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REVIEW ARTICLE

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Critical evaluation of different available guidelines for late-onset hypogonadism

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Abstract

Background: Late-onset hypogonadism (LOH) is a syndrome characterized by clinical and biochemical evidence of low testosterone levels with advancing age. In recent years, several guidelines, position statements and other recommendations have become available. It is unclear whether similar indications are reported in these documents.

Objective: To review similarities and differences among available documents on the management of hypogonadism, with a special focus on LOH.

Materials and methods: PubMed, Google and international societies websites were searched on March 2020 for documents published in the last 10 years on the management of hypogonadism and LOH.

Results: Nine documents were found, each developed by: (a) the American Urological Association; (b) the British Society for Sexual Medicine; (c) the Canadian Medical Association; (d) the Endocrine Society; (e) the Endocrine Society of Australia; (f) the European Academy of Andrology; (g) the European Association of Urology; (h) the International Consultation for Sexual Medicine; and (i) the International Society for the Study of Aging Male.

Discussion: Despite similar principles, differences were found both for the diagnostic workup and follow-up. Particularly, discrepancies were reported both for total and free testosterone levels for diagnosis and for total testosterone for monitoring.

Conclusion: Available documents differ in terms of specific recommendations for the management of hypogonadism and LOH. Given the relevant clinical implications of adequate management of these disorders, future guidelines should report more consistent measures to be adopted in clinical practice.

KEYWORDS

ageing, guidelines, hypogonadism, late-onset hypogonadism, review

1 | INTRODUCTION

In the last two decades, there has been a growing interest in the relationship between ageing and changes in the male reproductive system.[1,2] As a milestone in this field, the European Male Aging Study found the age-related decline in testosterone level to be associated with symptoms and signs among a random population sample of men aged 40-79. The definition of late-onset

hypogonadism (LOH) was progressively adopted in the scientific community to identify a syndrome characterized by clinical and biochemical evidence of low testosterone with advancing age.[3] Also, given this definition, testosterone replacement therapy (TRT) seemed to be the most physiological approach to reduce the impact of this condition in affected subjects.[4,5] Several years have passed, and on a closer look, several issues still need to be addressed when managing LOH in clinical practice. First, after which age should this syndrome be considered. Second, which signs and symptoms should raise the suspicion of this disorder and prompt a diagnostic workup. Third, which methods should be adopted for the biochemical evaluation and which cut-off of testosterone should be used when interpreting results. Fourth, the benefits to be expected from its management. Finally, whether TRT still represents the best therapeutic approach for LOH or whether the definition of a management plan based on lifestyle modifications, screening and treatment of comorbidities and medications, when needed, may reach similar outcomes.

Different national and international societies have developed and updated recommendations for the management of hypogonadism.[6-15] It has to be acknowledged that clinical guidelines are not designed to replace professional judgement in any field of medicine. However, they are developed to be of assistance to physicians and other stakeholders by providing guidance and recommendations for specific areas of practice.[9] From this perspective, the proposal of consistent recommendations, irrespective of the appointed task force, is key to letting patients receive the best counselling in clinical practice. The present narrative review was conceived to assess and discuss similarities and differences among available guidelines on the diagnosis and management of hypogonadism, with a special focus on LOH.

2 | MATERIALS AND METHODS

We searched PubMed, Google and international societies websites for documents published in the last 10 years on the management of hypogonadism and LOH. Guidelines, position statements and other recommendations published in English were selected. The last search was performed on 1 March 2020. The following information was extracted: (a) document type; (b) age for the definition of LOH; (c) symptoms and signs suggestive of testosterone deficiency; (d) laboratory methods for the assessment of testosterone; (e) cut-offs for the biochemical diagnosis of hypogonadism; (f) benefits to be expected from the management of LOH; (g) therapeutic options and targets; and (h) follow-up.

3 | RESULTS

Nine documents were included in the present narrative review. The documents were developed by the following societies: (a) the American Urological Association (AUA) in 2018[6]; (b) the British Society for Sexual Medicine (BSSM) in 2017[7]; (c) the Canadian Medical Association (CMA) in 2015[8]; (d) the Endocrine Society in 2018[9]; (e) the Endocrine Society of Australia (ESA) in 2016[10,11]; (f) the European Academy of Andrology (EAA) in 2020[12]; (g) the European Association of Urology (EAU) in 2020[13]; (h) the International Consultation for Sexual Medicine (ICSM) in 2019[14]; and (i) the International Society for the Study of Aging Male (ISSAM) in 2015.[15] One document focused on the management of functional hypogonadism only.[12]

3.1 | Is there any age cut-off for the definition of late-onset hypogonadism?

Hypogonadism is a common endocrine disorder characterized by both symptoms and signs of testosterone deficiency and unequivocally and consistently low testosterone levels.[9] It can be classified according to two main aspects: (a) the organ responsible for the disorder, either testis in primary forms or hypothalamus/pituitary gland in secondary forms; (b) the mechanism underlying hypogonadism, which could be differentiated between functional and organic forms. Particularly, to be classified as functional, hypogonadism should be reversible following the treatment of underlying causes. No structural, destructive or congenital disease should affect the hypothalamic-pituitary-testicular axis (HPT).[9,16,17] Even if a consensus has generally been reached on these definitions, the age after which testosterone deficiency can be classified as late-onset is still debated. In the 2015 World Health Organization World report on Ageing and Health, 60 years of age was used as the cut-off to describe the segment of the older population.[18] In the Testosterone Trials, a coordinated set of seven placebo-controlled double-blind trials in 788 men, 65 years of age was chosen as the cut-off to determine the efficacy of increasing the testosterone levels of older men with low testosterone.[19] Concerning the reviewed documents, sparse data were reported on this issue. According to the BSSM, LOH should be used to describe a functional disorder of androgen deficiency like features and low testosterone levels in men older than 50 years.[7] Similarly, in the CMA guidelines, a reference to the same age was reported, because of the prevalence of testosterone deficiency after this age.[8] Any age cut-off may seem simply academic more than clinically relevant. Indeed, when all the effects of ageing on the male reproductive system are considered, a moderate and gradual decline in gamete quality and fertility possibly starts as early as the 30 of 35 years age range.[2] Comorbidities (eg obesity) may play a key role and contribute to the apparent age-related decline of testosterone, as observed in middle-aged and elderly men in the European Male Aging Study.[12]

It is worth noting that a different nomenclature was adopted to define LOH, possibly leading to confusion on this topic as well. Indeed, until the 2000s, andropause, male climacteric, androgen decline in the ageing male (ADAM) and partial androgen decline in the ageing male (PADAM) were used. From the 2010s, the two most commonly used terms were testosterone deficit (syndrome)[7,8,14] and adult hypogonadism.[9,10,15] Of note, both the functional and chronic

organic forms of hypogonadism, regardless of their onset, were included under these definitions by some societies.[9,10,13,15] On the contrary, other societies considered LOH as a synonym of functional hypogonadism in an ageing male.[7,12]

3.2 | Which symptoms and signs should raise one's suspicion of testosterone deficiency in ageing?

Signs and symptoms of testosterone deficiency strictly depend on the age at onset, duration, severity and the underlying pathogenesis. Indeed, in a subject with eunuchoid habitus and small testes, a pre-pubertal organic form (eg Kallmann syndrome) is typically diagnosed.[9,15] Different domains may be involved including the following: (a) sexual (eg erectile dysfunction); (b) physical (eg gynaecomastia and decreased body hair); (c) psychological (eg changes in mood and well-being); and (d) cardiometabolic (eg changes in body composition and metabolic syndrome).[6-15] Concerning hypogonadism in middle-aged and older men, the association between testosterone and sexual function is a matter of fact. In the European Male Aging Study, poor morning erection, low sexual desire and erectile dysfunction were consistently associated with low serum testosterone levels, with thresholds of total testosterone ranging from 8 to 11 nmol/L (230–320 ng/dL).[20] These results were in line with previous studies.[21] However, it is common knowledge that subjects with LOH often complain or present with less specific symptoms and signs, including fatigue, irritability, depressed mood, poor concentration and memory, reduced physical performance, mild unexplained anaemia and sleep disturbance.[6-15] This raises the question as to whether a diagnostic workup should be prompted solely by the typical presentation of hypogonadism or whether one or more non-specific findings may be deemed sufficient. On one hand, the chance of success in diagnosing hypogonadism using the first approach is high, leading, hopefully, to the expected benefits of therapy. On the other hand, perhaps a wider approach would be beneficial in detecting and treating hypogonadism earlier, for example in patients with osteoporosis secondary to testosterone deficiency and one or more fractures. Among the included documents, an indication of the symptoms and signs to be considered as 'more specific' versus 'less specific' was reported in BSSM, the Endocrine Society, EAA and EAU[7,9,12,13] while a common list of conditions was reported in the other ones (Table 1).[6,8,14,15] Of note, what should be considered as specific differed among the former documents. For example, while the Endocrine Society included almost exclusively the typical clinical presentation of subjects with pre-pubertal forms of hypogonadism (eg incomplete or delayed sexual development and small testes), EAA and EAU referred to the post-pubertal ones (eg reduced libido, decreased spontaneous erections and erectile dysfunction).[9,12,13] The goal of the clinical evaluation is to increase the chances of finding affected subjects for whom the diagnosis of LOH will be made after a concordant laboratory assessment. Indeed, no therapy for hypogonadism is indicated in those subjects who present with symptoms and signs but have normal testosterone levels. Also, there is no evidence supporting the universal screening for hypogonadism by the means of the latter approach only, because possibility of randomly finding low levels of testosterone in a healthy asymptomatic man may be relevant.[12] One study focused on the association between symptoms and serum testosterone in men aged 50-86 years and found no clear-cut threshold for LOH. Rather, the prevalence of psychosomatic symptoms accumulated with decreasing androgen levels, with some specific symptoms (eg loss of libido) increasing in patients with testosterone concentrations below 15 nmol/L (433 ng/dL). A close relationship between the number of metabolic risk factors and the circulating testosterone levels was found in this study too, raising the question as to whether some symptoms should have been solely attributed to testosterone deficiency or to other causes as well.[22]

To improve the performance of the clinical evaluation in detecting hypogonadism including LOH and discriminating it from other disorders, different questionnaires and structured interviews have been developed. The most commonly used are the Aging Male's Symptoms Scale (AMS),[23] the Androgen Deficiency in Aging Males (ADAM),[24] the Massachusetts Male Ageing Study questionnaire or Smith's screener questionnaire (MMAS),[25] and the Androtest.[26] Despite the general adequate sensitivity (>80%), a limited specificity has been reported (<50%)[15]; then, the recommendation against their use for universal screening for hypogonadism was developed.[12] Different recommendations were reported on the use of these questionnaires on an individual basis, with BSSM and ISSAM supporting their use to provide a quantitative baseline assessment of patients symptoms and evaluate the clinical response to treatment and EAU not recommending their use in the assessment of testosterone deficiency.[7,13,15]

3.3 | Which laboratory methods should be used for the assessment of testosterone?

As previously stated, the diagnosis of LOH relies on both clinical and biochemical findings. The relevance of available laboratory methods may be of limited interest to the general physician. Nevertheless, given that clinical decisions can be based on laboratory findings both at diagnosis and during follow-up, assuring the reliability of these data is key. The laboratory workup for hypogonadism includes total testosterone (TT), free testosterone (FT), sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH) and luteinizing hormone (LH). While the analysis of TT is warranted in all, the assessment of FT may be indicated only in those patients who have conditions that alter SHBG levels or whose initial TT concentrations are at or near the lower limit of the normal range (see below).[9] For the present review, we focused on these two hormones only.

The concentrations of serum TT and FT can be determined by direct and indirect methods. Owing to their low levels (especially in severe forms) and the presence of molecules with a similar structure, their assessment has always been challenging.[27] The first methods for determination of testosterone were introduced about 40 years ago

TABLE 1 Symptoms and signs suggestive of testosterone deficiency

Society, year	Symptoms and signs	Other data
American Urological Association, 2018[6]	• Symptoms: reduced energy, reduced endurance, diminished work and/or physical performance, fatigue, visual field changes (bitemporal hemianopsia), anosmia, depression, reduced motivation, poor concentration, impaired memory, irritability, infertility, reduced sex drive and changes in erectile function • Signs, including gynaecomastia	Other conditions in which workup should be considered include anaemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction and chronic corticosteroid use
British Society for Sexual Medicine, 2017[7]	Sexual dysfunction, especially low sexual desire, decreased morning and night-time erections and erectile dysfunction are prominent, commonly presenting symptoms particularly suggestive when associated with each other. Less specific symptoms include fatigue, sleep disturbance, loss of physical strength, decreased energy and motivation and depressed mood. • Sexual: delayed puberty, small testes, infertility, decreased sexual decide and activity, decreased frequency of sexual thoughts, erectile dysfunction, delayed ejaculation, decreased volume of ejaculate, decreased or absent morning or night-time erections • Cardiometabolic: increased body mass index or obesity, visceral obesity, metabolic syndrome, insulin resistance and type 2 diabetes • Physical: decreased body hair, gynaecomastia, decreased muscle mass and strength, hot flushes or sweats, sleep disturbances, fatigue, osteoporosis, height loss and low-trauma fractures • Psychological: changes in mood (eg anger, irritability, sadness and depression), decreased well-being or poor self-rated health and decreased cognitive function (including impaired concentration, verbal memory and spatial performance)	Factors associated with an increased prevalence of hypogonadism include andrologic and endocrinologic disorders (delayed puberty, cryptorchidism and infertility varicocoele), metabolic diseases associated with insulin resistance (obesity, metabolic syndrome and type 2 diabetes), cardiovascular diseases (hypertension, coronary artery disease, cerebrovascular disease, chronic heart failure and atrial fibrillation), other chronic diseases (chronic obstructive pulmonary disease, obstructive sleep apnoea, end-stage renal disease, cirrhosis, osteoporosis, rheumatoid arthritis, HIV and cancer) and pharmacologic treatments (regular opioid use, antipsychotic medications, androgen deprivation therapy, methadone maintenance therapy, antiretroviral therapy, chemotherapy + radiation and anticonvulsivant therapy)
Canadian Medical Association, 2015[8]	• Sexual: decreased libido, erectile dysfunction, decreased frequency of morning erections and decreased performance • Somatic: increased visceral body fat/obesity, decreased lean muscle mass, decreased strength, fatigue/loss of energy, decreased physical activity/vitality, low bone mineral density, anaemia, flushes, loss of facial, axillary and pubic hair/slow beard growth, and decline in general feeling of well-being • Psychological: depression/depressed mood, mood changes, irritability, inability to concentrate and insomnia/sleep disturbances	Other conditions in which the workup in recommended include type 2 diabetes, insulin resistance, metabolic syndrome, HIV-associated weight loss, treatment with opioids, glucocorticoids or ketoconazole, chronic alcohol abuse or heroin use, liver disease, hemochromatosis, end-stage renal disease, chronic obstructive pulmonary disease, obstructive sleep apnoea, infertility, frailty, hyperprolactinaemia, sellar region mass, disease, radiation or trauma and testicular cancer treatment
Endocrine Society, 2018[9]	• Specific symptoms and signs: incomplete or delayed sexual development, loss of body (axillary and pubic) hair and very small testes (<6 mL) • Suggestive symptoms and signs: reduced sexual desire (libido) and activity, decreased spontaneous erections, erectile dysfunction, breast discomfort, gynaecomastia, eunuchoidal body proportions, inability to father children, low sperm count, height loss, low-trauma fracture, low bone mineral density, hot flushes and sweats • Non-specific symptoms and signs: decreased energy, motivation, initiative, and self-confidence, feeling sad or blue, depressed mood, persistent low-grade, depressive disorder, poor concentration and memory, sleep disturbance, increased sleepiness, mild unexplained anaemia (normochromic, normocytic), reduced muscle bulk and strength, increased body fat and body mass index	-

(Continues)

TABLE 1 (Continued)

Society, year	Symptoms and signs	Other data
Endocrine Society of Australia, 2016[10,11]	• Non-specific symptoms: lethargy, fatigue, decreased energy and/or endurance, low mood, irritability, poor concentration, impaired short-term memory, sleepiness, deteriorating work performance and hot flushes • Organ-specific symptoms on: bone (osteopenia, osteoporosis, fracture/loss of height), muscle (reduced muscle mass and strength), adipose tissue (increased fat mass) and breast tissue (gynaecomastia) • Sexual and reproductive symptoms: decreased libido and erectile dysfunction • Signs, including gynaecomastia	-
European Academy of Andrology, 2020[12]	• Specific symptoms: reduced libido, decreased spontaneous erections and erectile dysfunction • Less specific symptoms: decreased energy, decreased physical strength/function/activity, decreased motivation, low mood, decreased concentration and hot flushes • Less specific signs: loss of body/facial hair, decreased testicular volume, increased body fat/reduced muscle mass, osteoporosis/low bone density and central obesity	-
European Association of Urology, 2020[13]	• More specific sexual symptoms: reduced libido, erectile dysfunction and decreased spontaneous/morning erections • More specific physical symptoms: decreased vigorous activity, difficulty walking > 1 km and decreased bending • More specific psychological symptoms: low mood/mood deflection, decreased motivation and, fatigue • Less specific sexual symptoms: reduced frequency of sexual intercourse, reduced frequency of masturbation and delayed ejaculation • Less specific physical symptoms: hot flushes, decreased energy and decreased physical strength/function/activity • Less specific psychological symptoms: concentration or mnemonic difficulties, and sleep disturbances	-
International Consultation for Sexual Medicine, 2019[14]	• Sexual symptoms: reduced or absent libido, erectile dysfunction, difficulty achieving orgasm, reduced intensity of orgasm and reduced sexual sensation in the genital region • Non-sexual symptoms: fatigue, lack of energy, decreased vitality, depressed mood, irritability, clouded cognition ('brain fog') and decreased motivation • Signs: anaemia and decreased bone mass	-
International Society for the Study of Aging Male, 2015[15]	• Sexual symptoms: erectile dysfunction, diminished frequency of morning erections, decrease in sexual thoughts (low libido), difficulty in achieving orgasm and reduced intensity of orgasm • Non-sexual symptoms: fatigue, impotence, impaired concentration, depression and decreased sense of vitality and/or well-being • Signs: anaemia, osteopenia and osteoporosis, abdominal obesity and the metabolic syndrome	Other conditions in which workup is recommended include cognitive impairment, insulin resistance, arterial hypertension, type 2 diabetes, decreased muscle mass and strength, use of glucocorticoids, opioids and antipsychotics

Note: Symptoms and signs listed in each document are reported. General references to the physical examination are not listed.

and were represented by indirect assays. Depending on the serum concentrations of testosterone, an organic extraction of different blood volumes by means of a column (eg Sephadex) or paper chromatography should have been performed for the samples to be analysed with a radioimmunoassay (RIA).[28] Accordingly, these methods were expensive, cumbersome and time-consuming and their results strongly influenced by operator training. More recently, ready-made commercial kits have become available and were progressively introduced in central and local laboratories. These were based on direct methods and generally consisted of an automated immunoassay platform. However, these advantages were not always followed by adequate performance, and concerns about their reliability were raised.[27] To improve the accuracy of testosterone measurements, indirect assays based on pre-analytic procedures (organic extraction and gas or liquid chromatography) followed by mass spectrometry (MS) were developed and adopted as the gold standard.[29] However, it is common knowledge that an adequate number of analyses are needed for these methods to be sustainable. Then, new platforms

of direct methods (manual RIA and automated immunoassays) were developed and validated to increase accessibility.[30,31]

According to BSSM, EAA, EAU and ESA, TT should be analysed by using validated direct immunoassays methods if gold standard methods are not available.[7,10,12,13] CMA and the Endocrine Society recommended the use of assays traceable to internationally recognized standardized reference material, certified by the Centers for Disease Control and Prevention or verified by an accuracy-based external quality control programme.[8,9] Concerning FT, equilibrium dialysis represents the gold standard, yet it is technically difficult, expensive and seldom available to physicians.[9,12] Immunoassays do not provide reproducible results and are not recommended.[7] A method based on the calculation of FT from serum TT, SHBG and albumin applying the mass action equation has been proposed and validated [32-36] The calculation of FT is supported by and/or its reliability reported in several documents.[7,8,12-15]

3.4 | What cut-off level of testosterone should be used for the biochemical diagnosis of late-onset hypogonadism?

Hypogonadism is a continuous variable, with mild and severe forms, and dichotomously specifying a testosterone level threshold to define it may be an oversimplification. Therefore, one should keep in mind that the clinical implications of changes in TT levels around the cut-off may be limited (eg should a patient be differently classified if TT is 299 or 301 ng/dL?). However, this holds true only if the same cut-off is consistently used by all physicians. Also, the selection of a specific cut-off has relevant implications, for both the single patients and the healthcare system.

Testosterone is characterized by a significant variability, encompassing diurnal and seasonal changes and intra-individual variations. Its levels are influenced by the subject's age, genetic background, ethnicity, lifestyle factors and comorbidities.[37-45] Therefore, at least two measurements of TT levels in a fasting state between either 7.00 or 8.00 AM and 10.00 or 11.00 AM, preferably four weeks apart (not during acute illness) is widely considered to be the accepted diagnostic approach for the diagnosis of hypogonadism by the vast majority of available guidelines.[1,2,7,9-13] About 40% of TT is bound to SHBG and several conditions may also influence the levels of this protein. Therefore, in patients presenting with conditions associated with decreased concentrations of serum SHBG (eg obesity, diabetes, use of glucocorticoids, nephrotic syndrome, hypothyroidism and acromegaly), or increased concentrations of serum SHBG (eg ageing, HIV disease, cirrhosis and hepatitis, and hyperthyroidism) as well as in those with borderline TT levels (eg 6.9-13.9 nmol/L [200-400 ng/dL] for the Endocrine Society versus 8-12 nmol/L [231-346 ng/dL] for BSSM, EAA), TT may not adequately reflect the androgen status and FT should be assessed.[7,9,12,14,36,46] Notably, in a significant proportion of patients with LOH, FT analysis may be indicated according to the above mentioned conditions. Limited evidence is available in elderly men on the association between TT or FT when considered independently and with clinical variables, including muscle strength, bone mineral density (BMD), body mass index (BMI) and fat mass either in prospective studies or in randomized controlled trials.[47] Instead, only the combined measurement of TT and FT has been shown to be associated with BMI and sexual disturbances, including erectile dysfunction, decreased libido and decreased morning erection in prospective researches and, more recently, in randomized controlled trials.[5,20]

Concerning the included documents, TT and FT cut-offs are reported in Table 2. TT levels ranged from 9.2 to 12.1 nmol/L (264 to 350 ng/dL). FT levels were reported in three documents only and ranged from 225 to 347 pmol/L (65 to 100 pg/mL). Of note, while some documents reported a single TT/FT cut-off to exclude or diagnose hypogonadism,[6] others reported a larger cut-off above which hypogonadism is unlikely, a more strict one below which hypogonadism can be reliably diagnosed, and a borderline range.[7,12] Also, whether blood should be drawn in the morning and in fasting conditions was specifically questioned by ICSM.[14] As previously reported, a diurnal variation in testosterone levels (with higher levels in early morning) has been reported even in older men when the gold standard method for testosterone evaluation (eg mass spectrometry) has been used.[41,48] In addition, oral glucose load has been associated with a 15%-30% decrease in mean TT levels, irrespective of the type of glucose tolerance.[49,50] Hence, the vast majority of the current guidelines, with the only exception of ISSAM and ICSM, adequately recommend that testosterone blood testing should be performed in a fasting state (Table 3).[15] The confusion over the proposed cut-offs for biochemical diagnosis of LOH further increased after the publication of the Testosterone Trials. Indeed, <9.5 nmol/L (275 ng/mL) was chosen as the inclusion criterion by the Institute of Medicine of the National Academy of Science.[19,51] Finally, it is worth mentioning that patients with severe secondary hypogonadism with TT levels < 5.2 nmol/L (150 ng/dL) according to AUA, BSSM and the Endocrine Society or < 6 nmol/L (175 ng/dL) according to EAA and EAU should be evaluated through different procedures (eg magnetic resonance imaging and multiple pituitary hormone assessments), given that the risk of an organic form of hypogonadism due to pituitary or hypothalamic problem in this subgroup is high.[6,7,9,12,13,15] In conclusion, no agreement has yet been reached on the criteria for the biochemical diagnosis of hypogonadism. Also, whether the same cut-offs have to be used irrespective of the subjects' ages and/or comorbidities has yet to be defined.

3.5 | What benefits should be expected from the management of late-onset hypogonadism?

There is no doubt that significant clinical benefits have to be expected from the management of organic forms of hypogonadism, especially those with pre-pubertal onset, and that TRT represents the standard of care in these patients.[52] At the same time and generally speaking, if no treatment is started (of any type), conditions can only be expected to worsen. As regard to LOH, relevant

TABLE 2 Cut-off for interpretation of total testosterone and free testosterone

	Total testosterone		Free testosterone	
Society, year	**nmol/L**	**ng/dL**	**pmol/L**	**pg/mL**
American Urological Association, 2018[6]	10.4	300	-	-
British Society for Sexual Medicine, 2017[7]	12	346	225	65
Canadian Medical Association, 2015[8]	Local laboratory ranges	-	-	-
Endocrine Society, 2018[9]	9.2	264	-	-
Endocrine Society of Australia, 2016[10,11]	7.4 in young men and 6.6 men older than 70 y	216/190	-	-
European Academy of Andrology, 2020[12]	12	350	-	-
European Association of Urology, 2020[13]	12	350	225	65
International Consultation for Sexual Medicine, 2019[14]	12.1	350	225-347	65-100
International Society for the Study of Aging Male, 2015[15]	12	350	225-243	65-70

Note: According to the Endocrine Society, the harmonized reference range for TT in healthy, non-obese young men (aged 19-39 years) was 9.2-31.8 nmol/l (264-916 ng/dl) using the 2.5th and 97.5th percentile, and 10.5-29.5 nmol/L (303 to 852 ng/dL) using the 5th and 95th percentile.[9]

TABLE 3 Recommendations for testosterone testing

Society, year	Time of the day	Metabolic status
American Urological Association, 2018[6]	Early morning fashion	-
British Society for Sexual Medicine, 2017[7]	Between 7 and 11 AM	fasting testing is appropriate for a first test
Canadian Medical Association, 2015[8]	Between 7 and 11 AM	-
Endocrine Society, 2018[9]	Morning	Fasting
Endocrine Society of Australia, 2016[10,11]	Between 8 and 10 AM	Fasting results in higher serum testosterone levels
European Academy of Andrology, 2020[12]	Between 7 and 11 AM	Fasting
European Association of Urology, 2020[13]	between 7 and 11 AM	Fasting
International Consultation for Sexual Medicine, 2019[14]	Morning blood testing in men < 40 years; for men > 40 years, afternoon testing is permissible as long as a confirmatory morning blood test is subsequently obtained	There is insufficient evidence as yet to recommend fasting state
International Society for the Study of Aging Male, 2015[15]	Between 7 and 11 AM	There is insufficient evidence as yet to recommend fasting state

data on the efficacy and safety of TRT have recently been gathered. The Testosterone Trials were a coordinated set of seven placebo-controlled double-blind trials to determine whether testosterone treatment of elderly men with low serum testosterone concentrations and also symptoms and objective evidence of impaired mobility and/or diminished libido and/or reduced vitality would have been efficacious in improving mobility (Physical Function Trial), sexual function (Sexual Function Trial), fatigue

(Vitality Trial), cognitive function (Cognitive Function Trial), haemoglobin (Anemia Trial), bone density (Bone Trial) and coronary artery plaque volume (Cardiovascular Trial).[51] TRT was associated with: 1) increased sexual activity, sexual desire and erectile function; 2) slightly improved mood and decreased depressive symptoms; 3) increased haemoglobin in men who had anaemia of either known or unknown cause; and 4) increased volumetric bone mineral density and the estimated strength of the spine and hip. Conversely, it increased coronary artery non-calcified plaque volume as assessed using computed tomographic angiography. No changes in energy or cognitive function were found. Discordant results were found concerning the distance walked, with no change in men whose walk speed was slow despite an increase in all participants [19]

These results should also be interpreted in light of previous findings on the topic.[5,53-63] Concerning sexual function, scanty improvements of ejaculatory dysfunction were found in other studies.[61] Concerning bone health, despite improvements in BMD, limited evidence supports a direct effect of TRT on fractures risk. Therefore, in patients with hypogonadism and at high risk of fracture, a drug approved for the treatment of osteoporosis should be considered.[62] Concerning cardiovascular risk, TRT has been associated with improvements in other cardiovascular risk factors (eg HbA1c and lipids) and no increased risk of events.[63] Finally, concerning mobility, sarcopenia is a common finding in ageing men and it is associated with an increased likelihood of adverse outcomes.[55] Testosterone is known to influence body composition, as confirmed by meta-analyses of both randomized controlled trials and observational studies reporting a significant reduction in fat and with an increase in lean mass.[56-58] Therefore, the effect of TRT in ameliorating physical performance could be expected, although results from previous studies were conflicting.[59,60]

Recommendations reported in the included documents were generally in line with these findings. Particularly, while ESA stressed that clinical features are highly variable between men, ISSAM highlighted that the effects of TRT are time-dependent.[10,15] Changes in libido, quality of life or mood may be experienced early, while up to 2-3 years are generally needed to realize the full benefit of TRT on BMD.[15] AUA reported a specific recommendation on cardiovascular risk, stating that clinicians should inform patients that low testosterone is a risk factor for cardiovascular disease.[6] Different documents agreed that TRT should be proposed to patients with hypogonadism who meet specific criteria. They also agreed that it should not be used for weight reduction in patients with obesity or to improve glycometabolic control in men with type 2 diabetes and/or metabolic syndrome.[9,12] On the other hand, ICSM only stated that there may be a role for TRT in the management of metabolic conditions, including obesity.[14] Concerning LOH, EAA commented on the limited quality of the evidence available on the effect of TRT in patients with LOH, with meta-analyses marred by significant heterogeneity, low study quality, small participant numbers and short duration in the included studies.[12] Accordingly, routinely prescribing TRT to men > 65 years as an anti-ageing regimen, to frail men to improve exercise capacity/physical function or to ageing men to improve cognitive function was recommended against.[12] Conversely, in patients with symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anaemia) and consistently and unequivocally low morning testosterone concentrations, TRT should be considered on an individualized basis after explicit discussion of the potential risks and benefits.[9,12]

In conclusion, while evidence supports the use of TRT in men with hypogonadism to improve sexual disturbances, its effect on other symptoms and signs have been inconclusive or disappointing. Patients should be informed about the results to be expected and any decision shared. Also, further long-term studies focusing on LOH in non-sexual domains are needed.

3.6 | Does counselling on testosterone replacement therapy in a patient with LOH differ from other forms of hypogonadism?

The evidence-based use of TRT should always be performed in light of specific indications and contraindications.[64] First, it should not be used in patients who have not been diagnosed with hypogonadism. Second, it can be proposed only if the expected benefits outweigh the risks. Specific contraindications include the following: (a) breast cancer; (b) metastatic prostate cancer; (c) unevaluated prostate nodule or induration; (d) unevaluated prostate-specific antigen (PSA)> 4 ng/mL (>3 ng/mL in individuals at high risk for prostate cancer); (e) severe lower urinary tract symptoms (LUTS) associated with benign prostatic hypertrophy; (f) recent myocardial infarction or stroke; (g) uncontrolled or poorly controlled congestive heart failure; (h) untreated severe obstructive sleep apnoea; (i) haematocrit above upper limit of normal (eg > 48% at baseline [>50% for men living at high altitude] or 54% during TRT); (j) thrombophilia; and (k) desire for fertility in the near term.[6-15] Concerning LOH, the absolute prevalence of hormone-sensitive malignancies is low, and the implications of suppressed spermatogenesis in an ageing male are limited. However, a higher emphasis must be placed on possible effects on prostatic cancer or hyperplasia, cardiovascular safety and sleep disorders.

It is generally accepted that TRT is not harmful to prostate health. It should be noted that subjects with a history of prostate cancer, a high risk of prostate cancer or severe symptoms of benign prostatic hyperplasia were excluded in some studies.[65] However, several observational, randomized controlled trials and meta-analyses found TRT to be associated with increased PSA levels or prostate volume in the short term, but no higher prostate cancer risk or worsening of LUTS in the long term (more than 1 year).[65-67] Concerning cardiovascular events, conflicting evidence has been gathered so far. Two cohort studies, one randomized controlled trial and one meta-analysis of randomized controlled trials, found TRT to be associated with an increased risk of adverse outcomes.[68-71] Several warnings followed the publication of these studies.[5,72,73] However, those studies suffered from several limitations. Furthermore, no other meta-analyses found an increased cardiovascular risk related to TRT, when either aggregate or disaggregate events were considered.[5] Differences in included patients, doses or formulations, with an increased risk

found only with TRT prescribed at a higher dosage than those recommended by the available guidelines or when frail men were considered, may explain the heterogeneity of these findings.[74] To date, limited and discordant evidence supports the association between venous thromboembolism and TRT, as well. It is possible that testosterone supplementation may increase this risk solely in those patients with an undiagnosed thrombophilia-hypofibrinolysis status, highlighting the relevance of an accurate medical history before starting TRT.[5] Concerning sleep disorders, time-dependent alterations in ventilatory recruitment threshold and sleep breathing were found in subjects with hypogonadism and obstructive sleep apnoea during TRT.[75,76] Also, both TRT (especially when performed with short-term parenteral formulations) and obstructive sleep apnoea can be associated with erythrocytosis. It should be taken into account that testosterone deficiency can be a specific risk factor for some of the above mentioned conditions.[77,78] Therefore, assessing for these conditions is necessary before TRT can be safely started.

Shared decision-making is key to increasing patient compliance and the chances of achieving benefits for any workup. Concerning TRT, a relevant issue is the testosterone formulations themselves. Different options are available including oral, short- and long-acting injectable, buccal tablets, nasal gel, transdermal patches and gels.[79] Differences among these formulations were reported in several included documents.[9,11,13,14] Injectable long-acting (eg testosterone undecanoate) and transdermal formulations are the most commonly used, convenient and cost-effective treatment modalities according to ESA and EAA.[11,12] Particularly, the injectable long-acting formulations represent the ideal replacement therapy, being associated with serum TT concentrations in the normal range in most treated men and requiring infrequent administration.[79] Their main disadvantage is their long half-life, since the long duration of action prevents drug withdrawal in the event of adverse side-effects.[7] Therefore, according to EAA and EAU, transdermal testosterone should be considered as the preferred preparation in the initiation of TRT in patients with LOH. If the patient shows significant clinical benefits, switching to longer-acting testosterone preparations of TRT could then be discussed.[12,13]

While general agreement on the above issues is reported in the included documents, the same does not hold true for the serum TT levels to be targeted in patients diagnosed with hypogonadism on TRT (Table 4). The majority recommended the mid-normal range,[6,8,9,12-14] ESA the lower part of the reference range while BSSM the mid to upper range for healthy young men.[7,11] Finally, ISSAM underlined the lack of sufficient data to define optimal serum levels of TT during TRT.[15] Of note, these recommendations were generally given for the monitoring of any patient with hypogonadism, irrespective of his age; the only exceptions were represented by EAA, EAU and ISSAM.[12,13,15]

The clinical and laboratory follow-up should be generally performed at 3, 6, and 12 months and then annually in any patient on TRT, including those with LOH.[7,9,13-15] Both the efficacy and safety of TRT should be assessed. CMA, the Endocrine Society, EAA, EAU and ISSAM suggest performing digital rectal examination at each assessment.[8,9,12,15] Concerning the laboratory evaluation, TT, PSA and haematocrit should always be evaluated.[6-15] In cases of rising PSA levels > 1.4 ng/mL within 1 year from starting TRT or if PSA

TABLE 4 Total testosterone levels to be targeted during testosterone replacement therapy

Society, year	Target
American Urological Association, 2018[6]	In the middle tertile of the normal reference range (15.6-20.8 nmol/L; 450-600 ng/dL)
British Society for Sexual Medicine, 2017[7]	In the mid to upper range for healthy young men (15-30 nmol/L; 433-865 ng/dL)
Canadian Medical Association, 2015[8]	In the mid-normal range for healthy young men (14-17.5 nmol/L; 404-505 ng/dL)
Endocrine Society, 2018[9]	In the mid-normal range for healthy young men (9.2-31.8 nmol/L; 264-916 ng/dL)
Endocrine Society of Australia, 2016[10,11]	In the lower part of the reference interval for eugonadal men (not reported)
European Academy of Andrology, 2020[12]	In the mid-normal range for young men (9.6-30 nmol/L; 280-873 ng/dL)
European Association of Urology, 2020[13]	The average normal range for young men (9.6-30 nmol/L; 280-873 ng/dL)
International Consultation for Sexual Medicine, 2019[14]	Not reported
International Society for the Study of Aging Male, 2015[15]	In the normal range (not reported)

level is > 4 ng/mL at any follow-up, the Endocrine Society and EAA recommend urological consultation.[9,12] On the other hand, ESA recommended against routine PSA monitoring during TRT since it could lead to over diagnosis and harm from interventions for clinically insignificant organ-confined prostate cancers.[11] Lipids (with or without glycaemic profile) should be evaluated too according to EAU.[13] Finally, in patients with borderline TT levels, some documents suggest administrating a trial of TRT, ranging from 3 months for CMA to 6 months for BSSM.[7,8] As stated earlier, the effects of TRT are time-dependent and patients are likely to get only one trial in their lifetime. The duration of this trial may possibly be closer to the latter cut-off and/or adapted according to the clinical presentation of hypogonadism and the pharmacokinetic properties of chosen TRT formulation. Of note, the recommendation of a 6 months trial of TRT was reported in ICSM also for those men with symptoms suggestive of TD but whose TT or FT concentrations appear normal. This recommendation was not reported in other guidelines and seems to be contradictory. Indeed, the ICSM defined testosterone deficiency as a clinical syndrome associated with reduced serum testosterone concentrations and acknowledged the relationship between symptoms and testosterone levels.

3.7 | Should testosterone replacement therapy be considered as the only option for patients with late-onset hypogonadism?

In several endocrine disorders, hormone replacement therapy represents the standard of therapy, allowing hormones not being produced by the gland to be replaced. Concerning hypogonadism, its role in the organic forms deserves no discussion. However, whether the same also holds true for functional forms is still being debated. Testosterone levels can be influenced by a number of conditions, physiological (eg diet), pharmacological (eg steroids) and pathological (eg severe infections), as stated earlier. On one hand, it follows that improvements in modifiable factors should always be pursued. On the other hand, the assessment of their effects before considering TRT may be reasonable. Among the functional causes of hypogonadism, the following are included: (a) obesity; (b) some sleep disorders; (c) comorbid illness associated with ageing; (d) drugs (eg opioids, anabolic steroid use and glucocorticoids); (e) alcohol and marijuana abuse; (f) systemic illness; (g) nutritional deficiency/excessive exercise; (h) organ failure (liver, heart and lung); and (i) hyperprolactinaemia.[9] Classifying a form of hypogonadism as functional implies the association between the treatment of the underlying cause and the reversal of hypogonadism. Discordant findings have been found to date on this topic. Particularly, a body of evidence supports the significant improvements that can be achieved with TT following the management of obesity, either by lifestyle measures, pharmacological therapy or bariatric surgery, while no change in TT has been found in hypogonadal subjects with obstructive sleep apnoea following continuous positive airway pressure (CPAP).[17,80-82] The mechanisms and effects of physical exercise in obesity have been recently evaluated by using an animal model of metabolically induced hypogonadism.[83] It should be noted that, despite positive results, high failure rates have been reported for interventions targeting obesity, especially when treatment is discontinued; weight is regained, and a worsening of hypogonadism has to be expected in these patients.[84,85] Most of the included documents strongly encourage improving lifestyle measures (eg diet and physical activity for men with obesity) and the management of comorbidities that underpin the adult form of male hypogonadism. The potential to increase testosterone levels by these measures is acknowledged in AUA, BSSM, the Endocrine Society, EAA, EAU and ESA.[6,7,9,11-13] Also, the effects of these measures on conditions other than hypogonadism (eg type 2 diabetes) are reported. However, while the BSSM endorsed lifestyle modifications only when performed in conjunction with TRT, EAA and ESA recommended treating comorbidities first and starting TRT only in patients with persistently low testosterone levels.[7,11,12] Finally, EAU confirmed weight loss to be the first approach for all overweight and obese men with hypogonadism, while recognizing the increase in TT levels observed after lifestyle measures to be modest (with the exception of bariatric surgery) and the benefit possibly lower compared to TRT.[13]

Among the comorbidities associated with hypogonadism, obesity is reported, as stated, and this can be associated with metabolic syndrome or type 2 diabetes. Concerning the latter, there has been a long debate on the relative contribution of excess body weight and glycaemic control to the reversibility of functional hypogonadism to eugonadism. Both inhibit the HPT axis prevalently at hypothalamic–pituitary level, through a different mechanism and to a different degree.[86] Indeed, severe obesity (BMI > 40 kg/m^2) causes overt hypogonadotropic hypogonadism by impairing the regular pulsatility of GnRH-induced LH secretion.[87,88] Hyperglycaemia, independently of obesity, can reduce LH pulses in eugonadal men with type 2 diabetes, as well as both the secreted mass and pulses of LH in poorly controlled young men with type 1 diabetes.[50,89,90] Recently, preliminary results on the disorder to be preferentially targeted have been published. In obese patients with uncontrolled type 2 diabetes and hypogonadism were prescribed with lifestyle measures and metformin with or without glucagon-like peptide 1 receptor agonists or sodium-glucose cotransporter 2 inhibitors, losing more than 10% of the initial body weight was associated with a significant improvement in TT and FT and chances of achieving TT of at least 10.4 nmol/L (300 ng/dL) irrespective of changes in glycaemic control.[91] Therefore, current recommendations placing a high value on the management of obesity should be considered as reliable and up-to-date, even when the use of newly introduced pharmacologic therapies for the management of type 2 diabetes is considered.

Finally, among strategies for the management of hypogonadism, selective oestrogen receptor modulators (eg clomiphene citrate) and aromatase inhibitors (eg anastrozole) should be mentioned. These drugs were evaluated off-label in the management of hypogonadism, and interesting results were found. They have been shown to restore testosterone levels to eugonadal levels while promoting or preserving spermatogenesis in men with

testosterone deficiency. Also, they are well tolerated, usually with short-lasting and mild symptoms.[92-94] The use of some or both of these drugs is mentioned in AUA, BSSM and the Endocrine Society.[6,7,9] On the contrary, according to EAA these drugs should not be used according to the poor available evidence (eg limited number of randomized controlled trials, inadequate outcome data, short duration of the trials as well as the small numbers of subjects enrolled).[12]

4 | CONCLUSIONS

In recent years, a number of guidelines, position statements or other recommendations have been published by national and international societies on the management of hypogonadism and LOH. The goal of these documents is to support the physician in the identification of those candidates who would benefit from the management of these disorders, weighing possible benefits against possible drawbacks. Despite common principles to be adopted for diagnosis and follow-up, several differences exist. The biggest difference is that the EAA guideline was the only document to specifically focus on LOH. LOH has in its definition the concept of occurring in older men; however, a consistent age cut-off for its diagnosis could not be found. The same holds true for the symptoms and signs to be considered as specific of hypogonadism. Concerning the biochemical criteria, different cut-offs were proposed for TT levels to be used both for diagnosis and during follow-up; also, a cut-off level for FT for diagnosis was reported only in some documents. Finally, discrepancies were found for the relative contribution of TRT and non-pharmacological therapies in the management of hypogonadism.

Among all forms of hypogonadism, LOH is characterized by specific challenges. It has a high prevalence in the general population compared to other traditional forms of hypogonadism (eg Klinefelter syndrome). The burden of LOH is expected to increase significantly in the next decades, along with the trends in life expectancy and in the prevalence of disorders associated with functional hypogonadism (eg obesity). Also, a specific approach is warranted when counselling on hypogonadism in an ageing male, given that these subjects are often affected by other comorbidities. The number of documents that were published in the last 10 years confirms the high interest of the scientific community on this topic and the relevant clinical implications of appropriate management. In light of the above mentioned epidemiological and clinical issues, future guidelines should specifically focus on LOH and provide the physician with consistent recommendations for the identification of affected patients and their treatment.

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DISCLOSURES

All the authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

VAG conceived the review. VAG and VT performed database search. VAG and MC drafted the manuscript. All authors read, provided feedback and approved the final manuscript.

ETHICAL APPROVAL

The present review was conducted in accordance with the principles of the Declaration of Helsinki. Discussed data extracted from published papers.

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REFERENCES

1. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev*. 2005;26(6):833-876.
2. Kaufman JM, Lapauw B, Mahmoud A, T'Sjoen G, Huhtaniemi IT. Aging and the Male Reproductive System. *Endocr Rev*. 2019;40(4):906-972.
3. Tajar A, Huhtaniemi IT, O'Neill TW, et al. Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). *J Clin Endocrinol Metab*. 2012;97(5):1508-1516.
4. Barbonetti A, D'Andrea S, Francavilla S. Testosterone replacement therapy. *Andrology*. 2020 [Epub ahead of print]; https://doi.org/10.1111/andr.12774
5. Corona G, Torres LO, Maggi M. Testosterone therapy: what we have learned from trials. *J Sex Med*. 2020;17(3):447-460.
6. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. *J Urol*. 2018;200(2):423-432.
7. Hackett G, Kirby M, Edwards D, et al. British society for sexual medicine guidelines on adult testosterone deficiency, with statements for UK practice. *J Sex Med*. 2017;14(12):1504-1523.
8. Morales A, Bebb RA, Manjoo P, et al. Diagnosis and management of testosterone deficiency syndrome in men: clinical practice guideline. *CMAJ*. 2015;187(18):1369-1377.
9. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744.
10. Yeap BB, Grossmann M, McLachlan RI, et al. Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. *Med J Aust*. 2016;205(4):173-178.
11. Yeap BB, Grossmann M, McLachlan RI, et al. Endocrine Society of Australia position statement on male hypogonadism (part 2): treatment and therapeutic considerations. *Med J Aust*. 2016;205(5):228-231.
12. Corona G, Goulis DG, Huhtaniemi I, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males. *Andrology*. 2020 [Epub ahead of print];https://doi.org/10.1111/andr.12770
13. Salonia A, Bettocchi C, Carvalho J, et al.EAU guidelines on Sexual and Reproductive Health. Available at https://uroweb.org/guideline/sexual-and-reproductive-health/

14. Morgentaler A, Traish A, Hackett G, Jones TH, Ramasamy R. Diagnosis and treatment of testosterone deficiency: updated recommendations from the Lisbon 2018 international consultation for sexual medicine. *Sex Med Rev*. 2019;7(4):636-649.
15. Lunenfeld B, Mskhalaya G, Zitzmann M, et al. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. *Aging Male*. 2015;18(1):5-15.
16. Tajar A, Forti G, O'Neill TW, et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *J Clin Endocrinol Metab*. 2010;95(4):1810-1818.
17. Grossmann M, Matsumoto AM. A perspective on middle-aged and older men with functional hypogonadism: focus on holistic management. *J Clin Endocrinol Metab*. 2017;102(3):1067-1075.
18. World Health Organization. World report on Ageing and Health, 2015. https://apps.who.int/iris/bitstream/handle/10665/186463/9789240694811_eng.pdf;jsessionid=82CA7E613E123FC22EDD5BF4480DE1DF?sequence=1. Accessed March 1, 2020.
19. Snyder PJ, Bhasin S, Cunningham GR, et al. Lessons from the testosterone trials. *Endocr Rev*. 2018;39(3):369-386.
20. Wu FCW, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med*. 2010;363(2):123-135.
21. Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab*. 2007;92(11):4241-4247.
22. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *J Clin Endocrinol Metab*. 2006;91(11):4335-4343.
23. Heinemann LAJ, Zimmermann T, Vermeulen A, Thiel C, Hummel W. A new 'aging males' symptoms' rating scale. *Aging Male*. 1999;2:105-114.
24. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism*. 2000;49(9):1239-1242.
25. Smith KW, Feldman HA, McKinlay JB. Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in ageing men. *Clin Endocrinol (Oxf)*. 2000;53(6):703-711.
26. Corona G, Mannucci E, Petrone L, et al. ANDROTEST: a structured interview for the screening of hypogonadism in patients with sexual dysfunction. *J Sex Med*. 2006;3(4):706-715.
27. Trost LW, Mulhall JP. Challenges in testosterone measurement, data interpretation, and methodological appraisal of interventional trials. *J Sex Med*. 2016;13(7):1029-1046.
28. Giagulli VA, Vermeulen A. Leydig cell function in infertile men with idiopathic oligospermic infertility. *J Clin Endocrinol Metab*. 1988;66(1):62-67.
29. Travison TG, Vesper HW, Orwoll E, et al. Harmonized reference ranges for circulating testosterone levels in men of four cohort studies in the United States and Europe. *J Clin Endocrinol Metab*. 2017;102(4):1161-1173.
30. Vesper HW, Bhasin S, Wang C, et al. Interlaboratory comparison study of serum total testosterone [corrected] measurements performed by mass spectrometry methods [published correction appears in Steroids. *Steroids*. 2009;74(6):498-503.
31. Huhtaniemi IT, Tajar A, Lee DM, et al. Comparison of serum testosterone and estradiol measurements in 3174 European men using platform immunoassay and mass spectrometry; relevance for the diagnostics in aging men. *Eur J Endocrinol*. 2012;166(6):983-991.
32. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab*. 1999;84(10):3666-3672.
33. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab*. 2007;92(2):405-413.
34. Morris PD, Malkin CJ, Channer KS, Jones TH. A mathematical comparison of techniques to predict biologically available testosterone in a cohort of 1072 men. *Eur J Endocrinol*. 2004;151(2):241-249.
35. Antonio L, Wu FCW, O'Neill TW, et al. Low free testosterone is associated with hypogonadal signs and symptoms in men with normal total testosterone. *J Clin Endocrinol Metab*. 2016;101(7):2647-2657.
36. Fiers T, Wu F, Moghetti P, Vanderschueren D, Lapauw B, Kaufman JM. Reassessing free-testosterone calculation by liquid chromatography-tandem mass spectrometry direct equilibrium dialysis. *J Clin Endocrinol Metab*. 2018;103(6):2167-2174.
37. Rastrelli G, Corona G, Maggi M. Both comorbidity burden and low testosterone can explain symptoms and signs of testosterone deficiency in men consulting for sexual dysfunction. *Asian J Androl*. 2020;22(3):265-273.
38. Ruhayel Y, Malm G, Haugen TB, et al. Seasonal variation in serum concentrations of reproductive hormones and urinary excretion of 6-sulfatoxymelatonin in men living north and south of the Arctic Circle: a longitudinal study. *Clin Endocrinol (Oxf)*. 2007;67(1):85-92.
39. Plymate SR, Tenover JS, Bremner WJ. Circadian variation in testosterone, sex hormone-binding globulin, and calculated non-sex hormone-binding globulin bound testosterone in healthy young and elderly men. *J Androl*. 1989;10(5):366-371.
40. Brambilla DJ, O'Donnell AB, Matsumoto AM, McKinlay JB. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. *Clin Endocrinol (Oxf)*. 2007;67(6):853-862.
41. Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. *J Clin Endocrinol Metab*. 2009;94(3):907-913.
42. Orwoll ES, Nielson CM, Labrie F, et al. Evidence for geographical and racial variation in serum sex steroid levels in older men. *J Clin Endocrinol Metab*. 2010;95(10):E151-E160.
43. Crabbe P, Bogaert V, De Bacquer D, Goemaere S, Zmierczak H, Kaufman JM. Part of the interindividual variation in serum testosterone levels in healthy men reflects differences in androgen sensitivity and feedback set point: contribution of the androgen receptor polyglutamine tract polymorphism. *J Clin Endocrinol Metab*. 2007;92(9):3604-3610.
44. Ring HZ, Lessov CN, Reed T, et al. Heritability of plasma sex hormones and hormone binding globulin in adult male twins. *J Clin Endocrinol Metab*. 2005;90(6):3653-3658.
45. Terrier JE, Isidori AM. How food intakes modify testosterone level. *J Sex Med*. 2016;13(9):1292-1296.
46. Wang C, Nieschlag E, Swerdloff RS, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male*. 2009;12(1):5-12.
47. van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab*. 2000;85(9):3276-3282.
48. Guay A, Miller MG, McWhirter CL. Does early morning versus late morning draw time influence apparent testosterone concentration in men aged > or =45 years? Data from the Hypogonadism In Males study. *Int J Impot Res*. 2008;20(2):162-167.
49. Gagliano-Jucá T, Li Z, Pencina KM, et al. Oral glucose load and mixed meal feeding lowers testosterone levels in healthy eugonadal men. *Endocrine*. 2019;63(1):149-156.
50. Caronia LM, Dwyer AA, Hayden D, Amati F, Pitteloud N, Hayes FJ. Abrupt decrease in serum testosterone levels after an oral glucose load in men: implications for screening for hypogonadism. *Clin Endocrinol (Oxf)*. 2013;78(2):291-296.

51. Snyder PJ, Ellenberg SS, Cunningham GR, et al. The Testosterone Trials: Seven coordinated trials of testosterone treatment in elderly men. *Clin Trials*. 2014;11(3):362-375.
52. Giagulli VA, Triggiani V, Carbone MD, et al. The role of long-acting parenteral testosterone undecanoate compound in the induction of secondary sexual characteristics in males with hypogonadotropic hypogonadism. *J Sex Med*. 2011;8(12):3471-3478.
53. Giagulli VA, Guastamacchia E, Licchelli B, Triggiani V. Serum Testosterone and Cognitive Function in Ageing Male: Updating the Evidence. *Recent Pat Endocr Metab Immune Drug Discov*. 2016;10(1):22-30.
54. Walther A, Breidenstein J, Miller R. Association of testosterone treatment with alleviation of depressive symptoms in men: a systematic review and meta-analysis. *JAMA Psychiatry*. 2019;76(1):31-40.
55. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(4):601.
56. Giagulli VA, Castellana M, Pelusi C, Triggiani V. Androgens, body composition, and their metabolism based on sex. *Front Horm Res*. 2019;53:18-32.
57. Corona G, Giagulli VA, Maseroli E, et al. THERAPY OF ENDOCRINE DISEASE: Testosterone supplementation and body composition: results from a meta-analysis study. *Eur J Endocrinol*. 2016;174(3):R99-R116.
58. Corona G, Giagulli VA, Maseroli E, et al. Testosterone supplementation and body composition: results from a meta-analysis of observational studies. *J Endocrinol Invest*. 2016;39(9):967-981.
59. O'Donnell AB, Travison TG, Harris SS, Tenover JL, McKinlay JB. Testosterone, dehydroepiandrosterone, and physical performance in older men: results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab*. 2006;91(2):425-431.
60. Maggio M, Lauretani F, Ceda GP. Sex hormones and sarcopenia in older persons. *Curr Opin Clin Nutr Metab Care*. 2013;16(1):3-13.
61. Paduch DA, Polzer PK, Ni X, Basaria S. Testosterone replacement in androgen-deficient men with ejaculatory dysfunction: a randomized controlled trial. *J Clin Endocrinol Metab*. 2015;100(8):2956-2962.
62. Rochira V, Antonio L, Vanderschueren D. EAA clinical guideline on management of bone health in the andrological outpatient clinic. *Andrology*. 2018;6(2):272-285.
63. Zhang J, Yang B, Xiao W, Li X, Li H. Effects of testosterone supplement treatment in hypogonadal adult males with T2DM: a meta-analysis and systematic review. *World J Urol*. 2018;36(8):1315-1326.
64. Layton JB, Li D, Meier CR, et al. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. *J Clin Endocrinol Metab*. 2014;99(3):835-842.
65. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. *N Engl J Med*. 2016;374(7):611-624.
66. Cunningham GR, Ellenberg SS, Bhasin S, et al. Prostate-specific antigen levels during testosterone treatment of hypogonadal older men: data from a controlled trial. *J Clin Endocrinol Metab*. 2019;104(12):6238-6246.
67. Elliott J, Kelly SE, Millar AC, et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis. *BMJ Open*. 2017;7(11):e015284.
68. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013;310(17):1829-1836.
69. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363(2):109-122.
70. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*. 2014;9(1):e85805.
71. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*. 2013;11:108.
72. Food and Drug Administration. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. 3 March 2015. Available at: https://www.fda.gov/media/91048/download.
73. Government of Canada. Summary Safety Review – Testosterone Replacement Products – Health Canada. 15 July 2014. Available at: https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?linkID=SSR00058.
74. Corona G, Rastrelli G, Di Pasquale G, Sforza A, Mannucci E, Maggi M. Testosterone and cardiovascular risk: meta-analysis of interventional studies. *J Sex Med*. 2018;15(6):820-838.
75. Killick R, Wang D, Hoyos CM, Yee BJ, Grunstein RR, Liu PY. The effects of testosterone on ventilatory responses in men with obstructive sleep apnea: a randomised, placebo-controlled trial. *J Sleep Res*. 2013;22(3):331-336.
76. Hoyos CM, Killick R, Yee BJ, Grunstein RR, Liu PY. Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea: a randomized placebo-controlled trial. *Clin Endocrinol (Oxf)*. 2012;77(4):599-607.
77. Giagulli VA, Guastamacchia E, De Pergola G, Iacoviello M, Triggiani V. Testosterone deficiency in male: a risk factor for heart failure. *Endocr Metab Immune Disord Drug Targets*. 2013;13(1):92-99.
78. Corona G, Rastrelli G, Di Pasquale G, Sforza A, Mannucci E, Maggi M. Endogenous testosterone levels and cardiovascular risk: meta-analysis of observational studies. *J Sex Med*. 2018;15(9):1260-1271.
79. Giagulli VA, Triggiani V, Corona G, et al. Evidence-based medicine update on testosterone replacement therapy (TRT) in male hypogonadism: focus on new formulations. *Curr Pharm Des*. 2011;17(15):1500-1511.
80. Corona G, Rastrelli G, Morelli A, et al. Treatment of functional hypogonadism besides pharmacological substitution. *World J Men's Health*. 2020;38(3):256.
81. Cignarelli A, Castellana M, Castellana G, et al. Effects of CPAP on testosterone levels in patients with obstructive sleep apnea: a meta-analysis study. *Front Endocrinol (Lausanne)*. 2019;10:551.
82. Giagulli VA, Castellana M, Murro I, et al. The role of diet and weight loss in improving secondary hypogonadism in men with obesity with or without type 2 diabetes mellitus. *Nutrients*. 2019;11(12):2975.
83. Morelli A, Filippi S, Comeglio P, et al. Physical activity counteracts metabolic syndrome-induced hypogonadotropic hypogonadism and erectile dysfunction in the rabbit. *Am J Physiol Endocrinol Metab*. 2019;316(3):E519-E535.
84. Bray GA, Heisel WE, Afshin A, et al. The science of obesity management: an endocrine society scientific statement. *Endocr Rev*. 2018;39(2):79-132.
85. Wing RR, Rosen RC, Fava JL, et al. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD trial. *J Sex Med*. 2010;7(1 Pt 1):156-165.
86. Dhindsa S, Ghanim H, Batra M, Dandona P. Hypogonadotropic hypogonadism in men with diabesity. *Diabetes Care*. 2018;41(7):1516-1525.
87. Giagulli VA, Kaufman JM, Vermeulen A. Pathogenesis of the decreased androgen levels in obese men. *J Clin Endocrinol Metab*. 1994;79(4):997-1000.
88. Molina-Vega M, Asenjo-Plaza M, García-Ruiz MC, et al. Cross-sectional, primary care-based study of the prevalence of hypoandrogenemia in nondiabetic young men with obesity. *Obesity (Silver Spring)*. 2019;27(10):1584-1590.
89. Costanzo PR, Suárez SM, Scaglia HE, Zylbersztein C, Litwak LE, Knoblovits P. Evaluation of the hypothalamic-pituitary-gonadal axis in eugonadal men with type 2 diabetes mellitus. *Andrology*. 2014;2(1):117-124.

90. López-Alvarenga JC, Zariñán T, Olivares A, González-Barranco J, Veldhuis JD, Ulloa-Aguirre A. Poorly controlled type I diabetes mellitus in young men selectively suppresses luteinizing hormone secretory burst mass. *J Clin Endocrinol Metab*. 2002;87(12):5507-5515.
91. Giagulli VA, Castellana M, Carbone MD, et al. Weight loss more than glycemic control may improve testosterone in obese type 2 diabetes mellitus men with hypogonadism. *Andrology*. 2020;8(3):654-662.
92. Pelusi C, Giagulli VA, Baccini M, et al. Clomiphene citrate effect in obese men with low serum testosterone treated with metformin due to dysmetabolic disorders: A randomized, double-blind, placebo-controlled study. *PLoS One*. 2017;12(9):e0183369.
93. Krzastek SC, Smith RP. Non-testosterone management of male hypogonadism: an examination of the existing literature. *Transl Androl Urol*. 2020;9(Suppl 2):S160-S170.
94. Rastrelli G, Maggi M, Corona G. Pharmacological management of late-onset hypogonadism. *Expert Rev Clin Pharmacol*. 2018;11(4):439-458.

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