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REVIEW ARTICLE

Testosterone therapy for functional hypogonadism in middle-aged and elderly males: current evidence and future perspectives

Nikolaos Theodorakis[1,2] · Georgios Feretzakis[3] · Georgia Vamvakou[1] · Vassilios S. Verykios[3] · Antonis Polymeris[4] · Maria Nikolaou[1]

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Abstract
Population aging is a global phenomenon driving research focus toward preventing and managing age-related disorders. Functional hypogonadism (FH) has been defined as the combination of low testosterone levels, typically serum total testosterone below 300–350 ng/dL, together with manifestations of hypogonadism, in the absence of an intrinsic pathology of the hypothalamic-pituitary-testicular (HPT) axis. It is usually seen in middle-aged or elderly males as a product of aging and multimorbidity. This age-related decline in testosterone levels has been associated with numerous adverse outcomes. Testosterone therapy (TTh) is the mainstay of treatment for organic hypogonadism with an identifiable intrinsic pathology of the HPT axis. Current guidelines generally make weak recommendations for TTh in patients with FH, mostly in the presence of sexual dysfunction. Concerns about long-term safety have historically limited TTh use in middle-aged and elderly males with FH. However, recent randomized controlled trials and meta-analyses have demonstrated safe long-term outcomes regarding prostatic and cardiovascular health, together with decreases in all-cause mortality and improvements in various domains, including sexual function, body composition, physical strength, bone density, and hematopoiesis. Furthermore, there are numerous insightful studies suggesting additional benefits of TTh, for instance in cardio-renal-metabolic conditions. Specifically, future trials should investigate the role of TTh in improving symptoms and prognosis in various clinical contexts, including sarcopenia, frailty, dyslipidemia, arterial hypertension, diabetes mellitus, fracture risk, heart failure, stable angina, chronic kidney disease, mood disorders, and cognitive dysfunction.

Keywords Testosterone therapy · Functional hypogonadism · Late-onset hypogonadism · Benefits · Safety · Aging

Introduction

Population aging is affecting all of our developed societies due to prolonged life expectancy coupled with declining fertility rates [1]. A direct consequence is an increasing trend in morbidity and mortality of age-related conditions, including cardiovascular diseases (CVD), chronic kidney disease (CKD), dementia, frailty, osteopenia, and sarcopenia [2]. The physiological changes of the aging organism are unique and affect the totality of organ systems, including the hypothalamic-pituitary-testicular (HPT) axis [3].

Functional hypogonadism (FH), also known as late-onset hypogonadism, andropause, or the "male climacteric," has been defined as decreased testosterone levels, typically serum total testosterone (TT) below 300–350 ng/dL, accompanied by manifestations of hypogonadism, in the absence of an organic cause. It is usually seen in middle-aged or elderly males as a product of aging and accumulation of

✉ Georgios Feretzakis
gferetzakis@gmail.com

[1] Department of Cardiology & 65+ Clinic, Sismanogleio-Amalia Fleming General Hospital, 14, 25th Martiou Str, Melissia 15127, Greece

[2] School of Medicine, National and Kapodistrian University of Athens, 75 Mikras Asias, Athens 11527, Greece

[3] School of Science and Technology, Hellenic Open University, 18 Aristotelous Str, Patras 26335, Greece

[4] Department of Endocrinology, Metabolism and Diabetes Mellitus, Sismanogleio-Amalia Fleming General Hospital, 14, 25th Martiou Str, Melissia 15127, Greece

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comorbidities. Age-related testosterone decline has been associated with various disorders and age-related conditions, such as sarcopenia, osteopenia, anemia, dementia, depression, frailty, arterial hypertension (AH), dyslipidemia, metabolic syndrome, elevated cardiovascular (CV) risk, and elevated all-cause mortality [4]. Testosterone therapy (TTh) is the mainstay of treatment for organic hypogonadism with an identifiable intrinsic pathology of the HPT axis.

This literature review comprehensively analyzes the current evidence regarding the manifestations of FH and the indications, effectiveness, and safety of TTh in this context. Of note, the use of TTh in middle-aged and elderly males with FH has long been controversial, especially due to heterogenous results regarding CV safety from older studies. The reason why these studies yielded heterogenous and therefore less powerful results regarding CV safety was their variability in many aspects, including study type (e.g., observational vs. clinical trial), inclusion criteria (e.g., cut-off for blood testosterone levels during inclusion in the study), population characteristics (e.g., age and baseline CV risk), methods for the determination of plasma testosterone levels, sample size, endpoints, duration of follow-up, and TTh dosages and formulations [5]. During the last decade, meta-analyses and randomized controlled trials (RCTs) in which plasma testosterone levels were measured by mass spectrometry or other reliable methods have updated the body of evidence as regards the safety and efficacy of TTh in FH [6, 7]. Based on the results of these studies, this paper aims to raise awareness about the benefits and safety of TTh in middle-aged and elderly males with FH. Additionally, it highlights the gaps in evidence that future research needs to address.

Testosterone's biological effects

Testosterone is the major male androgen, and its secretion is controlled by the HPT axis [8]. Serum free testosterone (FT), the biologically active fraction of testosterone, represents only 2% of serum TT [9]. The enzyme 5-a reductase converts 5–8% of serum FT to dihydrotestosterone (DHT), the most potent androgen [10]. DHT mainly acts in a paracrine and autocrine manner and is responsible for the majority of androgen activity in the sites of conversion, including testicular descent during embryogenesis, development of external genitalia, seminal vesicles, and prostate, and effects on the skin, hair follicles, and brain [11]. On the other hand, DHT is deactivated in many tissues, including the liver, muscles, and adipose tissue [12]. Aromatase converts 0.3–0.5% of serum FT to estradiol in adipose tissue. [10]. Notably, testosterone requires conversion to estradiol for many of its actions, including the skeleton and adipose tissue, and stimulation of libido and erectile function [13].

Testosterone affects most body systems [14–16]. It increases muscle mass and strength and causes quantitative (i.e., increased bone density) and qualitative (i.e., wider shoulders) changes in the skeleton. Furthermore, testosterone has been shown to restrain fatty acid storage by suppressing lipoprotein lipase and acyl-coenzyme A synthetase activity inhibiting lipogenesis and accumulation of adipose tissue [17]. In the skin, testosterone stimulates growth of facial and body hair and production of sebum, while it has been associated with acne and male-pattern baldness [14]. Androgens, including testosterone, play a pivotal role in the pathophysiology of acne. The above is supported by the fact that acne is a well-known manifestation of hyperandrogenism, for instance, in females with polycystic ovarian syndrome [18]. Furthermore, the onset of acne around puberty coincides with the physiological increase in androgens. However, most acne patients have normal serum androgens, indicating the contribution of even normal androgen levels to its complex pathophysiology [19]. Additionally, testosterone causes thickening of the pharynx and larynx resulting in hoarseness. Its effects on reproduction include regulation of the development and maintenance of the prostate gland, seminal vesicles, and external genitalia, stimulation of spermatogenesis, and regulation of normal erectile function and libido [14]. Its effects on other hormones include improvement in insulin sensitivity and stimulation of erythropoietin, growth hormone, and insulin-like growth factor-1 (IGF-I) secretion [14–16]. Its effects on the brain include elevation of mood and stimulation of cognitive function, while supraphysiologic levels might increase self-perceived aggression [20]. Moreover, testosterone stimulates sodium and water retention via several mechanisms, including possible direct effects on the renal tubules, and indirect effects via aromatization to estrogens [16]. Testosterone could act directly on the kidney, because androgen receptors are expressed in renal tubules [21]. Finally, it can affect blood pressure (BP) and lipid metabolism with various complex mechanisms, while both low and supraphysiologic testosterone levels have been associated with dyslipidemia and AH [4, 14, 22].

The effects of aging and comorbidities on the HPT axis

The European Male Aging Study (EMAS) is a cross-sectional study ($n = 3.369$ males aged 40–79 years) that investigated the health impacts of age-related changes in male reproductive hormones [23]. Cross-sectional studies, including the EMAS, have demonstrated decreases in serum TT and DHT by 0.5% per year starting from the ages of 35 to

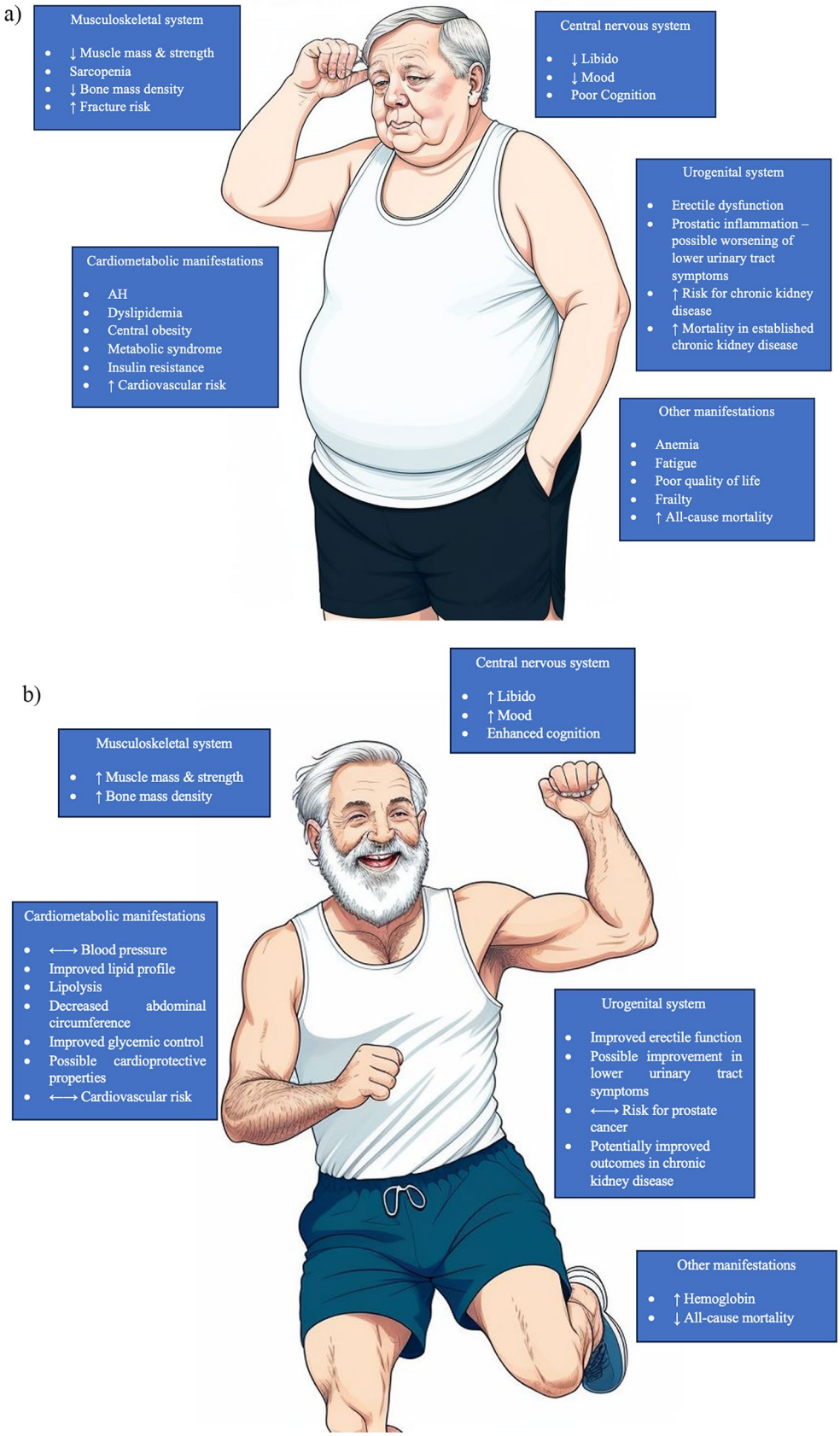

Fig. 1 Manifestations of functional hypogonadism **(a)** and benefits of testosterone therapy in middle-aged and elderly males with functional hypogonadism **(b)**

40 years, with more prominent decreases after the age of 80 years [23, 24]. Meanwhile, longitudinal studies, including the Massachusetts Male Aging Study (MMAS), have demonstrated larger annual decreases in serum TT of 0.8-2% and in serum FT of up to 3% [25–27]. Aging is associated with increased gonadotropin levels as a result of progressive testicular insufficiency, with FSH showing more prominent rises than LH [28]. However, these elevations are lower than the expected, indicating that aging is accompanied by a combination of primary (testicular) and secondary (hypogonadotropic) "hypogonadism" [29]. Some individuals present with compensated hypogonadism, which, according to the EMAS, is defined as serum TT above 300 ng/dL serum LH above 9.4 U/L [30]. Furthermore, aging is associated with increases in sex hormone-binding globulin (SHBG), mostly due to increased hepatic synthesis [31]. Since SHBG level is positively associated with serum TT levels, increased SHBG would theoretically lead to an increased serum TT [32]. However, in the context of aging, the presence of combined primary and secondary "hypogonadism" leads to a net reduction of serum TT. Furthermore, increased SHBG leads to decreased FT, this explaining why the age-related declines in serum FT might be greater than those of serum TT [25–27, 33]. Another important impact of aging is the loss of circadian rhythmicity of the HPT axis. Younger individuals show a prominent morning peak (at 8AM) of testosterone secretion, which is significantly dampened in the elderly [34].

Additionally, these hormonal changes are accompanied by a decrease in testicular volume by 15% from 25 to 80–90 years. However, the effect of aging on fertility has not been completely elucidated [35, 36]. Some studies have shown worse semen parameters in elderly males, while others have demonstrated similar sperm count and motility irrespective of age [37, 38]. In most cases, males maintain their fertility lifelong [35–38].

The presence of obesity and comorbidities can further affect the hormonal profile in the aging male, contributing to the decline in testosterone and the development of FH [23, 39, 40]. Obesity is associated with a higher activity of aromatase in adipose tissue, in particular in the presence of inflammatory and insulin-resistant states, leading to increased conversion of androgens to estrogens [39, 40]. Moderate obesity lowers SHBG levels due to the effects of insulin resistance and chronic inflammation, leading to decreased levels of serum TT [39, 40]. Of interest, the association between obesity and lower SHBG is stronger than the association between aging and higher SHBG [41]. Theoretically, the decreased SHBG would lead to an increased percentage of bioavailable testosterone and thus to an elevated FT. However, obesity also causes "hypogonadism" via multiple and complex mechanisms, including direct inhibitory effects in the testes and pituitary gland from insulin resistance and chronic inflammation, as well negative feedback in the HPT axis by estrogens [39, 40]. As a result, moderate obesity is usually characterized by a normal rather than an elevated serum FT. In this scenario, the reduced serum TT due to decreased SHBG is often not enough to diagnose hypogonadism. On the other hand, severe obesity causes significant hypogonadism leading to even further reductions in serum TT and decreased FT. In this scenario, the serum LH levels are low or inappropriately normal, signifying that hypogonadism in severe obesity is primarily secondary [39, 40]. As a result, utilization of serum FT and SHBG is crucial when assessing HPT function in obesity. Of interest, low SHBG is a better predictor of metabolic syndrome than low serum TT levels [42]. We should note that weight loss can lead to restoration of serum TT and FT levels [39, 43–45]. In addition to the effects of obesity on the hormonal profile, data from cross-sectional and longitudinal studies, including EMAS and MMAS, have indicated that multimorbid individuals have a higher incidence of primary and secondary hypogonadism, this occurring via complex and unclear mechanisms [25, 30, 43–45].

Table 1 Factors affecting sex hormone-binding globulin levels

Factors increasing sex hormone-binding globulin levels	Factors decreasing sex hormone-binding globulin levels
Aging	Obesity
Smoking	Hyperinsulinemia & insulin resistance
Estrogens	Androgens
Hyperthyroidism	Hypothyroidism
Cirrhosis	Nephrotic syndrome
Chronic inflammatory illnesses	Acromegaly
	Cushing's syndrome

Age-adjusted reference ranges for serum TT

A recent study established age-adjusted reference ranges for serum TT based on the results of four large cohorts, including EMAS ($n = 9054$ males, $n = 6933$ of whom were non-obese) [46]. Testosterone concentrations were measured in 100 community-dwelling men from each of the four cohorts using a reference method at Centers for Disease Control and Prevention. Specifically, the 2.5th and 97.5th percentiles for non-obese males aged 19–39 years were 267 and 929 ng/dL, respectively. For older non-obese individuals, the 2.5th percentiles were 235 ng/dL, 219 ng/dL, 218 ng/dL, and 157 ng/dL in age groups 40–49, 50–59, 60–79, and 80–99 years, respectively. When including the totality of patients (obese and non-obese), the 2.5th percentiles were 229 ng/dL, 208 ng/dL, 192 ng/dL, 190 ng/dL, and 119 ng/dL, in age groups 19–39, 40–49, 50–59, 60–79, and 80–99 years, respectively

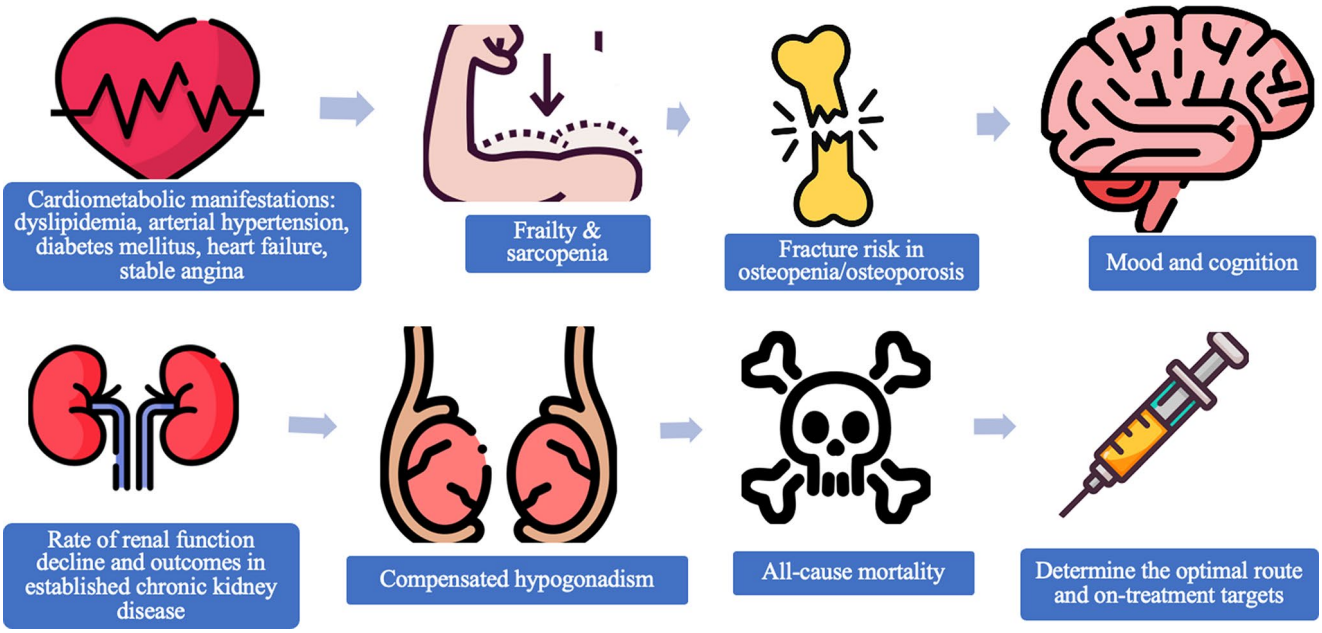

Fig. 2 Implications for future research regarding the potential efficacy and safety of testosterone therapy in various outcomes

[46]. This information is important because it will allow established harmonized reference ranges for TT in men that can be applied across laboratories by cross-calibrating assays to a reference method and standard.

Definition and causes of FH

According to the definition of Grossmann and Matsumoto, endorsed by the European Academy of Andrology, FH is the coexistence of consistently low testosterone (serum TT < 300–350 ng/dL) together with manifestations of androgen deficiency in the absence of an intrinsic structural, destructive, or congenital pathology of the HPT axis [43]. Serum TT levels should be measured in a fasting state at their peak, usually from 7 to 11AM, in the absence of acute illness, in blood samples obtained on two different days [43–45, 47, 48]. FH can be etiologically classified as primary, secondary, mixed, or due to androgen resistance. Some causes can result in either primary, secondary, or mixed hypogonadism, including aging, acute or critical illness, chronic organ failures (heart failure - HF, respiratory failure, CKD, cirrhosis), and various other comorbidities (e.g., obesity, type 2 diabetes mellitus - T2DM). Additional causes of primary FH include alcohol or cannabinoid abuse, and androgen synthesis inhibitors (e.g., ketoconazole, aminoglutethimide, mitotane, and metyrapone). Additional causes of secondary FH include acquired immunodeficiency syndrome, malnutrition, excessive exercise, hyperprolactinemia, Cushing's syndrome, and drugs (e.g., opioids, androgenic anabolic steroids, glucocorticoids, and GnRH analogs). Causes of FH due to androgen resistance include increased SHBG and drugs (anti-androgens and 5a-reductase inhibitors) [43–45].

Prevalence of age-related testosterone decline and FH

The prevalence of low testosterone with advancing age is variable due to different cut-offs used in the studies, with the typical threshold for serum TT being 300–350 ng/dL. Generally, up to 25–30% of middle-aged or elderly males might have biochemical hypogonadism, while the prevalence of FH ranges from 2.1 to 12.3% in different studies [6, 10, 30, 33, 35, 36, 47, 48, 50].

The EMAS defined FH as the presence of at least three sexual symptoms (low libido, loss of morning erections, and erectile dysfunction) together with serum TT < 320 ng/dL (11 nmol/L), measured by mass spectrometry, and serum FT < 64 pg/mL (220 pmol/L), calculated with the use of Vermeulen's formula. The overall prevalence of FH was 2.1%, while age sub-analysis demonstrated an increasing frequency with advancing age, which was 0.1%, 0.6%, 3.2%, and 5.1% at ages 40–49, 50–59, 60–69, and 70–79 years, respectively [33]. The prevalence of biochemical hypogonadism was 23.3% and was further classified as primary (serum TT < 300 ng/dL with LH > 9.4 U/L) (2%), secondary (serum TT < 300 ng/dL with LH ≤ 9.4 U/L) (11.8%) and compensated (serum TT ≥ 300 with LH > 9.4 U/L) (9.5%). The prevalence of compensated and primary hypogonadism

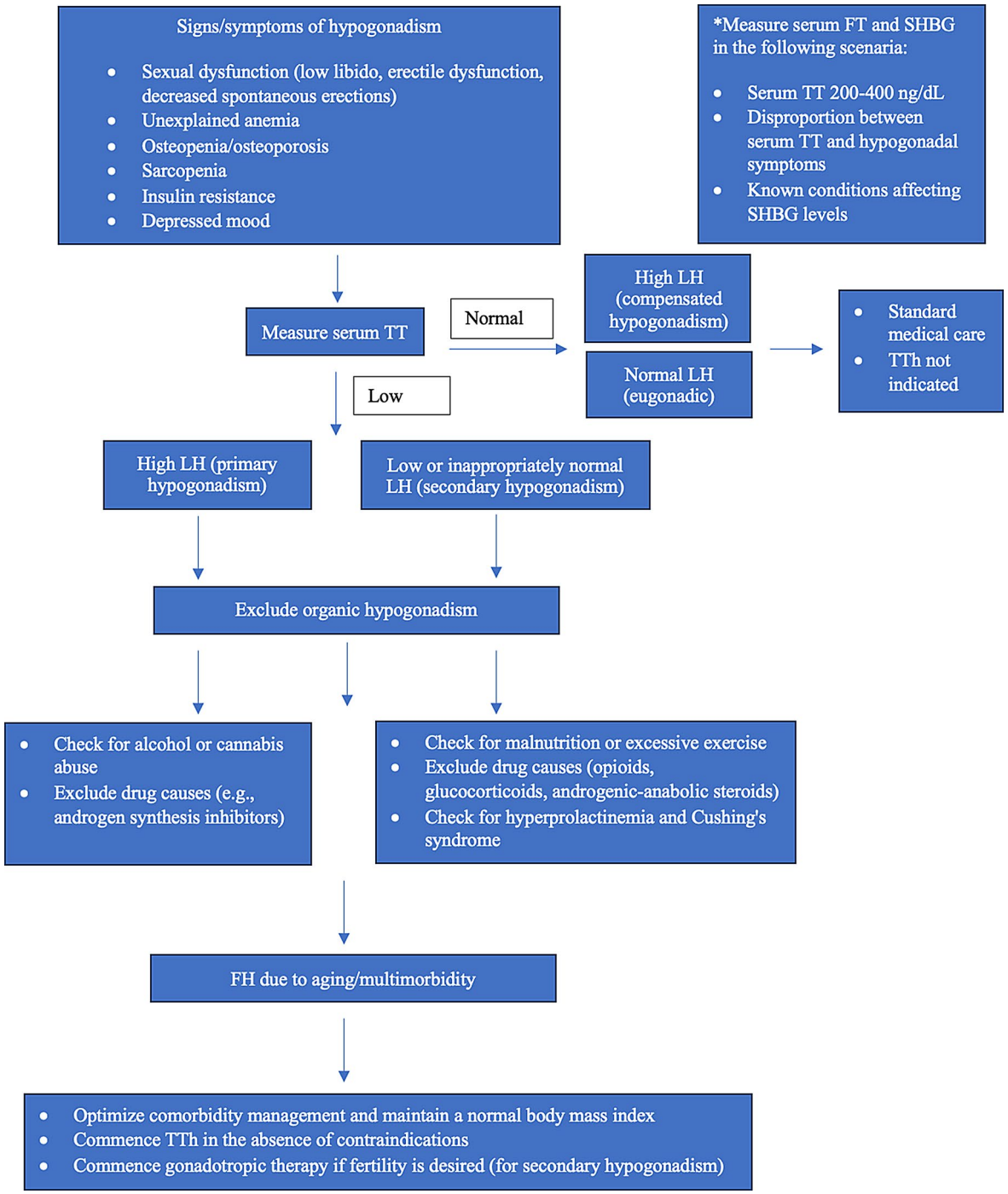

Fig. 3 Algorithm for the diagnosis and treatment of functional hypogonadism in middle-aged and elderly males. *Abbreviations* FT (free testosterone); FH (functional hypogonadism); LH (luteinizing hormone); SHBG (sex hormone-binding globulin); TT (total testosterone); TTh (testosterone therapy)

increased with age, while secondary hypogonadism remained equally frequent irrespective of age [30].

The MMAS defined FH as the presence of at least three hypogonadism-related manifestations together with serum TT < 200 ng/dL (measured with radioimmunoassay) or the combination of serum TT 200–399 ng/dL with serum FT < 8,91 ng/dL. The overall prevalence of FH at follow-up was 12.3%. Age sub-analysis demonstrated an increasing prevalence of FH with advancing age, which was 7.1%, 11.5%, and 22.8% at ages 48–59, 60–69, and 70–79 years, respectively [49].

Table 2 Indications for testosterone therapy in functional hypogonadism based on the current guidelines

Current guidelines	Indications for testosterone therapy
ESE & EAA (2020)	• Morning fasting serum TT < 320 ng/dL and/or FT < 220 pmol/L on two occasions AND • Sexual dysfunction symptoms despite lifestyle modification and withdrawal/modification of drugs interfering with testosterone production (*strong recommendation*, *high LE*)
EAU (2019)	• Morning fasting serum TT < 350 ng/dL and/or FT < 243 pmol/L on two occasions AND • Signs/symptoms of testosterone deficiency despite lifestyle modification and optimization of comorbidity management (*strong recommendation*, *moderate LE*)
BSSM (2023)	• Morning fasting serum TT < 350 ng/dL and/or FT < 225 pmol/L on two occasions (prediabetes: use a higher threshold of serum TT for treatment − 400 ng/dL - to prevent progression to overt type 2 diabetes mellitus) AND • Signs/symptoms of testosterone deficiency (*strong recommendation*, *moderate LE*)
Society for Endocrinology (UK) (2022)	• Serum TT < 320 ng/dL and FT < 220 pmol/L AND • Three sexual symptoms (decreased libido, loss of morning erections, and erectile dysfunction), and/or anemia, and/or low bone mass density
Endocrine Society (USA) (2018)	• Morning fasting serum TT < 264 ng/dL) and/or low FT on two occasions AND • Signs/symptoms of testosterone deficiency (e.g., low libido or unexplained anemia) (*conditional recommendation*, *low LE*) OR HIV-positive men with weight loss (*conditional recommendation*, *low LE*)
AAU (2018)	• Morning serum TT < 300 ng/dL on two occasions AND • Signs/symptoms of testosterone deficiency (*moderate recommendation*, *moderate LE*)
ACP (2020)	• Low serum TT (especially < 300 ng/dL) AND • Sexual dysfunction symptoms (*conditional recommendation*, *low LE*)
CUA (2021)	• Low morning TT and/or FT (do not propose specific thresholds) AND • Signs or symptoms of testosterone deficiency despite managing any potentially reversible causes of testosterone deficiency (*strong recommendation*, *moderate LE*) OR one of the following irrespective of the presence of other symptoms of testosterone deficiency: HIV-positive men with weight loss, unexplained anemia or sarcopenia, chronic use of glucocorticoids or opioids (*weak recommendation*, *moderate LE*)
ISSAM (2021)	• Morning fasting serum TT < 350 ng/dL and/or FT < 225 pmol/L AND • Signs/symptoms of testosterone deficiency
EMAS position statement (2023)	• Morning fasting serum TT < 350 ng/dL and/or FT < 225 pmol/L AND • Sexual dysfunction symptoms • Severe insulin resistance or type 2 diabetes mellitus adjunctive to standard medical care • Low bone mass density adjunctive to standard medical care • Mild depressive symptoms or low perceived quality of life as a monotherapy • Major depressive disorder adjunctive to standard medical care

Abbreviations AAU (American Association of Urology); ACP (American College of Physicians); BSSM (British Society for Sexual Medicine); CUA (Canadian Urological Association); EAU (European Association of Urology); ESE & EAA (European Society of Endocrinology & European Academy of Andrology); FT (free testosterone); HIV (human immunodeficiency virus); ISSAM (International Society for the Study of Aging Male); LE (level of evidence); TT (total testosterone)

Manifestations of FH and the role of TTh

Several studies have demonstrated correlations between the age-related testosterone decline and various disorders, including manifestations of aging [6, 36, 47, 48]. As a result, analysis of these correlations is crucial for selecting the possible candidates who will benefit from TTh.

The clinical presentation of FH is often more subtle compared to that of organic hypogonadism. The most frequent features include decreased libido, loss of spontaneous erections, erectile dysfunction, and obesity (especially central). Since obesity can also be a cause of FH, their relationship is bidirectional. Other possibly related manifestations are often non-specific and might include fatigue, osteopenia, sarcopenia, decreased physical strength, decreased motivation, low mood, decreased concentration, hot flushes, and loss of body/facial hair. On the other hand, significant testicular atrophy is uncommon in FH [43–45, 48].

The manifestations of FH are a continuum that often depend on the level of serum TT and usually appear at levels below 350 ng/dL. Fatigue and loss of libido might

Table 3 Contraindications for testosterone therapy based on the current guidelines

Active untreated breast or prostate cancer
Severe heart failure (New York Heart Association class III or IV)
Major acute cardiovascular event within six months (including stroke and myocardial infarction)
Hematocrit above 48–50%
High risk for venous thromboembolism (including thrombophilia)
Prostate-specific antigen > 4 ng/mL
Prostate-specific antigen > 3 ng/mL in patients at high risk of prostate cancer without previous urological evaluation
Untreated severe obstructive sleep apnea
Severe lower urinary tract symptoms
Men actively seeking fertility

appear at higher levels, even up to 430 ng/dL [48]. Changes in body composition usually appear at levels below 350 ng/dL, while insulin resistance, depressive mood, and cognitive dysfunction are evident at levels below 300 ng/dL. Hot flushes and ED usually manifest at levels below 250 ng/dL. Serum FT and SHBG are not necessary for the diagnosis of FH, but they might be helpful in circumstances where the clinical features are disproportional to testosterone levels, especially if serum TT 200–400 ng/dL, or in the presence of conditions that alter the SHBG levels, as presented in Table 1 [23, 43–45, 48]. The usual cut-off for FT is 220–225 pmol/L [43–45, 48]. Of note, the number of cytosine-adenine-guanine (CAG) triplets in the gene of androgen receptors can affect sensitivity to testosterone and contribute to variation of the symptomatic threshold among males [48].

Significant effects with the use of TTh in elderly males with FH have been revealed in the recently conducted testosterone trials (TTrials) [6]. The TTrials were a set of seven RCTs ($n = 788$ men aged 65 + years) that evaluated the effects of TTh in the form of gel in elderly males with low serum TT (< 275 ng/dL) observed in two different morning blood samples. The TTrials excluded patients with a history of prostate cancer, high risk for prostate cancer, severe cardiac, renal, or hepatic disease, and severe lower urinary tract symptoms (LUTS). These trials evaluated the following seven parameters: physical function, cognitive function, bone, vitality, sexual function, anemia, and CVD [6].

The manifestations of FH and the potential benefits of TTh in middle-aged and elderly males with FH are illustrated in Fig. 1.

Musculoskeletal system and adipose tissue

Serum TT levels below 350 ng/dL have been consistently associated with sarcopenia, decline in physical function, osteopenia, increased risk for fractures, and increased adiposity with visceral fat redistribution [36, 47, 48, 50]. Furthermore, a recent study demonstrated that gonadotropin and especially FSH levels are positively correlated with muscle mass in males [51]. This might indicate that in the elderly, secondary hypogonadism is more strongly associated with sarcopenia compared to primary hypogonadism, since FSH levels are higher in the latter. The above is concordant with results from the EMAS, which showed that sexual symptoms were more common in primary FH and physical symptoms in secondary and compensated FH [30]. Multiple studies, including recent meta-analyses, have shown that TTh improves body composition, increases bone and muscle mass, improves strength and physical performance, and decreases body fat [36, 47, 48, 52–56]. However, evidence of reduction in fracture risk with TTh is lacking. A recent RCT has demonstrated that TTh does not decrease the risk of fractures in middle-aged and elderly males with hypogonadism [57]. The TTrials demonstrated a modest improvement in walking as assessed by the 6-minute walking test and a self-reported questionnaire, as well as impressive improvement in bone mass density and strength of the spine and hip [6]. Future RCTs are needed to specifically investigate the outcomes of TTh in sarcopenia. Interestingly, a recent meta-analysis demonstrated that intramuscular TTh is superior to transdermal in increasing muscle mass, bone mass, and strength. Interestingly, transdermal TTh did not produce statistically significant increases in lower limb muscle strength versus placebo [58, 59].

Sexual function

Various studies have associated low testosterone levels with sexual dysfunction, and, in particular, decreased libido, typically for serum TT levels < 350 ng/dL. On the other hand, there has been a debate as to whether low testosterone levels are associated with erectile dysfunction (ED) [36, 47, 48]. Specifically, evidence from the EMAS and MMAS, and a meta-analysis of 17 RCTs showed that ED is mostly associated with very low testosterone levels, typically for serum TT levels < 250 ng/dL, and especially in primary hypogonadism [30, 48]. Data from recent meta-analyses have demonstrated that TTh can significantly improve both libido and erectile function in middle-aged and elderly males, including diabetic patients [60–62]. Of interest, a sub-group analysis in one of these meta-analyses showed that this improvement was only evident with high-dose intramuscular testosterone undecanoate [62]. The TTrials demonstrated that TTh improved sexual function and particularly libido with an effect proportional to the increase in serum TT [6].

Mood and cognition

The association between low testosterone levels and depressive mood, as well as cognitive dysfunction, has been

established in the literature, typically for serum TT levels < 300 ng/dL [36, 47, 48]. Recent meta-analyses demonstrated that low testosterone levels might be associated with all-cause dementia and Alzheimer's disease [63, 64]. Additionally, meta-analyses have shown that TTh has positive effects on various aspects of cognition and the treatment of depression [63–67]. Meanwhile, administration of androgens in healthy individuals might increase self-reported aggression, as indicated by a recent meta-analysis [20]. By contrast with the above evidence, the TTrials showed that TTh caused only slight improvements in mood and executive function [6]. As a result, *evidence of* the impact of TTh in the outcomes of mood and cognition should be examined by future large-scale long-term RCTs.

Cardiometabolic effects

CVDs are a major cause of morbidity and mortality in the elderly. The main conditions predisposing to CVD are DM, AH, dyslipidemia, obesity, and metabolic syndrome. For long, the associations between testosterone levels and the above conditions have been controversial, recent studies, however, having provided strong evidence for the CV safety of TTh [7, 68–69].

As already stated, low testosterone levels (serum TT levels < 350 ng/dL) are associated with obesity and visceral obesity, while TTh has beneficial effects on the above conditions [36, 43–45, 47, 48, 56]. Furthermore, various observational studies, including meta-analyses, have associated low testosterone levels (serum TT levels < 300 ng/dL) with metabolic syndrome and T2DM [36, 47, 48, 70]. Specifically, the relationship between low testosterone levels and diabesity (a new term causally combining T2DM mellitus with obesity) is complex and bidirectional [70]. The prevalence of low testosterone in patients with T2DM or obesity is up to 2-fold greater than in the general population [4]. Recent meta-analyses and a 2-year RCT demonstrated that TTh can improve glycemic control in patients with T2DM [71–73]. Notably, the T4DM trial demonstrated that TTh in prediabetic patients with serum TT < 400 ng/dL decreased progression to T2DM by 40% over 2 years, with concurrent improvements in lean mass and sexual symptoms, compared to men on active lifestyle interventions plus placebo [72]. Whether testosterone can reduce the risk of diabetic complications is expected to be answered in future RCTs.

The relationship between testosterone levels and lipid metabolism is far from simple. Hypogonadal males have a high prevalence of dyslipidemia, while TTh can cause decreases in total cholesterol, but the effects on low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides is variable from decreases to no change [56, 70, 73]. On the other hand, supraphysiological testosterone levels can lead to significant elevations in total cholesterol and LDL and reductions in HDL [4].

Additionally, the relationship between testosterone levels and BP is complex. Hypogonadal males have a higher prevalence of AH, which could be postulated to lower levels of nitric oxide, a potent vasodilator [14, 47, 48, 70, 74]. However, according to recent meta-analyses and RCTs, the effect of TTh on systolic and diastolic BP is usually neutral [56, 75, 76]. On the other hand, supraphysiological testosterone levels can lead to significant elevations in BP due to complex and largely unknown mechanisms, possibly including sodium and water retention and increased blood viscosity from polycythemia [22].

According to numerous studies, including meta-analyses, both low and supraphysiologic testosterone levels are associated with an elevated CV risk [4, 14, 22, 36, 47, 48, 74]. Yeap et al. (2024) published a meta-analysis of eleven prospective cohorts ($n = 24.109$ community-dwelling men, follow-up of at least 5 years) which associated circulating sex steroid hormone levels, measured with mass spectrometry, with all-cause mortality, CV mortality, and risk for incident CV events [75, 76]. According to the results of this study, irrespective of several covariates (including age and BMI), men with serum TT levels below 213 ng/dL, LH levels above 10 IU/L, or estradiol levels below 5.1 pmoL/L had increased all-cause mortality, while men with serum TT levels below 153 ng/dL had an additional increase in CV mortality. The above indicate that low serum TT levels, especially in the context of primary hypogonadism, are possibly a marker of poor overall health and increased risk of death, while severely low serum TT levels are possibly associated with the development of fatal CV events. The same study showed that higher SHBG levels (suggesting lower serum FT levels) were associated with higher all-cause and CV mortality, after controlling for several covariates (including age and BMI) [75, 76]. Finally, the study demonstrated a U-shaped association of DHT levels with all-cause and CVD-related mortality risks, which were higher at lower (below 0.69 nmoL/L) and very high (above 2.45 nmoL/L) DHT concentration. Furthermore, patients with serum DHT levels below 0.59 nmoL/L had an additional increase in the risk of incident CV events [75, 76]. We should note that data regarding the actions of DHT are very limited, while the use of 5α-reductase could be of help in future RCTs needed for further clarification of the above issues.

The relationship between TTh and CV risk has been controversial for a long time. Observational studies investigating CV risk in patients receiving TTh have shown conflicting results due to the heterogenous design [36, 47, 48]. In contrast, the RCT TTrials demonstrated an increase in noncalcified atherosclerotic plaque volume in the TTh group compared to placebo. However, the number of

patients included in the CV trial of the TTrials was small ($n = 138$), while there was absence of other adverse CV outcomes in the TTh group [6]. Furthermore, a RCT of TTh in very frail and multimorbid elderly patients ($n = 205$, mean age 74 years) showed improvements in muscle strength, but it was terminated early due to a statistically significantly higher risk of CV adverse outcomes in the TTh arm [77]. However, the small sample size and the elevated baseline risk of these patients cannot lead to definite conclusions about the efficacy and safety of TTh in frail elderly. By contrast, strong evidence regarding the CV safety of TTh has been derived from recent studies. Two large meta-analysis of RCTs demonstrated that TTh does not increase the risk of CV mortality, stroke, acute coronary syndrome, arrhythmia, and venous thromboembolism, for short- and medium-term use (median duration 9.5 months) [68, 69]. Long-term evidence of the CV safety of TTh was provided in 2023 by the TRAVERSE trial, which demonstrated non-inferiority of a composite CV endpoint in the TTh arm compared to placebo after a follow-up period of up to 45 months [7]. Specifically, the frequency of CV death, non-fatal stroke, non-fatal myocardial infarction (MI), and coronary revascularization did not show statistically significant differences between the TTh arm (median serum TT levels of 375 ng/dL) and the placebo arm (median serum TT levels of 230 ng/dL). As already stated, the meta-analysis by Yeap et al. showed that serum TT levels below 153 ng/dL are associated with increased CV mortality. However, whether the administration of TTh in this group would decrease CV mortality remains unknown due to lack of evidence, since the TRAVERSE trial did not include males with such low baseline serum TTh levels. Notably, patients in the TTh group of the TRAVERSE trial had a higher incidence of acute kidney injury, atrial fibrillation, and pulmonary embolism. However, it is known that most reported cases of venous thromboembolism with testosterone use are among males with thrombophilia, and especially during the first 6 months of treatment. As a result, caution should be exercised with testosterone use in males with a history of venous thromboses [7, 78]. Additional evidence supporting the safety of TTh in the CV profile came from an observational Finnish study with a follow-up period of 18 years, which showed slightly lower all-cause and CV mortality in TTh users, although it was not statistically significant [79]. The above studies demonstrate that testosterone is safe in the long term for most CV outcomes, with the Finnish study showing a potential to decrease CV mortality after many years [7, 68, 69, 79]. There is a need to update the guidelines for the use of TTh in FH globally, since all of them were issued before the publication of the above studies that demonstrate long-term CV safety. However, efficacy and CV safety of TTh in very frail and multimorbid elderly patients remains to be determined in future trials. Furthermore, supraphysiologic testosterone levels during TTh should be avoided, since they are associated with dyslipidemia, AH, left ventricular hypertrophy, endothelial dysfunction, atherosclerosis, and elevated CV risk [4, 22, 74].

Based on a recently published review, testosterone has a variety of cardioprotective actions, including beneficial effects in inotropy and conduction, increased myocardial perfusion (improving anginal symptoms), decreased ventricular remodeling, as well as anti-fibrotic, anti-apoptotic, antioxidant, and anti-inflammatory effects [80]. Furthermore, the TOSCA registry provided evidence that over 90% of patients with HF have deficiency in one of the following anabolic hormones: testosterone, dehydroepiandrosterone sulfate, IGF-1, or triiodothyronine, and 70% had deficiency in two or more of the above hormones. The patients with multiple hormone deficiency had a significantly increased risk of hospitalization or CV death [81]. As a result, TTh could be a promising management strategy for HF. The available RCTs examining the use of TTh in patients with HF have demonstrated safety and improvement in symptoms, functional capacity, and quality of life [82]. However, the samples of these studies are small, while patients with severe HF have been excluded from most trials. Future multicenter event-driven RCTs are needed to investigate the hard endpoints of TTh and possibly GH therapy in HF, as well as the possible benefits of TTh in stable angina.

During the period directly following a stroke or MI, there are theoretical considerations that TTh could be unsafe due to potential BP fluctuations (via water retention and elevations in Hct), procoagulant effects (via aromatization to estrogens), or modulation of the inflammation/healing process in the plaque [4, 7, 14, 22, 78]. Coupled with the lack of RCTs regarding testosterone administration in the direct window after an acute CV event, as well as the fact that benefits of TTh are long-term, the international guidelines recommend against initiating TTh during the first 6 months post stroke or MI, based on expert opinion [43–45].

The routes of testosterone administration might have different CV safety profiles. Specifically, intramuscular testosterone injection might be the best option with the smallest CV risk compared to oral and transdermal administration, as demonstrated by a recent meta-analysis [83].

Erythropoiesis

Testosterone is a well-known stimulator of erythropoiesis, at least partly via its increase of the secretion of erythropoietin [6, 85]. Testosterone was widely used in the treatment of anemia before the availability of erythropoietin and its synthetic analogs. Average elevation in hemoglobin (Hb) with TTh is approximately 20%. In the TTrials, TTh led to an

increase in Hb by approximately 1 g/dL after 6–12 months, irrespective of baseline testosterone levels or the cause of the anemia [4]. However, particularly in patients with high-normal Hb, TTh might cause polycythemia, increasing BP and blood viscosity, which poses high risks for arterial and venous thromboses [84].

Obstructive sleep apnea

The association between testosterone and obstructive sleep apnea (OSA) remains controversial [85, 86]. According to most guidelines, severe OSA is considered a contraindication for TTh [85, 86]. Strong evidence from RCTs focusing specifically on the issue is very limited. The available evidence tends to suggest that short-term high-dose TTh could worsen OSA, while long-term low-dose TTh might improve OSA [85, 86]. The latter assertion is further supported by a recent meta-analysis which demonstrated that OSA is inversely associated with serum testosterone levels in males, independent of body mass and age [87]. However, supraphysiological testosterone levels might have opposing effects thus worsening OSA.

Prostate

There have always been concerns regarding prostate safety in patients under TTh. Nevertheless, there is an abundance of evidence, including the TTrials, showing that TTh is not associated with adverse prostate events, such as worsening of LUTS, worrisome elevations in prostate-specific antigen (PSA), or increased risk for prostate cancer development [7, 36, 43–45, 47, 48, 77, 88–91]. Of note, a recent large RCT has demonstrated that the prostatic adverse effects did not differ between TTh and placebo after a follow-up of up to 4 years [91]. Additional evidence supporting prostate safety was derived from the previously mentioned observational Finnish study with a follow-up period of 18 years, which showed no elevated prostate cancer risk with TTh [77]. On the contrary, hypogonadal males with benign prostatic hyperplasia could well exhibit improvement in LUTS with TTh, since it has been shown to reduce prostatic inflammation [48, 88]. Furthermore, the current evidence, including meta-analyses, suggests that TTh is likely to be safe even in patients with a history of non-high risk prostate cancer following curative treatment [92, 93]. The above will be further clarified by the SPIRIT trial, the first RCT to study the use of TTh in this clinical scenario [94]. On the other hand, evidence concerning the use of TTh in patients with prostate cancer under active surveillance is even more limited, albeit promising [93, 95].

Renal function

Although the evidence between testosterone levels and renal function is scarce, a meta-analysis demonstrated that low testosterone is associated with an increased risk for CKD development [96]. Furthermore, at least two meta-analyses have shown that low testosterone levels are associated with increased incidence of CV events and elevated CV all-cause mortality in patients with established CKD [96, 97]. Additionally, a prospective cohort study demonstrated that approximately 50% of patients with stage III or IV CKD had hypogonadism, with testosterone levels being inversely associated with all-cause mortality [98]. Data on TTh in CKD are very limited. Two RCTs with very few patients have demonstrated that TTh in CKD of varying severity, including patients on hemodialysis, can with safety improve sexual symptoms, Hb, and grip strength without causing overhydration or other significant adverse effects [99, 100]. However, the small number of studies limits the generalization of these results, necessitating future larger RCTs evaluating the safety and efficacy of TTh in CKD.

Frailty

Frailty is a common syndrome among the elderly, characterized by progressive functional decline, decreased physiological reserve, and reduction in resistance to endogenous and exogenous stressors, leading to increase in the individual's vulnerability to stress [101]. A recent meta-analysis demonstrated that both serum TT and FT are associated with frailty in males, but not females [102]. As a result, TTh could represent a de-frailing intervention in elderly patients with low testosterone levels. Nonetheless, the data on efficacy and safety on TTh in frail patients are to date limited and should be investigated in future studies.

All-cause mortality

There is abundant evidence that low testosterone levels (typically serum TT levels < 300–350 ng/dL) are associated with increased all-cause mortality [4, 14, 36, 47, 48, 96–98]. Furthermore, most of the evidence, including meta-analyses, has demonstrated that TTh decreases all-cause mortality [103, 104]. Hence, TTh might not only constitute a lifestyle intervention, but also an effective measure to improve prognosis and extend life expectancy, all of which should be taken into serious consideration during clinical decision-making. Given the recent evidence of the CV safety of TTh, the possibility of initiating TTh to extend life-expectancy in middle-aged and elderly patients with low testosterone levels in the absence of hypogonadal symptoms should be investigated in future RCTs.

The implications for future research regarding the potential efficacy and safety of TTh as regards various outcomes are illustrated in Fig. 2.

Time to benefit from TTh

Following initiation of TTh, the time required for the benefits to be observed can vary [44, 48]. Generally, based on the results from the TTrials, most symptoms improve within 3 months [6]. Improvement of libido, energy, and quality of life are noted within 3–6 weeks, while improvement of erectile function often requires 12 weeks. Mood elevation is evident after 3–6 weeks, while maximum effects might require several months. Effects on body weight, body composition, muscle mass, and strength usually require at least 3–4 months to 2 years. Improvement of bone density and strength requires 6 months, with maximum effects evident after 2–3 years or later. Effects on the lipid profile are visible after a month, while insulin sensitivity improves within a few days [44, 48]. However, the time needed until maximum effects in the lipid profile and in glycemic control are achieved is usually several months to a year [48]. Regarding levels of Hb and hematocrit (Hct), they tend to rise during the first 6 months and then plateau [44, 105]. The current guidelines suggest cessation of TTh if no symptomatic improvement is observed after 6 months of proper and consistent use [43–45, 48].

TTh formulations and route of administration

Current approved options for administration of testosterone include transmucosal, intramuscular, subdermal, and transdermal (patches, gels) formulations. All the above options are safe and effective, and the route of choice is decided upon consultation with the patient [4, 11, 40]. In the past, oral TTh was limited to testosterone undecylenate, which is no longer on the market. It was absorbed mainly via the lymphatic circulation bypassing the liver, while for adequate absorption, high-fat meals and a dosing frequency of twice or thrice daily were required [10, 48]. The options for intramuscular testosterone injection include testosterone propionate (twice to thrice per week), enanthate (from once weekly to once monthly according to the formulation, stated in the summary of the product characteristics), cypionate (once weekly or every 2 weeks), and undecanoate (once every 10–14 weeks) [10]. The main disadvantages of intramuscular testosterone injection include cost, the need for self-injection, and the unpredictable serum levels in the course of time, which can be decreased to hypogonadal levels before the next dose, in particular for testosterone undecanoate [10, 48]. Testosterone gels are applied once daily, mimicking the circadian rhythm, with minimal topical adverse effects [10, 48]. Among the above routes of administration, transcutaneous gels and intramuscular testosterone undecanoate have the most favorable safety profile [48]. Specifically, gel is the most used route of administration in RCTs. Current guidelines support the use of short-acting gels (1–2%) as the route of choice in TTh due to the potentially reversible nature of FH, and the option of rapid withdrawal in the event of side effects. However, as already stated above, there is evidence of superior efficacy particularly in the musculoskeletal system, as well as decreased CV risk, with intramuscular compared to transdermal and oral testosterone, which should be a topic for investigation in future RCTs [58, 59]. With testosterone gel, patients should not shower for 6 h following application and should avoid skin-to-skin contact during the same period [43–45].

Treatment targets and monitoring

There are limited data regarding the optimal on-treatment targets after initiation of TTh. However, as a general recommendation based on the guidelines, serum TT should be maintained within the normal range for younger adults, avoiding supraphysiological levels, which are known to be associated with worse outcomes [4, 10, 43–45, 48]. The optimal serum TT levels during TTh should be investigated by future RCTs. The timing of monitoring serum TT levels depends on the preparation used, while for gels, the initial evaluation should be made 2–6 h from gel application, after 2–3 weeks from TTh initiation [43–45].

According to the current guidelines, clinical evaluation, performance of digital rectal examination, and measurement of Hct, and PSA are recommended at baseline, after 3–6 months, and then annually following initiation of TTh [43–45]. Clinical evaluation should focus on the performance of a digital rectal examination and investigation for the presence of potential side effects, including headaches, irritability, aggression, mood swings, edema, prolonged painful erections, alopecia, acne, gynecomastia, and worsening of LUTS or OSA [4, 10, 43–45, 48, 106]. Furthermore, the possibility of pulmonary oil microembolism, which is usually self-limiting and presents with cough, is a rare side effect of intramuscular ejection of testosterone and especially undecanoate [43, 107]. Discontinuation of testosterone therapy (TTh) is warranted in cases where Hct levels exceed 54%. In some patients, the development of polycythemia may necessitate phlebotomy and further evaluation to uncover underlying causes such as OSA, lung disease, or polycythemia vera, which TTh by itself might unmask.

Furthermore, discontinuation of TTh and urologic evaluation is advised if PSA increases by more than 1.4 ng/mL or to a value above 4.0 ng/mL, in cases of detection of an abnormality on digital rectal examination, or in worsening of LUTS [43–45, 106].

Indications and contraindications of TTh in FH based on current guidelines

Based on the current guidelines, TTh for FH is indicated in the presence of serum TT levels below 300–350 ng/dL, accompanied by features of hypogonadism. However, before initiation of TTh the guidelines recommend an initial trial of lifestyle measures, including weight loss, together with optimal management of comorbidities, the management of obesity in particular being capable of restoring testosterone levels and hypogonadal symptoms [43–45, 48, 106, 108]. According to the current guidelines, the strongest features of hypogonadism that prompt TTh in the context of low testosterone levels (serum TT levels below 300–350 ng/dL) are sexual symptoms (decreased libido, loss of morning erections, and erectile dysfunction) [43–45, 48]. Other guideline-derived indications for TTh include unexplained anemia or osteopenia in the context of low testosterone levels [43–45, 48]. According to the recent EMAS statement, additional possible indications include prediabetes, T2DM, depression, or low perceived quality of life, always in the context of low testosterone levels [107]. The efficacy of TTh in symptomatic compensated hypogonadism remains to be investigated in future RCTs. The above should be particularly important for individuals with significant variation in CAG triplets in the androgen receptor gene, which can cause significantly reduced sensitivity to testosterone [48]. The indications for TTh in FH based on the current guidelines are presented in Table 2 [43–45, 48, 106, 108]. An algorithm for the diagnosis and management of FH in middle-aged and elderly males is illustrated in Fig. 3.

The contraindications for TTh based on the current guidelines are presented in Table 3. In men with secondary hypogonadism, TTh can further suppress the HPT axis and inhibit spermatogenesis. In these patients, cessation of TTh and initiation of gonadotropin therapy is recommended while they actively seek fertility [43–45, 106].

The contribution of machine learning to the diagnosis of FH

In the evolving landscape of medical diagnostics, the integration of machine learning techniques is revolutionizing our approach in the diagnosis of complex conditions such as FH. An example of this advancement is illustrated by a study where machine learning methodologies, specifically decision trees combined with the AdaBoost algorithm, a method used in machine learning to reduce errors in predictive data analysis, were employed to refine the diagnostic accuracy for FH [109]. This study used symptoms, biochemical markers, and comorbidities to construct predictive models. These models demonstrated markedly improved sensitivity and specificity over traditional screening tools. The use of AdaBoost enhanced the decision tree's performance, making it a robust tool for clinical decision-making. Another significant contribution to this field is the study by Kim et al. (2021), which utilized genetic algorithms—a sophisticated form of machine learning—to refine the Aging Male Symptom (AMS) questionnaire traditionally used for assessing FH. By deploying genetic algorithms, Kim and Moon were able to effectively improve the AMS questionnaire, thereby significantly enhancing its diagnostic sensitivity and specificity [110]. This method can be helpful and easily applied to other questionnaires.

Conclusions

Age-related testosterone decline can affect up to one in four middle-aged and elderly males and has been associated with a variety of age-related disorders, poor quality of life, and increased all-cause mortality. TTh has been proven effective in a variety of clinical scenarios for patients with FH. Recent studies have demonstrated a favorable long-term safety profile of TTh. Current guidelines generally make weak recommendations for TTh in patients with FH, mostly in the presence of sexual dysfunction. However, given its numerous benefits and association with prolonged life expectancy, future studies should investigate the use of TTh in middle-aged and elderly males with low testosterone levels even in the absence of typical hypogonadal symptoms. Future research should elucidate the role of TTh in a variety of clinical contexts, including cardio-renal-metabolic diseases.

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