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Age-Related Testosterone Decline is due to Waning of Both Testicular and Hypothalamic-Pituitary Function

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Abstract

Hypogonadism is a condition in which the endogenous secretion of testosterone is either insufficient or inadequate to maintain serum testosterone levels within normal range, and may manifest as a variety of signs and symptoms. Age-related hypogonadism is due to a combination of primary hypogonadism (testicular failure) and secondary hypogonadism (hypothalamic-pituitary axis failure). This review provides insight into the mechanisms resulting in the multifactorial nature of acquired androgen-deficiency, and outlines the current controversy regarding testosterone-replacement therapy in aging males.

Keywords

aging; testosterone; hypogonadism; late-onset hypogonadism

Introduction

The age-related decline in testosterone (T) along with the associated symptoms has been referred to as male menopause, andropause, partial androgen deficiency of the aging male, and the currently preferred term, late-onset hypogonadism (LOH).[1–4] The decline in testosterone seen in aging men has clinical implications beyond the laboratory test of serum testosterone: hypogonadal men are more likely to have decreased bone mineral density, decreased lean body mass, and greater likelihood of both metabolic syndrome and cardiovascular disease.[5]

Defining age- or symptom-specific T thresholds for diagnosing hypogonadism in aging men has proven a challenging task, as different symptoms appear at different T thresholds with age being an important confounder.[6–9] Hypogonadal symptoms tend to be specific to the individual, with not all men experiencing symptoms despite having low T levels. In the European Male Aging Study by Wu et al., the clinical features of hypogonadism that were demonstrated to be most associated with biochemical T deficiency included only three sexual symptoms (decreased frequency of morning erection, decreased frequency of sexual

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thoughts, and erectile dysfunction) in men older than 40 yrs. Interestingly, physical symptoms (an inability to engage in vigorous activity, an inability to walk more than 1 km, and an inability to bend, kneel, or stoop), and psychological symptoms (loss of energy, sadness, and fatigue) were not associated with low serum testosterone. In contrast, we identified that lack of energy was the only symptom that was positively associated with a low serum testosterone in men younger than 40. [10]

According to the 2010 Endocrine Society guidelines, hypogonadism can be diagnosed in men with signs and symptoms of androgen deficiency along with at least two low T measurements obtained from morning blood samples. In men proven to be androgen-deficient, it is further recommended that the practitioner obtains a serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the patient to distinguish between primary (testicular failure) and secondary hypogonadism (hypothalamic-pituitary axis failure).

Primary hypogonadism, or hypergonadotropic hypogonadism, is a result of testicular failure and is characterized by low serum T and high serum gonadotropins (FSH and LH). Secondary hypogonadism, or hypogonadotropic hypogonadism, is a result of a perturbation of the hypothalamic-pituitary-gonadal axis (HPGA) and is characterized by low serum T as well as low serum FSH and LH. Of the hypogonadal men in the European Male Aging Study, nearly 9% of men presented with primary hypogonadism, 50% with secondary hypogonadism, and 41% with compensated hypogonadism defined as biochemical thresholds of T greater or less than 10.5 nmol/L (~300ng/dL) and LH greater or less than 9.4 U/L.[11] Despite these findings, age-related hypogonadism, often involves a more likely combination of both primary testicular failure and the secondary disruption of the hypothalamic-pituitary axis.

Relationship between Aging and Primary Hypogonadism

Testosterone biosynthesis by Leydig cells within the testis occurs in response to luteinizing hormone, which is secreted by the pituitary. Once LH binds to the LH receptors on the Leydig cell, there is the rapid synthesis of the transport molecule, steroid activating receptor (StAR), which actively transports cholesterol across the mitochondrial membrane so that it may initiate the rate-limiting conversion of cholesterol to pregnenolone.[12] Pregnenolone then passes from the mitochondria to the smooth endoplasmic reticulum, where the remainder of the enzymatic reactions occurs to synthesize testosterone.

Leydig cells are less responsive to gonadotropin stimulation in elderly males (>65 yrs of age) as compared to younger males (<50 yrs of age).[13] Rubens and colleagues demonstrated the decreased responsiveness of Leydig cells in older men by stimulating males >65yrs or <50yrs with human chorionic gonadotropin (HCG) and measuring the increases in serum levels of T. The mean response to hCG stimulation was a 142% increase in T production in young men whereas only a an 85% increase was observed in elderly men. Age-related decline in Leydig cell responsiveness to LH has been confirmed *in vitro* using the brown Norway rat, a model for male reproductive aging.[14] Chen and colleagues stimulated isolated Leydig cells from young and old rats with LH, and found both a reduced basal and

diminished LH-stimulated testosterone concentration in older mice as compared to young mice.

In addition to the diminishing responsiveness of Leydig cells to LH as men age, Neaves and colleagues using cadaveric tissue demonstrated that older men have a decreased numbers of Leydig cells compared to younger men.[15] This finding was confirmed in animal models of aging in which the testes of young and old rats were analyzed for Leydig cell volume.[14] While the precise mechanism of the decrease in number of Leydig cells remains to be elucidated, it is hypothesized that chronic microvascular arteriosclerotic disease of the aging testis can result in pronounced fibrotic changes to testicular parenchyma.[16–18] Taken together, the mechanism of primary hypogonadism in aging men may be a combination of decreased number of Leydig cells, acquired defects in the steroidogenic pathway, as well as a disruption of the regulatory systems within the cells.[19]

Relationship between Aging and Secondary Hypogonadism

Secondary hypogonadism is the result of a disruption of the HPGA, and may be due to decreased production of GnRH or gonadotropins, or increased suppression. Gonadotropin-releasing hormone (GnRH) is released in a pulsatile manner, the periodicity and amplitude of which determines the pattern of secretion of the gonadotropins, LH and FSH, from the anterior pituitary.[20] Decreased production of GnRH by the hypothalamus with aging has been demonstrated in both human and animal studies. Using a GnRH-receptor antagonist, Takahasi and colleagues found attenuated GnRH signaling in aging men.[21] Decreased GnRH gene expression has been similarly demonstrated in the older brown Norway rats as compared to younger rats suggesting that decreased production of the peptide is in some part responsible for the attenuated GnRH signaling seen in older individuals.[22]

The pulsatility and amplitude of GnRH and subsequently LH secretion decreases as men age. A small study by Urban and colleagues showed that older men have a blunted increase in levels of serum LH in response to the antiestrogen, tamoxifen (21,450 vs. 42,044 mIU/ml/min; $p<0.01$), while basal bioactive LH release was not impaired in the group of older men.[23] Veldhuis and colleagues demonstrated that older men had increased LH pulse frequency and decreased pulse amplitude from the pituitary.[24] *In vitro* animal studies in which young and old male rats were infused with luteinizing hormone releasing hormone demonstrated that aged male rats released less LH from the anterior pituitary as compared to the younger males.[25]

There is an association between aging and increased sensitivity to negative feedback by androgens. Winters and colleagues showed that in the presence of exogenous androgens, older men had increased inhibitory feedback on both LH and FSH amplitude and pulse frequency.[26] Kisspeptin and neurokinin B are two important regulators of GnRH neurosecretion, believed to provide negative feedback on the hypothalamus. Molnar and colleagues established immunohistochemical evidence of increased expression of kisspeptin and neurokinin B in aging men suggesting that with increasing age, testosterone becomes unable to suppress these proteins as well.[27]

It is worth noting that increasing age is associated with increasing co-morbidities, many of which may influence the HPGA and thus result in secondary hypogonadism. Examples of these conditions include AIDS, end-stage renal and liver disease, hemochromatosis, obesity, chronic opiate use, vasculitis, infarction, glucocorticoid therapy, and anabolic steroid abuse.[28] The Healthy Man Study by Sartorius et al. examined men with self-reported excellent or very good health and measured their T, DHT, E2 and documented co-morbidities including BMI and smoking status. While they found that there were no changes in mean serum T among men in different decades of age, they did find that obesity and ex-smokers had lower mean values of androgens.[29] A follow up analysis of the EMAS by Camacho et al. investigated modifiable factors contributing to the age-associated declines in T. While they did detect age-related declines in serum androgens, they similarly noted that weight gain and smoking history contributed to declines in T. They did not find an association between increased co-morbidities and reduced T, though they did exclude men with medical conditions or taking medications known to affect the HGPA.[30]

As men age, there is a decrease in GnRH secretion from the hypothalamus and alterations in the pulse amplitude and frequencies of gonadotropins, either due to increased sensitivity to negative feedback or innate production defects. There is also a higher likelihood of co-morbidities in older men, which may negatively affect the HPGA.

Testosterone-Supplementation Therapy and Hypogonadism

Despite the relationship between aging and the accumulation of co-morbidities that affect the HGPA, testosterone-supplementation therapy (TST) does play a role in treating males with signs and symptoms of hypogonadism. The 2015 European Association of Urology guidelines state that after attempting lifestyle modifications, TST does provide multiple benefits to symptomatic males with hypogonadism, which include improved body composition, reduced BMI, and improved sexual function.[31] The importance of screening for and addressing modifiable risk factors was similarly echoed in the 2015 International Society for the Study of Aging Male guidelines, though there are clear benefits for TST.[32]

Testosterone products approved by the Food and Drug Administration (FDA) are indicated for replacement therapy in men with a deficiency or absence of endogenous testosterone, either primary or secondary, congenital or acquired. However, since the publication of large epidemiological studies that evaluated the association between testosterone and CV risk, FDA convened an advisory panel in 2014.[33] There is a recommended label change now – that testosterone is only FDA-approved in men with low T levels due to disorders of the testicles, pituitary gland, or brain. Examples of these conditions include Klinefelter syndrome, hypogonadotropic hypogonadism, radiation-induced testis damage, etc. The FDA expressed there is an absence of strong evidence surrounding the efficacy and safety of testosterone supplementation for age-related testosterone declines.[34] These warnings to all parties including the manufacturers of testosterone products, physicians who prescribe testosterone for age-related hypogonadism, and most importantly the patients seeking these therapies will impact the way this disease is treated.

The increase in the number of aging men receiving TST has been attributed by some to a combination of direct–to-consumer product advertising (DTCPA) and guidelines based on consensus rather than controlled trials by the professional community. Authors of a recent editorial advocate for better product labeling to include that the use of TST has not been well studied in the aging male population, along with the cessation of mass marketing by the pharmaceutical industry to an aging population.[35]

Until an established benefit for testosterone therapy in elderly men has been demonstrated, it appears that the FDA and physicians should approach this treatment option with caution. The ongoing Testosterone Trials (T Trials) are investigating the use of TST in men over the age of 65 years with T <250 and symptoms of hypogonadism.[36] Given the recent concerns over testosterone and cardiovascular risk, the inclusion criteria of this study have been modified to exclude individuals with prior cardiac or cerebrovascular events. Nevertheless, this study will provide insightful information into the use of TST in aging men.

Considering the multifactorial nature of acquired androgen-deficiency in aging males, prescribers will likely need to further consider factors such as age, co-morbidity, symptoms and goals of care prior to commencing testosterone therapy. The risks and benefits of testosterone therapy in elderly men needs to be individualized based on symptoms and blood tests. Aging-associated testosterone decline should not be considered a contraindication to testosterone therapy.

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