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Late Onset Hypogonadism [LOH]. Current Concepts and Controversies - A Review

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Review Article

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Abstract

Male hypogonadism is a clinical syndrome complex, which includes symptoms-with or without signs and biochemical evidence of testosterone deficiency. Lower serum testosterone (T) is common in ageing men, but only a small proportion of them develop the syndrome of low T with diffuse sexual physical and psychological symptoms. This syndrome is not classical primary (testicular failure) or secondary (pituitary or hypothalamic failure) hypogonadism because it may have elements of both presentations. This syndrome is also known as male menopause or climacterium, andropause and partial androgen deficiency of the ageing male (PADAM). Late onset hypogonadism (LOH) describes it best and is therefore the preferred term. A problem with the diagnosis is that often the symptoms of hypogonadism and low circulating T do not coincide in the same individual.

The European Male Ageing Study (EMAS) has suggested a strict diagnostic criterion for LOH that includes the simultaneous presence of low serum T and three sexual symptoms (erectile dysfunction, and reduced libido and morning erections). By these criteria, only 2% of 40 to 80 year old men have LOH. Evidence based information on treatment is limited. The easiest approach is lifestyle modification, weight reduction and good treatment of comorbid diseases. T replacement is also widely used as a treatment modality, but evidence-based information about its benefits and short and long term risks, is not yet available.

In this review, we will summarize the current concepts and controversies in the pathogenesis, diagnosis and treatment of LOH.

Keywords: Male Hypogonadism; Testosterone Deficiency; Lower Serum Testosterone; Erectile Dysfunction

Abbreviations: PADAM: Partial Androgen Deficiency of the Ageing Male; LOH: Late Onset Hypogonadism; EMAS: European Male Ageing Study; T: Testosterone; UN: United Nations;; AOH: Adult-Onset Hypogonadism; HP: Hypothalamic-Pituitary; SHBG: Sex Hormone Binding Globulin; HIV: Human Immunodeficiency Virus; TTh: Testosterone Therapy; MACE: Major Adverse Cardiac Events; LUTS: Lower Urinary Tract Symptoms; BPH: Benign Prostatic Hyperplasia.

Introduction

United Nations (UN) estimates that the population on Earth will have increased fourfold from two and a half billion in 1950 to almost ten billion by 2050 [1]. The average life span has also increased due to improved hygiene, reduction of new-born mortality, and more effective prevention and therapy of diseases in adult age globally. Consequent to this phenomenon is a systematically growing population of older people and the emergence of age-related health problems that have not been seen before. These changes have increased the focus on the health and quality of life of older people.

Aging is a slow physiological process which is inevitable. During the process of aging, the humans undergo a series of morphological and functional modifications within all organs, tissues, and cells. This is characterised by a general tendency towards reduced physiological efficiency and atrophy of various organs and systems [2,3]. Involutional processes occur in both peripheral glandular secretions as well as in the hypothalamus and pituitary gland which reflects in the fundamental change in the secretion of most hormones. There is a slow gradual decline in testicular testosterone production as the man ages which is a well-documented fact [4,5]. Factors contributing to this are obesity and deteriorating health upon aging [6]. When the decrease of Testosterone is associated with symptoms of androgen deficiency the condition is known as late-onset hypogonadism (LOH). The trend of decline of Testosterone is 0.5–2% per year, and it remains within the reference range of young men in most elderly men. In some men the decrease is more profound which may be biochemical (<200ng/dl) or even clinical.

Definition

The Sexual Medicine Society of North America defines adult-onset hypogonadism (AOH) as a clinical and biochemical syndrome characterized by a deficiency of testosterone (T) with symptoms and signs that can be caused by testicular and/or hypothalamic-pituitary (HP) dysfunction. Manifestations of Low testosterone levels include symptoms of sexual dysfunction, muscle weakness, obesity, osteoporosis, hot flushes, insomnia, fatigue, poor concentration and depression. The combination of low T and an array of the above symptoms have been termed with many names, including male menopause or climacterium, partial androgen deficiency of the aging male (PADAM), andropause and late-onset hypogonadism (LOH). The current definition 'LOH is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum T levels (below the young healthy adult male reference range)'.

Incidence

It is well-documented phenomenon that testicular testosterone (T) production decreases in men with ageing, by 1%–2% per year after the age of 40 years. However, on average serum levels of T remain within the normal range of young men [5-8]. The age-dependent reference range for T has not been defined and the criteria on cut off levels for hypogonadism remain somewhat controversial. When only hormonal criteria are used (i.e. T below the lower limit of the reference range of young men (about 10 nmol−1), the prevalence of 'biochemical hypogonadism' is high, 23.3% in 40- to 79-year-old men of the European Male Ageing Study (EMAS) [9] In another study, the incidence of hypogonadal T levels increased to about 20% of men over 60, 30% over 70 and 50% over 80 years of age, and the prevalence of low free T in each age group was even higher due to the ageing-related increase of sex hormone binding globulin (SHBG) levels. This may not manifest clinically, because most men with low T remain asymptomatic [10]. Age-related hypogonadism is a clinically and biochemically defined disease of older men with serum testosterone level below the reference parameters of younger healthy men and with symptoms of testosterone deficiency, manifested by pronounced disturbances of the quality of life and harmful effects on multiple organ systems [11]. In middle-aged men, the incidence of biochemical hypogonadism varies from 2.1% to 12.8% [12]. The incidence of low testosterone and symptoms of hypogonadism in men aged 40-79 years varies from 2% to 6% [12,13]. Hypogonadism is more prevalent in older men, in obesity, in those with co-morbidities, and in men with a poor health status [14].

Pathogenesis of LOH

Ageing and Hypothalamic-pituitary-Testicular axis: Testicular function declines somewhat with advancing age [15]. Purely age-dependent change is usually small and probably of the same magnitude as that of other organs of the body [16]. The morphological changes in the testis upon ageing include degeneration of the germinal epithelium and increased proportion of connective tissue. The total number of Sertoli and Leydig cells decreases to around half of that of the young testis [17,18]. LOH is a consequence of the aging process, deterioration of hypothalamic-pituitary function, and Leydig cell function in the testes [19]. As the men age there is disorder of pulsed secretion of GnRH by dysregulation of the hypothalamic pulse generator and reduction of the frequency and amplitude of LH pulses. The amount and

activity of Leydig cells decreases mainly by progression of atherosclerosis and degenerative changes in Leydig cells. Only the free, unbound testosterone is biologically active. SHBG levels increase with age, so the proportion of bioactive free testosterone decreases. In older men, it often leads to an increase in aromatase activity, which metabolises testosterone to oestradiol. This phenomenon is compounded by the co-occurrence of obesity, diabetes mellitus, cardiovascular disease, and cancer [20].

The concentration of serum T reaches its maximum around 25–30 years of age and starts a slow steady decline thereafter at a rate of about 1% per year. A recent longitudinal study showed that serum total T decreases between 55 and 68 years of age by 1.4% per year, free T by 2.7%, while SHBG increased at the same time by 2.7% [21]. The aging-related decline of T shows great inter individual variability, with about 20% on men over 60 years having serum T in the upper normal range of young men, and about 20% being below the reference range, and even a larger proportion of men have their bioavailable T in the subnormal range [22]. About half of circulating T is bound to SHBG, and another half to albumin, and only 0.5%-3% of T remains in free, non-protein-bound form, representing the biologically active fraction [23]. The concentration of SHBG increases with ageing which results in proportionate decrease in free T.

Impact of Low Testosterone on Health

LOH and its Association with Systemic Diseases

Since LOH is more common in older men with chronic diseases it becomes difficult to separate the influence of comorbidities from the influence of aging. High BMI, central adiposity, and MetS are associated with low serum total T and to a lesser extent low free T level. Low serum total T level is a predictor of the development of central obesity. Lowering the serum T levels in men with prostate cancer by treatment with GnRH analogues resulted in increased body fat mass. Prospective studies indicated that men with higher T levels had a 42% lower risk of DM2, also men with higher SHBG levels had a 52% lower risk of DM Type II. Estradiol levels were significantly elevated in the diabetic group.

Low serum SHBG, low total T, and clinical AD were significantly associated with increased risk of developing MetS. In the EMAS, BMI was significantly associated with the risk for secondary hypogonadism [24]. The patients with a BMI of 30 kg/m2 were 3 times more likely to develop LOH [25]. The presence of 1 or more comorbidities was significantly associated with secondary hypogonadism in the EMAS.

In the Hypogonadism in Males study- Significant presence of hypogonadism in patients who also suffered from diabetes, hypertension, hyperlipidemia, asthma/chronic obstructive pulmonary disease, and/or prostate disease in comparison to men without these conditions. The presence of low T level, therefore, may be a marker of poor health and the possible presence of comorbidities.

LOH in the Immune Suppressed

Testosterone deficiency is more common in human immunodeficiency virus (HIV)-infected males than in the general population [26].

The pathophysiology of HIV-associated AOH includes [27-30].
(1) Poor clinical or nutritional status,
(2) Use of certain prescription medications used to treat HIV,
(3) Illicit drugs including opiates and methadone,
(4) Pituitary dysfunction [31],
(5) Hepatitis C and other opportunistic infections,
(6) Advancing age and increasing length of time diagnosed with HIV,
(7) Changes in body composition,
(8) increased levels of estradiol and increased levels of SHBG,
(9) Normal age-related declines,
(10) Low CD4 cell count [32-36],
(11) High HIV viral load and disease progression,
(12) Lean body mass,
(13) Metabolic syndrome, and
(14) Wasting lipodystrophy

Medications and LOH

Opioids, glucocorticoids, cimetidine, tricyclic anti-depressants, nicotine, and marijuana are some of the examples of the drugs associated with hypogonadism men who use anabolic steroids often show T levels that are the same as castrate levels after stopping these drugs. Opiate medications inhibit the HPG axis, causing a decrease in T levels [37,38]. Evidence that Statin drugs have been implicated in hypogonadism is still not definitive [39]. Chemotherapy affects the testes directly and has a toxic effect on the Leydig cells, decreasing T production [40].

LOH, Sleep Apnoea and Stress

Men with obstructive sleep apnea seem to have a higher incidence of secondary hypogonadism than age-matched controls. Obesity is the common link between the increased prevalence of sleep disorders and hypogonadism [41].

Literature suggests that sleep apnea is an independent risk factor for hypogonadism possibly due to the fact that men with sleep apnea secrete blunted levels of LH during sleep [42]. Stress often manifests physiologically as a pro inflammatory state, which may cause HPG axis disruption, which is why in conditions like acute myocardial infarction, elective surgery, and brain injury, T levels reduce. Psychosocial stress and work-related stress also decrease T levels [43-45].

Clinical Features: Common clinical symptoms of LOH are lethargy, fatigue, decreased sense of well-being, reduced physical and mental activity, diminished libido, increased sweating, depressive mood, reduced muscle and bone mass or even osteoporosis, erectile dysfunction, and mild anaemia. When clinical symptoms are present, the laboratory work-up should focus on total serum testosterone levels. Total testosterone levels <200ng/dl indicates hypogonadism. In cases of testosterone levels between 200 and 400ng/dl, measurement should be repeated and supplemented by determination of free testosterone, either by appropriate laboratory methods or the calculation of free testosterone index.

Management

Diagnosis

Diagnosis is based on the presence of three sexual symptoms combined with a total testosterone level of less than 11nmol per liter and a free testosterone level of less than 220pmol per liter. The application of these new criteria can guard against the excessive diagnosis of hypogonadism and curb the injudicious use of testosterone therapy in older men.

Testosterone Therapy (TTh)

Once LOH is accurately diagnosed, the physician must discuss all treatment options for TRT, including the option of no treatment. When considering TRT, the goals of therapy should include restoration of testosterone levels to the mid-normal range, approximation of endogenous production, avoidance or reduction of significant adverse effects, and alleviation of the associated the signs and symptoms of AOH. Overall, there is evidence suggesting improvement in physical condition, sexual libido, glucose control, lipid metabolism, mood, and cognition. TTh significantly improves erectile function and other sexual parameters as measured by IIEF in hypogonadal men [46]. These results argue that sexual dysfunction should be considered a hallmark manifestation of T deficiency, since those symptoms can be significantly improved with normalization of serum T. In addition, these results suggest that TTh alone may be considered a reasonable treatment for hypogonadal men with milder degrees of erectile dysfunction, whereas the addition of other treatments, such as phosphodiesterase type 5 inhibitors, may be more appropriate for men with more severe erectile dysfunction [47].

Oral

Oral testosterone undecanoate undergoes first-pass metabolism and is inactivated in the liver. An oral preparation was created to bypass first-pass metabolism with the methylation at the 17α. Significant hepatotoxic adverse effects have been noted long-term with this modality, and as such, its use is not recommended [48]. This formulation needs to be taken 2 to 4 times daily with a normal meal, but without adequate dietary fat content, absorption may be incomplete and testosterone levels may not equilibrate.

Buccal

The testosterone buccal system (Striant) is the only available oral testosterone therapy in the United States. Buccal systems are applied every 12 hours to the upper gum, overlying the incisor tooth, with patches alternating between the left and right sides [49]. Administration provides a steady delivery of testosterone, which is maintained in physiologic ranges. Two noninferiority trials comparing Striant to either a testosterone transdermal system (Androderm) or testosterone gel (Androgel) demonstrated equivalent physiologic testosterone levels [50-52]. Safety and tolerability data from two open-label phase III trials demonstrated a 12% rate of discontinuation over a 2-year period due to adverse events, most commonly altered taste and gum irritation.

Transdermal

Multiple transdermal systems of testosterone delivery are currently available with similar pharmacokinetic and adverse event profiles. Although the sites of delivery vary between formulations, all therapies achieve normal physiologic concentrations of testosterone in over 75% of patients, with slight differences in the rates and peak levels of testosterone achieved [53-57]. Dose adjustment is important because transdermal absorption varies between men, and may vary in an individual over time, depending on long-term skin changes at administration sites. Skin irritation with blisters is more common with patches compared to gels. Patients undergoing transdermal testosterone supplementation should be cautioned to the potential for direct transference to others, particularly to women and children. As direct skin-to skin contact is required for transference, this may be

avoided by placement of clothing over the administered site and thorough hand washing following topical application.

Injections

Injection therapies with testosterone provide an alternative method for testosterone supplementation. Deep intramuscular injections are performed every 1 to 4 weeks in the gluteal or quadricep areas. A characteristic of injectable testosterone is the rapid rise to supraphysiologic levels of testosterone within 1 to 2 days of administration, with a gradual decline into the hypogonadal range at the end of the dosing interval. Testosterone Enanthate 200 mg administered intramuscularly every 2 weeks achieves normal physiologic testosterone levels for 72% of the treatment interval compared to 82% with the testosterone transdermal system. Although costs vary, in general, intramuscular therapies are currently the least expensive alternative for testosterone supplementation. Adverse events with injectable testosterone include local pain and higher levels of polycythemia secondary to the supraphysiologic surge of testosterone associated with the injections.

Pellets

A long-lasting option for testosterone supplementation is subcutaneous testosterone pellets inserted into the lateral buttock or lower abdomen every 3 to 4 months. Different pellet presentations are available around the world. The procedure involves local anesthetic, with the pellets inserted into subcutaneous fat with a small trocar. Subcutaneous testosterone pellet insertion achieves peak testosterone levels approximately 12 hours following insertion, with a half-life of approximately 71 days. The total and duration of physiologic testosterone levels vary based on the number of pellets inserted and the patient's body mass index. Patients with elevated body mass indices achieve lower peak concentrations and may require a larger number of pellets compared to men in the low or normal body mass index range [58-61]. Common adverse events associated with testosterone pellet administration include, local pain, erythema, pellet extrusion, and ecchymosis.

Monitoring

Monitoring for treatment efficacy and possible adverse events should be based on the Endocrine Society's guidelines for monitoring patients on TRT [62]. Once this started, follow-up should be set up for 3 to 6 months, at which time symptoms can be assessed, testosterone levels can be rechecked, and monitoring can be continued for weight, Hct, and PSA. Should TT remain <400ng/dL, consideration to increase dosing may be pursued. If Hct >54%, TRT should be stopped until it returns to a normal level, and TRT may be reinitiated at a lower dose. In men older than 40 years with a baseline PSA >0.6ng/mL, one should perform a PSA and digital rectal exam before TRT and at intervals of 3 and 6 months once TRT is initiated. If PSA remains stable, follow-up can continue annually thereafter. If the patient has tolerated TTh well with no laboratory abnormalities, follow-up can continue annually. After 1 to 2 years of TTh in men with osteoporosis or history of low trauma fracture, a bone mineral density test should be pursued. If no improvement is noted after 3 to 6 months of TTh, one should consider other causes of the initial presenting symptoms.

Risks of TRT

Testosterone Replacement Therapy and Cardiovascular Events

There has been an increased use of testosterone therapy (TTh) in the last decade. This increase in usage has been attributed to many factors including age, poor general health and medical conditions such as obesity and diabetes. Many studies in the last 20 years have published data that TD is associated with an increased risk of developing atherosclerosis, CV disease, worsening osteoporosis and increased mortality and TTh has been found to have a beneficial effect on multiple risk factors. Diabetes, dyslipidemia, hypertension and obesity are risk factors for CV disease, and that TD contributes to increased fat mass and insulin resistance, it is reasonable to believe that TD increases CV disease by potentiating these risk factors. Any therapeutic modality that mitigates these risk factors is expected to reduce the risk of developing CV disease. Many intervention studies with the use of TTh demonstrate improvements in lipid profile, inflammation, obesity, waist circumference, glycemic control and blood pressure [63-66].

Clinical Trials Reporting Increased Cardiovascular Risk

The first trial which reported adverse CV effects after TTh was the Testosterone in Older Men with Mobility Limitations (TOM) trial [67] This was a prospective, placebo-controlled, randomized trial that was designed to determine the effects of 6 months of TTh on lower-extremity strength and physical function in older men (n=209) with TD and limited mobility. The study a benefit for functional status and muscular strength response but the trial was terminated early because of increased CV

adverse effects in the treatment group (21.6% vs. 4.8% in placebo group). Of the 23 reported CV events, only four were considered major adverse cardiac events (MACE).

Prostate Cancer

No adequately designed or appropriately powered study has been conducted to date to assess prostate cancer related risks of TTh. The detrimental effect of testosterone in locally advanced or metastatic prostate cancer has been well established, with early studies demonstrating significant progression of disease following exogenous testosterone administration [67-69]. Hsing [70] noted no difference in the incidence of prostate cancer in patients undergoing TTh compared to the general population. Two meta analyses of placebo-controlled TRT studies revealed no increased risk of the development of prostate cancer for patients undergoing TRT [71,72]. As such, the available evidence suggests it is safe to administer testosterone in the setting of LOH without increasing an individual's long-term risk of prostate cancer. Several retrospective studies have studied TRT in patients who have undergone definitive therapy for their prostate cancer and have demonstrated no increased risk of prostate cancer recurrence. Current evidence recommends against TRT in the setting of untreated prostate cancer but permits administration at a prudent interval following successful definitive local therapy with no evidence of recurrence.

Lower Urinary Tract Symptoms (LUTS)

Although androgens are thought to play a large role in prostate development, no difference in prostatic androgens has been noted in men with and without benign prostatic hyperplasia (BPH). Multiples studies have demonstrated either no change or improved parameters of voiding and LUTS in patients with BPH undergoing TTh, and thus, BPH should not be a contraindication to TTh in the setting of LOH [73-77].

Polycythemia

Polycythemia (erythrocytosis) is a common adverse event associated with TRT, that is both dose and serum-level dependent [78,79]. The overall effect noted varies by dose and patient age, but the risk of an increase in Hct >50% has been noted to be 3 to 4 times higher in patients receiving TRT compared to controls [68,69]. The initial rise in hemoglobin and Hct is seen in the first 5 to 6 months, with a decline noted 3 to 12 months after TRT discontinuation [80]. Although it has been hypothesized that enhance blood viscosity may be a risk for CVE, a causal relationship for TRT and its related erythrocytosis with CVE and mortality have not been well-defined through current studies, as described noted. As such, the Endocrine Society's Clinical Practice Guidelines are used to guide clinical management of TRT-related polycythemia and state that Hct values >54% warrant discontinuation of TRT until further assessment. In cases of extremely elevated or persistent polycythemia, therapeutic phlebotomy has been described as a management option.

Conclusion

Late-onset hypogonadism is a new entity afflicting elderly men. Evidence supports the authenticity of this entity and its health relevance. However, it is important to realise the presence of gaps in the understanding of this syndrome and its treatment. Improved clinical management can be expected to result from rigorous investigation of diagnostic criteria and demonstration of efficacy and safety of treatments for this syndrome.

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