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REVIEW ARTICLE

Is Testosterone the "Fountain of Youth" for Aging Men?

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Abstract: ***Background*****:** Late-Onset Hypogonadism (LOH) is defined as a clinical and biochemical syndrome associated with advancing age. It is characterized by specific symptoms and less specific manifestations due to deficiency of serum testosterone (T) levels.

Objective**:** This review aims to summarize the evidence related to LOH definition, diagnostic approach, and treatment to answer a clinical question: "Is Testosterone the fountain of youth for aging men?".

Methodology**:** MEDLINE/PubMed and institutional websites were searched for original papers, guidelines, and position statements published in the last ten years.

Results**:** Observational and randomized controlled studies on T replacement therapy in older men have been reported.

Discussion and Conclusion**:** Despite some heterogeneities regarding diagnostic definition, therapeutic target, and testosterone prescription, all guidelines agreed that male hypogonadism should be diagnosed and managed in aged men as in adulthood. However, trials assessing the efficacy of T therapy conducted for male rejuvenating are lacking; thus, T prescription for this purpose is not recommended.

Keywords: Testosterone deficiency, late-onset hypogonadism, testosterone replacement therapy, guidelines, older adults, anti-aging.

1. INTRODUCTION

Over the last two decades, there has been growing interest in the relationship between male aging and the adult/elderly form of hypogonadism, also defined as Late-Onset Hypogonadism (LOH) [1, 2]. Aging is a strong determinant of gonadal function as paradigmatically observed in women's biology, and an age-related decline in gonadal function has also been described in some but not all men. The European Male Aging Study, a cohort study of community-dwelling middle-aged and older men in Europe, found a progressive decline in serum testosterone (T) levels consisting in 0.4% per year and pointed out that sexual symptoms were primarily associated with consistently low serum T levels with an increase in LOH prevalence along with aging [3]. LOH defines a clinical condition characterized by a relevant reduction of circulating serum T concentration accompanied by sexual dysfunction symptoms, as observed other forms of male hypogonadism [2]. Additional symptoms such as fatigue, irritability, depressed mood, poor concentration, reduced physical performance, and sleep disturbances should be considered fewer specific signs and symptoms of male hypogonadism since they are part of the normal aging process [4, 5]. The focus of the debate is addressing the identification of those candidates who would benefit from testosterone replacement therapy (TRT), also considering possible TRT-related adverse events [6-8]. To date, different international professional societies in the field have published at least nine official guidelines addressing the management of adult hypogonadism [9-18]. Even though all guidelines agree with the criteria for hypogonadism diagnosis, there are differences in the threshold of serum T levels to consider and which disturbances should be addressed, especially among older adults [10, 16, 18]. These inconsistencies may generate confusion in clinical practice and could increase heterogeneity in the rate of T prescriptions. Lastly, recently published data about an evident pathophysiological dichotomy between functional (secondary) hypogonadism, mainly found in adult and older adults, and organic hypogonadism has further generated different diagnostic and therapeutic approaches [10, 16-18]..

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Table 1. Summary of criticisms in defining diagnosis, recommendation for TRT, criteria for positive response to treatment, therapeutic goals, possible contraindications, and appropriate T formulations in male hypogonadism*.

A				
-	**Signs and Symptoms**	**Total T Cut-Off**	**Free T Cut-Off**	**Expected Response**
Adult	Well-defined (specific and less-specific) symptomatology	264 to 350 ng/dl	Less than 65 pg/ml	Not applicable
Elderly	Wide range of symptoms	Not well established 190 ng/dl (>70y)	Not established	3 months for sex drive 12 months for ED and sperm quality Non-sexual symptoms: not proven to be benefit-to-risk effective.

B			
-	**Target**	**Contraindication**	**T Formulations**
Adults	The mid-normal range for most guidelines	Brest/prostate cancer Severe sleep apnea Severe lower urinary tract symptoms Severe heart failure Recent acute cardiovascular event (*e.g*., myocardial infarction, stroke)	Not specific complaints, usually patient's preference
Elderly	Not well established	The same as for adults	Transdermal gels (trial) and long-acting parenteral formulations (*e.g*., T undecanoate)

***[6-15]**

This descriptive review addresses the question: "Is testosterone the fountain of youth for aging males?". It is essential to recognize that the normal aging process also involves gonadal function, even if this phenomenon is particularly evident only in a minority of individuals. Therefore, an adequate diagnostic workup should be considered only in suspected cases that will benefit from TRT, as T supplementation *per se* is not evidence-based. In addition, after recognizing candidates for TRT, it is essential to have well-defined therapeutic goals, what should be the expected results, and how quickly to obtain a positive response. Data to drown the purposes mentioned above are currently not well-established by guidelines and recommendations, and herein we will show criticisms in defining diagnosis, a recommendation for TRT, criteria for a positive response to treatment, therapeutic goals, possible contraindications, and kind of more appropriate T formulations in male hypogonadism (Table **1**).

2. METHODOLOGY

MEDLINE/PubMed and websites of major professional organizations were searched for original papers and guidelines (GL) published in the last ten years (2011-2021), using the following key search terms: "testosterone deficiency", "male hypogonadism", "late-onset hypogonadism", and "guidelines". Articles related to older men (>65 years) with constantly low serum T levels (≤ 275 ng/dl) were selected [19].

2.1. Summary of Findings

The authors retrieved some RCTs and a total of nine clinical practice guidelines: the International Society for the Study of Aging Male (ISSAM) [9], the Endocrine Society (ES) [10], the International Society for Sexual Medicine (ISSM) [11], the American Urological Association (AUA) [12], the European Association of Urology (EAU) [13], the British Society for Sexual Medicine (BSSM) [14], the Canadian Medical Association (CMA) [15], the Endocrine Australian Society (ESA) [16,17], and the European Academy of Andrology (EAA) [18].

2.2. Nomenclature and Definition

The nomenclature of hypogonadism in adult /older adults has changed over time. Up to the 2000s, it was defined as "andropause" [or male climacteric, androgen decline in the aging male (ADAM), partial androgen declines in the aging male (PADAM)], in analogy to the definition of female menopause. However, since the 2010s, professional societies have mainly provided two definitions for this clinical condition: T Deficit Syndrome (TD) [11, 14, 15] and adult hypogonadism (LOH) [9, 10, 13, 16]. In these definitions, most professional societies have also included the chronic organic forms of male hypogonadism regardless of whether pre-pubertal or post-pubertal [9, 10, 13, 16]. The guidelines from EAA are the only exception, as they exclusively encompass the functional forms of age-declined hypogonadism (LOH) [18].

The estimated prevalence of symptomatic TD is around 2%, increasing to 5.1% for men aged 70-79 [3]. Although the endocrine function of the hypothalamic-pituitary-testes axis (TPT) declines with aging, most healthy men maintain normal serum T levels and sperm count lifelong [20, 21]. However, a small group of elderly subjects shows T levels constantly be-

low the threshold for healthy adult men [4, 22, 23]. The diagnosis of hypogonadism in adult/older men (LOH) occurs when low T levels are associated with signs and related symptoms of T deficiency such as a decline in libido and sex drive, decreased morning erections, erectile dysfunction (ED), and other less specific symptoms and signs, in part overlapping with those typically related with senescence. The latter include decreased energy, motivation, initiative, and self-confidence, feeling sad, depressed mood, poor concentration and memory, sleep disturbance, increased sleepiness, mild unexplained anemia, reduced muscle mass and strength, increased body fat and body mass index, breast discomfort or gynecomastia, height loss, low trauma fracture, osteopenia or osteoporosis, hot flashes, and sweats [9-18].

2.3. Diagnostic Tools

Over the last twenty years, different researchers have better-developed questionnaires or structured interviews to differentiate normal male aging versus LOH. So far, several questionnaires have been validated for this purpose. Among these questionnaires, the Aging Male's Symptoms Scale (AMS) [24], the Androgen Deficiency in Aging Males (ADAM) [25], the Smith's screener (MMAS) [26], and the Androtest [27] were found to be the most reliable tools. Morley *et al*. [28] compared the most employed questionnaires using the bioavailable T as a marker for male hypogonadism. Although most of the questionnaires presented high sensitivity (>80%), their specificity was low (< 50%), suggesting potential limitations in their use in clinical practice [15]. Some researchers found a relationship between circulating T levels and signs and symptoms related to T deficiency [29]. It has been shown that some signs and symptoms considered less specific by the ES, BSSM, ESA, and EAA [10, 14, 16, 18], such as strength reduction, increase in fat mass, reduction of motivation, were already present when circulating T levels were below 433 ng/dl (15 nmol/L) [30].

Signs and related symptoms of male hypogonadism may be observed in men with several chronic comorbidities. Although lower than normal circulating T levels are frequently observed in this cluster of patients, it is hard to establish, whereas TD rather than underlying comorbidities could cause signs and symptoms [31]. Randomized controlled studies showed partial failure or only a mild improvement of questionnaire results after T therapy [32].

2.4. Symptomatology

Each professional society has subdivided signs and symptoms of male hypogonadism as specific, suggestive, and nonspecific. However, the EAA considers only specific (sexual) and less specific signs and symptoms, explicitly focusing on functional adult hypogonadism [18]. In general, signs and symptoms are divided into sexual disturbances (*i.e*., ED), gynecomastia, cognitive impairment and mood (*i.e*., depression), and general disturbances (*i.e*., impaired strength) [12-15].

These differences may predispose to confusion in discriminating between the specific clinic of overt hypogonadism and symptoms related to the physiological aging process, therefore, curbing the translation of clinical guidelines into a daily approach.

2.5. Laboratory Tests

Although there is a general agreement for diagnosing hypogonadism in adult/older adults among professional societies, identifying specific reference thresholds for low T levels is not achieved. Indeed, several factors may have concurred to hamper the standardization of a cut-off: encompassing diurnal, seasonal [33, 34], and intra-individual variations [35], age of subjects [36], genetic and ethnicity [37-39], lifestyle factors [40], and co-morbidities [41]. The measurement (at least two times) of fasting morning (between 8 and 11 am) serum total T levels is considered the widely accepted parameter for diagnosing male hypogonadism. An exception to this statement is when changes in SHBG levels are expected due to age, medications (glucocorticoids, progestogenic steroids, estrogens), thyroid dysfunction, chronic liver disease, obesity, metabolic syndrome, and type 2 diabetes mellitus [42]. In this case, the determination or calculation of the free T appears more appropriate. From a clinical point of view, there has been limited evidence comparing the association of total T and free T to clinical variables (muscle strength, bone mass density, body mass index, lean and fat mass) in older men, either in prospective or randomized controlled trials (RCTs) [30]. The combined measure of free and total T has been proved to be related to the body mass index in obese patients and sexual dysfunction, such as ED, decreased libido, and decreased morning erection, in both prospective studies and, more recently, RCTs [3, 43]. Therefore, the measurement of endogenous total T is the principal parameter that should be employed in the case of suspected hypogonadism. At the same time, the determination of free T should be limited to the cases in which the clinical suspicion of hypogonadism is strong, even in the presence of low/normal total T levels [41]. All scientific societies generally accept this statement and are strongly recommended by the ISSM, which tends to raise the threshold of total T up to 350 ng/dl [11]. Nevertheless, these thresholds for defining low T levels in the elderly and men with co-morbidities have not been agreed upon by traditional scientific societies so far. Therefore, discrepancies are still present [44].

Commonly, the determination of serum total and free T can be accomplished by direct and indirect methods. However, the sensitivity and specificity of plasma TT and FT have remained a challenge since their initial employed techniques [32]. Furthermore, owing to their small concentration (especially in children, women, and severe form of male hypogonadism) and the presence of structurally similar molecules, the assessment of plasma T and its fractions levels has always shown several technical problems in both genders. The first employed methods for T determination (indirect assays) were initially used about 40 years ago. However, these methods were more expensive and complicated to use since they employed both a step of organic extraction of different blood volumes (depending on the serum concentration of T) and a step of column (*e.g*., Sephadex) or paper chromatography purification before performing the radioimmunoassay (RIA) [45]. More recently, nearly all clinical and research laboratories have employed ready-made commercial kits using a rapid and easy automated immunoassay platform (direct methods). However, even if these methods are less expensive, fast, and easy to use, they exhibit less sensitivity and specificity [46]. Furthermore, the recent standardization of direct methods

(manual RIA and automated immunoassays), with the identification of the normal range for serum T for each laboratory, has shown that serum T assessment by immunoassay can effectively distinguish eugonadal from hypogonadal men [47, 48].

Taking together these data, ISSAM [9], CMA [15], BSSM [14], and EAU [13] rely on validated direct immunoassays methods, especially if the liquid chromatography-tandem mass spectrometry (LC-MS/MS) method is not available. ES [10], however, recommends using a harmonized reference range for LC-MS/MS certificated by the Centers for Diseases Control and Prevention Hormone Standardization Program for T [49]. EAA advises using the T range assessed by gas chromatography-mass spectrometry (GC-MS) [18]. The EAU [13] suggests using laboratory-specific reference ranges (349 ng/dl), while AUA [12] and CMA [15] recommend employing the absolute TT value (< 300 ng/dl). Finally, EAS [16] suggests using an age-stratified reference interval (Z-score) for T, though there have been insufficient data to adopt this method. Finally, the Institute of Medicine of the National Academy of Science [50] chooses to include aging men whose serum T levels were unequivocally lower than 275 ng/dl.

Among the methods employed for FT determination, equilibrium dialysis is nowadays considered the gold standard [51-53]. However, given that this assay is challenging to perform routinely, an alternative method is based on the FT calculation from serum TT, SHBG, and albumin levels [1, 22]. This method has been validated by surveys conducted with many male participants [54, 55]. However, most guidelines report that FT measurement is required when TT measurement is unreliable or in case of alterations in the circulating SHBG levels [9, 10, 13, 14, 18]. Therefore, the FT threshold of 65 pg/ml (225.4 pmol/L) can be regarded as the lower cut-off of the normal range.

2.6. Medical Management

2.6.1. T replacement therapy (TRT) in men with LOH

While TRT is a well-established therapy for patients with organic hypogonadism, especially the pre-pubertal forms [21], the role of TRT in adult men with functional hypogonadism is debated [10, 16, 17]. Inconsistent improvement of some disturbs affecting aging men with LOH, such as cognitive impairment [56] and muscle strength, and possible adverse events related to prolonged use of TRT have raised concerns [57]. Overall, observational studies, randomized controlled trials (RCTs) [5], and meta-analyses pointed out that T therapy effectively improves erectile function and restores sex drive in men with serum TT below 12 nmol/l. These results are more evident in those men with overt baseline hypogonadism (TT<8 nmol/L), and TRT performs better in restoring libido rather than ED [26]. Conversely, improvement of ejaculatory dysfunction is scanty and inconclusive [58]. TRT appears to improve mood in hypogonadal men [59] but with a more pronounced effect only in those with milder symptoms [60], while there are no significant improvements in memory or multiple other domains of cognitive function [56, 61]. Studies assessing the effects of TRT in men with dementia or on those exhibiting a progression from mild cognitive impairment to dementia are still lacking [61]. The role of TRT in ameliorating physical performance in older men with low or low-normal serum T levels and physical mobility limitation has yet to be fully elucidated as inconclusive findings have been reported [62]. TRT in healthy hypogonadal men increases areal and volumetric vertebral and femoral bone mineral density and vertebral and femoral bone strength. Nevertheless, no specific studies have addressed the effects of TRT on fracture risk so far, and high-risk patients should be treated with osteoporosis-approved medications for both primary and secondary prevention [63]. Androgens play a central role in determining and maintaining body composition [64]. Although recent trials did not provide available data [65], studies indicated that TRT in hypogonadal men increases fat-free mass and reduces fasting glycemia and insulin resistance [65].

TRT in men with age-related hypogonadism is evidence-based for sexual disturbances. Inconclusive results have been provided for other disturbs, such as physical and cognitive dysfunctions, metabolic disorders, and osteoporosis. Hence, further controlled studies are probably needed to draw definitive conclusions and recommendations.

2.6.2. Side effects and contraindications to TRT in men with LOH

Undoubtedly, cardiovascular (CV) safety of TRT in aging men with functional hypogonadism is still the most conflicting issue. Very few studies published between 2010 and 2014 [66, 67] showed significant limitations, raising possible warnings [68, 69]. Controversial results were found regarding a possible relationship between TRT and thromboembolism risk in aging men [28]. As observed in estrogen replacement in postmenopausal women, venous thromboembolism is likely to occur in men with undiagnosed thrombophilia or hyperfibrinolysis status. Therefore, accurate medical history is needed before starting TRT [70].

Hematocrit is an essential biomarker of T exposure during TRT and correlates directly with CV risk; hematocrit exceeding 54% leads to TRT withdrawal. In most cases, short-term parenteral T formulations could induce more T fluctuations and are accompanied by possible side effects. Conversely, long-acting T undecanoate and transdermal preparations are less prone to increase hematocrit levels and may have a blunted impact on thromboembolism risk [71].

TRT should be considered safe for prostate health [65]. Even though TRT can only cause an increase in prostate antigen (PSA) levels or prostate volume after short-term treatment, long-term (more than one year) administration of TRT cannot increase the risk of new-onset prostate cancer [65]. In a recent RCT enrolling older men with unequivocally low T levels (<275 ng/dl), serum PSA levels increased by 0.47±1.1 ng/ml after 12 months of TRT; only 5% of those patients exhibited a rise in PSA concentration over 1.7 ng/L. Once again, this controlled study cannot address whether TRT can or cannot increase the risk of prostate cancer in elderly hypogonadal men [72]. To sum up, the evidence reports that TRT administered at recommended doses may be safe in case male hypogonadism has been correctly diagnosed [61]. It is noteworthy that none of the RCTs were sufficiently powered to exclude adverse risks, given that they have usually been conducted for brief periods (generally a few months).

2.6.3. TRT Therapeutic Targets by the Different Guidelines

Improvement of the clinical picture is the main guiding principle in the management of male hypogonadism replaced with T formulations [9-18]. Guidelines from different professional societies provide recommendations for patients with borderline low T levels. ISSM [11], BSSM [14], and CAM [15] suggest starting a trial of TRT for three (CAM) or six consecutive months (BSSM and ISSM), waiting for possible benefits. Conversely, treatment should be discontinued if clinical improvement is not achieved with TRT trials. Other guidelines (EAU, ISSM, CMA, ES, and EAA) recommended a panel of medical investigations to make a differential diagnosis between primary and secondary hypogonadism (serum gonadotrophin and prolactin assessment). Notably, ES recommends evaluating patients through different procedures (multiple pituitary hormone assessments, genetic analysis, magnetic resonance imaging) when serum T levels are below 150 ng/dl [10]. Furthermore, ISSM [9], ES [10], EAU [13], EAA recommend to measure or calculate free T levels in addition to total T in patients with altered levels of SHBG and serum T levels between 8-12 nmol/L (231-346 mg/dl) for ISSM [9], EAU [13] and EAA [18], and between 6.9-13.9 nmol/L (200-400 ng/dl) for ES.

Most guidelines strongly encourage lifestyle changes (*i.e.*, diet and physical activity for overweight and obese men) and adequate management of co-morbidities instead of TRT [10-18]. Certain medications that interfere with T secretion or metabolism should also be discontinued [18]. ES, EAS, and EAA guidelines [10, 13, 18] recommend against TRT prescription in dysmetabolic conditions such as obesity, metabolic syndrome, type 2 diabetes mellitus, or to reduce fracture risk in hypogonadal men with severe osteoporosis [10, 16-18]. Furthermore, the most recent guidelines [10, 16, 18] recommend against TRT as rejuvenation therapy in men complaining of fewer specific signs and symptoms, in agreement with recent evidence provided by the seven RCTs from the Institute of Medicine of the National Academy of Science [21]. Moreover, all professional societies recommend against TRT in the case of men who are planning fertility [9-18].

All guidelines claim shared decision-making with patients to select appropriate T formulations considering safety, efficacy, costs, and patient preferences [9-18]. All guidelines generally aim to obtain a mid-to-normal T level during TRT. However, a few small differences among them depend on different thresholds considered by professional societies as the lower value for the normal range. The AUA defines T range for patients in pharmacotherapy at 15.6-20.8 nmol/L (450-600 ng/dl) [12], the ES considers 10.5-29.5 nmol/L (300-850 ng/dl) [10]; CMA [15] 14-17.5 nmol/L (404-505 ng/dl), and BSSM [14] suggests as target range 15-30 nmol/L (433-865 ng/dl).

Nowadays, different formulations can attain standards of suitability and effectiveness of TRT in hypogonadal men. Among different formulations, transcutaneous (gel) and long-acting injectable T formulations (testosterone undecanoate) display ideal characteristics for an optimal replacement therapy [71] and are cost-effective [41]. Among different guidelines, the ISSAM [12] and EAS guidelines [41] provide an accurate list of available T formulations. EAA encourages initiating a TRT trial preferring gel compounds, and allocating the administration of long-acting injectable T if short-term proof provides clinical improvements after a deep discussion aiming at balancing the benefits and risks [18].

Most guidelines [10, 11, 12, 13, 14, 15, 16, 17, 18] recommended a clinical and biochemical follow-up generally at 3, 6, and 12 months and then yearly. The investigation panel measures serum T, PSA, and hematocrit determined during the established clinical follow-up. In particular, the ES [10] and EAA [18] recommend a urological evaluation if PSA levels are higher than 1.4 ng/ml within one year from starting TRT or if PSA level is greater than four ng/ml at any monitoring time. Conversely, the EAS [17] suggests that a routine assessment of plasma PSA levels during TRT may lead to a possible overdiagnosis of clinically insignificant prostate cancer.

Furthermore, the ISSAM [9], ISSM [11], and CMA [15] recommend serum lipid monitoring during TRT. Also, the ISSAM [9], ISSM [11], CMA [15], ES [10], and EAA [18] suggest carrying out a digital rectal exam at every follow-up visit. Lastly, the ISSAM [9] guideline provides a timetable to predict when the improvement of signs and symptoms of male hypogonadism should be expected to avoid unnecessary overtreatment of patients who do not exhibit relevant clinical improvements. Under this point of view, an essential improvement in libido is expected within the first 3-6 months of treatment. Improving erectile performance and ejaculatory function is usually reported within 12 months of TRT.

2.6.4. TRT-Related Complications in Aging Men with LOH

Most guidelines recommend against TRT prescription to all adult/elderly hypogonadal men with breast cancer, active prostate cancer, or high-risk patients. Similarly, patients with high hematocrit, untreated severe sleep apnea, severe lower urinary tract symptoms, thrombophilia, uncontrolled heart failure, recent (<6 months) myocardial infarction, or stroke must not be treated with TRT [6-15]. The EAU [13] also recommends TRT during brachytherapy or external-beam radiation therapy in low-risk prostate cancer patients.

The ES [10] and EAA [18] guidelines suggest discussing with patients to balance potential risks and benefits before starting TRT [10, 18]. The EAU [13], BSSM [14], and CMA [15] guidelines suggest that patients with no evidence of active prostate cancer could be treated with TRT.

There is a complete agreement among professional societies that TRT could increase cardiovascular risk [9-18]. The CMA guideline [15] supports the use of TRT only in patients with stable CVD, while the EAU [13], BSSM [14], and EAA [18] guidelines recommend against the use of TRT in hypogonadal men with severe heart failure (New York Heart Association (NYHA) class III and IV). Different guidelines recommend against TRT in all those patients showing elevated hematocrit as follow: ES (7) >48% and EAU [13], BSSM [14], and EAA [18] >54%.

3. PERSPECTIVES

It has been published nationally representative data showing the determination (by immunoassay) of plasma T levels in men aged from 20 to >60 years, lean, never-smoking, and without dysmetabolic and morbid conditions [73]. This study aimed to well-defined T thresholds and therapeutic targets for

aging men. However, guidelines have not shed light on TRT in adult/older adults with LOH.

Several professional societies do not recommend screening for asymptomatic men for low T [10, 12, 16, 18]. TRT effectively improves erectile function and restores libido in men with low serum T concentration, especially overt hypogonadism. However, controlled intervention studies did not show TRT's positive effects on those health domains that could affect the quality of life in older adults (cognition, mood, fracture risk, physical performance, and mobility). Controversy remains about the adverse effects of TRT on CV risk. On this basis, particular attention should be paid to patients with hypercoagulative status, and TRT should be similarly discontinued in case of erythrocytosis [10, 16, 18]. TD is frequently observed in chronic heart failure men [74-76]. Even though TRT, either alone or in combination with other hormonal replacements in case of multimodal hormonal deficiency [77], has been used in CHF patients [77], there is concordance about avoiding TRT prescriptions in patients with NYHA class III and IV heart failure or in those with a recent occurrence of CVDs [9-18]. TRT initiation requires a precise diagnosis of hypogonadism and should be discussed with the patient, especially in older men. The decision-making process should consider patient desires, real therapy expectations, and chronic treatment compliance.

Besides, clinical and laboratory monitoring is mandatory for assessing any improvement of signs and symptoms of hypogonadism in a reasonable time and promptly recognizing adverse events [10, 16, 18]. TRT should be avoided in patients with prostate cancer [9-18], even if [13-15] other guidelines suggest that TRT can be considered in patients with prostate cancer not exhibiting evidence of recurrence or progression [78].

CONCLUSION

Hypogonadism can lead to signs and symptoms which resemble those of senescence. This issue is well-established in the Klinefelter syndrome, as affected patients exhibit precocious manifestations of cardiovascular, metabolic, and neuropsychiatric disturbances primarily due to hypogonadism [79, 80]. Despite this evidence, the perspective of TRT as a "fountain of youth" should be definitively consigned to the past.

TRT effectively improves erectile performance in patients with ED having overt hypogonadism, but this effect is less relevant in patients with dysmetabolic complications [30]. The last word may not be said yet for the appropriate use of TRT in functional male hypogonadism [10, 16, 17]. Indeed, there is the first evidence on how the functional forms can be overcome [81]. Weight loss may improve T serum levels in obese men [82, 83]. The same has been observed in obese and diabetic men, with a more relevant cumulative effect than glycemic control alone [84]. In diabetic and obese patients with functional hypogonadism, selective estrogen receptor modulators (*e.g*., clomiphene citrate) may reactivate the hypothalamic-pituitary-testis axis, and serum T can be restored [85-87]. In addition, combined use of diet, metformin, liraglutide, and testosterone seems to be associated with a relevant improvement of ED [88, 89].

A current topic related to the ongoing pandemic of Coronavirus Disease 2019 (COVID-19) is attributable to the role of TD in adults and elderly males in predisposing affected patients to worse progression once the infection has occurred [90-92]. Further observational and intervention trials are needed to elucidate this phenomenon better.

In conclusion, for a better comprehension of the male aging process, it is essential to pass through a better understanding of the hallmarks of testicular aging in terms of inflammation, oxidative stress, apoptosis, enzymatic and mitochondrial activity [93-94]. Based upon a mechanistic/pathophysiological approach, the use of certain medications (*e.g*., glucocorticoids, cyclooxygenase-2 inhibitors, immune cell blockers), nutraceuticals with antioxidative properties (*e.g*., resveratrol, curcumin, quercetin, melatonin), vitamins (*e.g*., vitamin D), probiotics (*e.g*., Lactobacillus reuteri), and nicotinamide nucleotide may have a perspective role in preventing, delay or even treat testicular aging and aging-related male hypogonadism [95-97].

LIST OF ABBREVIATIONS

CV	=	Cardiovascular
LOH	=	Late-Onset Hypogonadism
T	=	Testosterone
TRT	=	Testosterone Replacement Therapy
NYHA	=	New York Heart Association

AUTHORS' CONTRIBUTIONS

V.A.G. conceived the review. V.A.G., G.L., and V.T. searched databases independently, selected relevant articles, and wrote the manuscript. All the authors read the manuscript, provided criticisms, and approved the final version of the paper.

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