been observed when compared to baseline concentrations or to controls [120]. However, the available meta-analyses failed to document a beneficial effect of TRT in improving cognitive function of ageing men ([117, 121, 122]; Table 3 and Supplementary Table 4). A first meta-analysis of 14 RCTs and 1406 patients without definite cognitive impairment, reported a small, albeit significant, improvement in psychomotor speed and executive function in TRT compared to placebo group [122]; but no effects on various cognitive domains were observed in two other larger meta-analyses, even in the subgroup of subjects with hypogonadism only [117, 121].

**Remarks**

It should be emphasized that the majority of available RCTs and meta-analyses included mixed eugonadal/hypogonadal populations. Only few studies dedicated to subjects with hypogonadism are available, overall reporting no effect of TRT on cognitive function. The current evidence does not allow to draw specific recommendations on the role of TRT on cognitive function in subjects with hypogonadism.

**Frailty and mobility**

We recommend against prescribing testosterone replacement therapy to improve muscle strength, with a clinically meaningful aim, in frailty of subjects with hypogonadism (I ØØØØ).

**Evidence**

Observational studies repeatedly reported an association between low T and frailty [123, 124]. In line with these a meta-analysis including 7 cross-sectional studies and 4 cohort studies showed either reduced fT or fT concentrations were related to an increased risk of frailty in men but not in women [125]. Impairment of mobility and balance, common features in frail individuals, has been frequently found associated with low T concentrations [126]. Accordingly, patients with LOH display an increased risk of falls and functional disabilities [127]. Despite this evidence, the role of TRT in frail patients with low T remains controversial [128–130].

In fact, although TRT was shown to reverse sarcopenia in aging men with LOH [131–133], data derived from available meta-analyses failed to confirm a meaningful improvement of muscle strength and mobility (Table 3, Supplementary Table 5; [94, 127–129]). Data derived from TTrials demonstrated that TRT significantly improved the six minutes walking distance test in the overall cohort and in patients without baseline mobility limitations, but not in patients affected by mobility limitations at baseline (primary outcome). In addition, although TRT was able to significantly improve the parameter of self-reported physical function, the evaluation at the six minutes walking test failed to demonstrate an objective improvement among patients with functional limitation at enrollment [133].

**Remarks**

The majority of RCTs do not support a beneficial effect of TRT on physical function of frail men; however, some improvement in frailer patients, improvement in body composition and sarcopenia have been consistently reported in aging subjects with hypogonadism. Therefore, a beneficial impact of TRT on these outcomes in frail men cannot be completely ruled out.

**Body composition and metabolic parameters**

We recommend TRT to improve body composition (reducing fat mass and increasing lean mass) in subjects with hypogonadism with or without metabolic syndrome (MetS) or type 2 diabetes (T2DM) (I ØØØØØ).

We suggest TRT to improve fasting and post-load glycemic control in subjects with hypogonadism with MetS or pre-diabetic conditions to reduce the risk of developing T2DM (2 ØØØØØ).

We suggest not considering TRT to control dyslipidemia or to improve glycated hemoglobin in patients with or without T2DM (2 ØØØØØ).

We suggest TRT to reduce waist circumference in subjects with hypogonadism with MetS (2 ØØØØØ).

**Evidence**

The beneficial effects of T on body composition are well studied. Several RCTs have proven that T can reduce fat mass. In detail, TRT has been demonstrated to reduce both visceral [134, 135] and subcutaneous fat mass [136] in subjects with hypogonadism with or without MetS and T2DM. Some double-blind, placebo-controlled studies have shown that TRT can reduce waist circumference and increase lean mass [135–138]. These findings mirror meta-analytic studies [94, 139] and were confirmed by the T4DM trial, where two years of TRT reduced waist circumference (-2.1 cm), total fat mass (-2.7 kg), and abdominal fat mass (-2.3%), while increasing total muscle mass (+ 1.7 kg), over life-style interventions and placebo [140].

There is a well-known relation between low endogenous serum T concentrations and risk of T2DM in observational studies, however data from RTCs are more controversial.
Some RCT found TRT positively affecting glycemic control in subjects with MetS and/or T2DM. In the Burntwood Lichfield Atherstone Sutton Tamworth (BLAST) study, 199 men with T2DM were enrolled to study TRT’s effects on glycated hemoglobin (HbA1c). A significant improvement of HbA1c concentrations was achieved after 30 weeks of long-acting injectable T undecanoate administration [141]. However, in the TIMES-2 trial, a larger study on 220 patients with T2DM or MetS treated for six months with 1% T gel or placebo, no significant difference in HbA1c concentrations was found between groups [142]. Similar results were obtained in other double-blind, placebo-controlled studies [136, 143, 144]. The T4DM, the largest (1007 men) RTC, demonstrated that T is able to prevent T2DM, over an intensive lifestyle program, to an extent greater than seen for metformin in the Diabetes Prevention Program. The T4DM trial found a significant TRT-related reduction in fasting glucose and an approximately 40% lowering of the relative risk to have a 2-h glucose on oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L after two years of TRT over lifestyle interventions; however, as previous studies, they found no significant effect on Hb1Ac concentrations advocating the discrepancy—when compared the impressive changes in glucose concentrations—due to a TRT-related change in red blood cell turnover that hampers the possibility to detect Hb1Ac improvements by measuring its circulating concentrations [140].

Results of clinical studies on the effect of T on circulating lipids are contrasting. In some RCTs including subjects with hypogonadism, with or without MetS and T2DM, a reduction of total cholesterol [137, 141–143, 145, 146] and low-density lipoprotein cholesterol [143, 146, 147] was observed in the TRT group. In contrast, other studies reported no change in lipid parameters [136, 138, 144, 148]. Moreover, T seems to have an unfavorable effect on high-density lipoprotein cholesterol concentrations [140, 142, 146, 147]. Unfortunately, the T4DM did not analyzed lipid concentration changes because of budget constraints [140]. A comparison of available meta-analysis is reported in Supplementary Tables 6–8 [5, 94, 96, 139, 149–159].

**Value**

Although it is unequivocally the effect of TRT in improving body compositions, we place a great value in implementing lifestyle changes needed to control and reduce obesity prior to considering TRT. In those subjects failing to restore normal T concentrations after life style interventions, TRT can prevent the development of T2DM and improve body composition. Dyslipidemia seems not adequately targeted by TRT, suggesting that additional pharmacological interventions might be needed to restore normal lipid concentrations.

**Remarks**

Hyperinsulinemia, T2DM and MetS are associated with reduced SHBG concentrations; therefore, in the affected subjects, it is recommended to calculate cFT to avoid unnecessary TRT (see Fig. 2). The encouraging data on TRT on diabetes mellitus prevention are limited to a 2-year observation in subjects with borderline hypogonadism who underwent a concomitant lifestyle program, whether the same findings can be expected in all subjects with hypogonadism remains to be established and balanced with long-term safety profile.

**Chronic diseases (HIV end-stage renal disease, bowel inflammatory diseases, chronic pulmonary diseases)**

We suggest not considering TRT in subjects with hypogonadism with chronic diseases (such as human immunodeficiency virus infection (HIV), chronic obstructive pulmonary diseases (COPD), end-stage renal disease (ESRD), and bowel inflammatory diseases) to improve disease outcomes (2 ØØOO).

**Evidence and remarks**

Many chronic diseases, such as HIV infection/AIDS, COPD, ESRD, and bowel inflammatory diseases, have been associated with hypogonadism [5, 17, 160, 161]. Data suggest that lean mass may improve in HIV men receiving TRT [155, 161, 162] and COPD patients [155, 163]. However, evidence from RCT is too weak to indicate that TRT may beneficial in this subset of patients and improve their morbidity and mortality. Similar considerations can be drawn for coronavirus disease 19 (COVID-19) infection [164–170]. For this reason, the task force agreed that are the specific outcomes, as detailed in the previous recommendations, to drive decisions and TRT should be individualized based on the signs and symptoms and severity of hypogonadism.

**Monitoring**

We recommend evaluating clinical outcomes, including biochemical parameters (hematocrit, PSA and testosterone) every 3/6 months during the first year and at least annually thereafter (1 ØØØO).

We suggest further evaluation, if there is: (a) confirmed PSA > 4 ng/mL at any time and (b) detection of a prostatic abnormality on digito-rectal examinations (DRE) or a substantial worsening of LUTS (2 ØØOO).
Evidence

Sexual problems are among the commonest issues complained by subjects with hypogonadism. Data derived from TTrials and meta-analysis have shown that sexual function can be significantly improved after three month of therapy [87, 171]. Hence, three months appear a reasonable time to check, for the first time, TRT outcomes. Given the well-known stimulatory effects of T on erythropoiesis [172], and its potential effects on the prostate [54], the PSA and hematocrit (HCT) evaluation should be mandatory considered before and early checked during TRT. The optimal target concentrations for circulating T upon TRT have not been completely clarified. TTrials showed that maintaining the serum T concentration within the normal range for young men (280–873 ng/dL or 9.6–30 nmol/l; [171]) resulted in a good benefit/risk ratio. However, lower or higher concentrations should be tailored according to individual comorbidities, specific symptoms and HCT levels. In fact, although the data are still not completely clarified, there is a general consensus that a HCT level higher than 54% require phlebotomy, along with TRT withdrawal, to reduce the risk of cardio-vascular complications [15]. However, particularly in the presence of specific conditions, as COPD or OSAS, HCT levels between 48 and 51% should be carefully considered, and handled on an individual basis, before and during TRT [18].

Considering the strong association between LOH and metabolic disturbances, baseline and, at least, annually glycometabolic profile evaluations are suggested. Similarly, bone density scan may be also considered at baseline and 18 to 24 months following TRT, particularly in those subjects with more severe hypogonadism [102].

Overall, complete and andrological clinical evaluation is mandatory before and during TRT patient evaluation. DRE must be performed at any time to rule-out the presence of prostate abnormalities.

Remarks

The correct timing for T concentration evaluation should be managed according to the type of T preparation used (see Table 2). SHBG evaluation and fT calculation should be considered for a better estimation of circulating T levels. Although PSA value above 4 ng/mL still represents a well accepted threshold for further prostate evaluation, it should be recognized that the latter varies according to several other parameters [173]. In particular, the risk of PC is increased in African descent and in those with a first-degree relative with diagnosed PC or previously positive prostate biopsy, and in those with baseline PSA concentrations > 1 ng/mL at age 40 years or > 2 ng/mL at age 60 years [173]. Hence, those subjects deserve particular attention during TRT. The PSA velocity, previously considered a marker for TRT withdrawn and prostate biopsy, has been criticized [174, 175]. Accordingly, the European Association of Urology guidelines suggest that PSA density (PSAD) with a Prostate Imaging Reporting and Data System (PI-RADS) score (≥ 3) might help in decision for further evaluations [173].

Conclusions

Whereas the development of male hypogonadism during fetal and pre-pubertal condition can profoundly affect sexual development and the appearance of sexual secondary characteristics, the underlying pathogenetic mechanisms, and the clinical significance of adult- and late-onset hypogonadism are still not completely clarified. Sexual impairment is the main condition tightly related to the development hypogonadism in adult or aging men. Conversely, the role played by age-associated low T in the characterization of several other symptoms including mood discrepancies, frailty and cognitive impairment is more conflicting. Similarly, metabolic derangements such as obesity T2DM and MetS are frequently associated with low T in aging men. In the latter cases, emerging evidence suggests that TRT can positively influence body composition and metabolic profile in less complicated subjects. Conversely, the role of T substitution in older frailty and more complicated subjects is still contradictory. Available data do not support a role of TRT in increasing CV risk when subjects with hypogonadism are correctly diagnosed, T appropriately prescribed and subjects adequately followed up during the treatment. However, it should be important to recognize that the duration of existing studies is too limited (up to three years) to draw any final conclusions. Hence, further and longer studies are strongly advisable the better clarify the long-term benefit/ratio of TRT in adult and aging men with hypogonadism.

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Declarations

Conflict of interest No conflict of interest was reported by any of the authors.

Ethical approval This article does not contain any study with human participants or animals performed by any of the authors.

Informed consent For this type of study informed consent is not required.
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