

Andropause: Pathophysiology, Problems, and Practice Guidelines

Thomas Mulligan, MD

Objectives:

1. Participants will understand the pathophysiology of age-associated hypogonadism.
2. Participants will know the risk, benefits, and treatment options for age-associated hypogonadism.
3. Participants will understand the current clinical practice guidelines on hormone replacement therapy for older men.

INTRODUCTION

The term menopause usually refers to the cessation of menstruation in women between the ages of 45-55. This change is caused by the age-associated changes in gonadal steroid (e.g., estrogen) secretion. Although men don't menstruate, they do exhibit age-associated changes to their gonadal steroid (e.g., testosterone) secretion. Herein, we review the extant scientific data on the effect of aging on testosterone secretion and the potential use of testosterone supplementation in older men.

In men, multiple neural inputs, endogenous opioids, testosterone, estradiol, and various other factors influence hypothalamic secretion of gonadotropin releasing hormone (GnRH) and the ability of GnRH to drive luteinizing hormone (LH) release. Pulsatile release of GnRH reaches the pituitary gland via the hypothalamic-pituitary portal venous system, and stimulates episodic secretion of LH. Pituitary secretion of LH reaches the testes via the systemic circulation, and promotes both tonic and episodic Leydig cell secretion of testosterone. Unbound testosterone in the plasma acts upon multiple target tissues and completes the feedback loop resulting in inhibition of GnRH and LH secretion.¹

Importantly, serum testosterone concentration demonstrates both circadian and ultradian rhythms. The circadian rhythm results in peak testosterone serum concentrations during the early morning hours, suggesting maximum testosterone secretion during nocturnal sleep.² In contrast, the ultradian (occurring more than once every 24 hours) rhythm has a cycle whereby the serum testosterone concentrations fluctuate approximately every 90 minutes. This ultradian rhythm represents the burst-like secretory pattern of testosterone, which is superimposed on testosterone's basal or tonic secretion.

Male aging is associated with diminished testosterone availability, even among those men who have no known health disorders, ingest no medications, don't smoke, and don't ingest alcoholic beverages.³ Testosterone availability is even lower among men with chronic diseases.⁴ Testosterone deficiency can be associated with decreased muscle mass and strength,⁵ diminished bone mineral density,⁶ hip fracture,⁷ and loss of sexual interest.⁸ Hypoandrogenism has also been associated with coronary artery disease,⁹ and impaired spatial cognition.¹⁰ Although the exact relationships between diminished testosterone availability and frailty, disability, or death have not been studied, such associations are likely.

PATHOPHYSIOLOGY

The hypothalamic neurons that secrete GnRH are derived from the fetal olfactory placode. These cells migrate to the hypothalamus, where they form gap junctions and synapses with each other, allowing large numbers of cells to function as a single unit (the pulse generator of the hypothalamic-pituitary-testicular axis). The function of these neurons is modulated by neural input (e.g., alpha adrenergic pathways in the monkey, and dopaminergic pathways in the human) and neurotransmitters (e.g., galanin, neuropeptide Y, opioids). At puberty, these cells demonstrate increased perikaryon size,¹¹ Golgi apparatus, and secretory vesicles, and, there is a doubling of the number of GnRH-

staining cells. Ultimately, they secrete GnRH in a pulsatile fashion, dependent upon the presence of Ca^{2+} , glucose, insulin, and voltage-dependent Ca^{++} channels. Pulsatile release of GnRH induces pituitary synthesis and secretion of LH and FSH, which induce testicular secretion of testosterone and inhibin.

With aging, although the GnRH mRNA content (per cell) does not change, the number of GnRH secreting neurons decreases (in the rat).¹² And, there is an apparent decrease in the release of neuropeptide Y, an excitatory peptidergic signal to GnRH-secreting neurons.¹³ Furthermore, since beta receptors, which may be coupled to GnRH release,¹⁴ become less functional in aged men and aged male rats, and hypothalamic norepinephrine content, also agonistic to GnRH secretion, decrease with aging in male rats,¹⁵ it is plausible to suspect that diminished GnRH impulse strength is the proximate cause of the relative hypogonadism of old age. This has been suggested by Vermeulen¹⁶ and Veldhuis¹⁷ based on diminished LH pulse amplitude in older men.

Pituitary secretion of LH is regulated by various factors that are extrinsic and intrinsic to the pituitary gland. For example, there is a dose-response (and typically a 1-to-1 pulsatile) relationship between the quantity of GnRH delivered to the pituitary gland as a pulse and the quantity of LH released in vivo and in vitro. However, with aging the GnRH-receptor-activated voltage-dependent Ca^{2+} channels are less able to mobilize the Ca^{2+} needed for LH release.¹⁸ Steroid hormones are important extrinsic regulators of LH release. For example, in addition to testosterone's inhibitory effect on the hypothalamus (in some species), testosterone can inhibit GnRH-stimulated pituitary secretion of LH. Dihydrotestosterone has no effect on LH secretion in men when levels are decreased via finasteride (a 5 alpha-reductase inhibitor) treatment, although patients with 5 alpha-reductase deficiency exhibit increased LH pulse amplitude. Hence, testosterone and perhaps its 5 alpha-reduced metabolite modulate LH secretion. LH secretion is further modulated by the hypothalamic opioidergic and, probably, dopaminergic systems. For example, based on clinical experiments using naloxone or naltrexone, endogenous opioids have a pronounced ability to diminish LH secretion in young men, but less so in older men. However, bromocriptine (a dopamine receptor agonist) may restore opioidergic suppression of LH secretion in aged men,¹⁹ suggesting a possible interaction between the opioidergic and dopaminergic systems.

In contrast to the modulators of pituitary secretion in health (e.g., GnRH, testosterone), the stress of illness also affects pituitary function. This may be mediated by cytokines, such as interleukin-1 alpha (IL-1 alpha), which activate the corticotropin-adrenal axis and impair gonadotropin secretion.²⁰ Stress-activated corticotropin releasing hormone (CRH) and opiates suppress the GnRH pulse generator in various experimental animals. Recent work by Shalts et al., in the ovariectomized monkey, demonstrates that IL-1 alpha reduces both the frequency and amplitude of LH secretion through the intermediary arginine vasopressin (AVP).²¹ In support of this concept, synapses have been found between AVP and GnRH-immunoreactive neurons.²² In the human, older men show wider dispersion of LH and testosterone serum concentrations, which may reflect variations in health status. For example, multiple physical, medical, and psychological stressors are commonly encountered in older individuals, and older men

exhibit a profound suppression of serum LH concentrations during acute illness. Therefore, the stress-related inhibition of pituitary LH secretion is more prominent in aged compared to young men.

Available data regarding age effects on GnRH's stimulatory actions are conflicting. For example, Snyder et al. reported that GnRH administration resulted in less of an increase in serum LH concentrations in aged men compared to young men.²³ In contrast, Winters et al. reported no such age-related difference in GnRH-mediated LH release.²⁴ And, Zwart et al. reported that GnRH administration resulted in more of an increase in serum LH concentrations in aged men compared to young men.²⁵ Similarly, there has been conflict regarding the effect of age on the pulse frequency of LH secretion. Deslypere et al. reported that the number of high-amplitude LH pulses decreases with aging,²⁶ and Veldhuis et al. corroborated this inference but also reported an increase with aging in total (low amplitude) LH pulse frequency. Finally, and perhaps most importantly, extant data show considerable variability in GnRH-stimulated bioactive LH secretion, which decreases in some but not all older individuals.²⁷

Testosterone is secreted with a pulsatile and basal component. Pulses of testosterone secretion follow LH secretory pulses by 10 - 20 minutes.²⁸ As outlined above, with aging, mean serum testosterone concentrations decrease and circadian rhythmicity is lost.²⁹ The cause of this relative hypogonadism has been attributed in part to an age-associated decrement in testicular steroidogenesis.³⁰ Indeed, hCG stimulation tests indicate that older men may exhibit decreased testosterone release compared to younger men. Importantly, however, the specific contributions of decreased hypothalamic, pituitary, or testicular function have never been isolated. Nevertheless, it is plausible to suspect a primary defect in the amplitude of GnRH secretory events, no apparent defect in GnRH driven LH secretion, diminished LH feedforward activity on testosterone secretion, and diminished testosterone secretory capacity.

TESTOSTERONE SUPPLEMENTATION

Although a consensus has not yet developed, scientific data are accumulating to suggest that testosterone supplementation should be offered to older men similarly to the way it is offered to post-menopausal women. For example, in the absence of contraindications (e.g., prostate cancer) it may prove to be reasonable to offer older men, especially deconditioned older men, testosterone replacement therapy. Testosterone replacement therapy appears to increase molecular markers for muscle and bone anabolism, increase muscle strength, improve the symptoms of ischemic heart disease, and not have the worrisome effect on lipids that many have suspected.

Hagenfeldt et al. demonstrated that testosterone supplementation increases serum concentrations of vitamin D and insulin-like growth factor-1, mediators of bone metabolism, in hypogonadal young men.³¹ And, testosterone supplementation increases plasma growth hormone (GH) concentrations in hypogonadal men, suggesting that testosterone replacement therapy may increase muscle mass via GH.³² Perhaps most important, Urban et al. demonstrated that physiologic replacement doses of testosterone, given to older men, increases muscle strength, muscle protein synthesis, and IGF-1

mRNA concentration.³³ Therefore, testosterone replacement therapy improves microscopic and macroscopic measures of muscle function in young and older men with testosterone deficiency.

Many clinicians have been concerned, however, that testosterone supplementation may result in high serum cholesterol concentrations or other risk factors for heart disease. In this regard, testosterone supplementation appears to increase platelet aggregation,³⁴ which could result in coronary artery thrombosis. In contrast, Zgliczynski et al. demonstrated that testosterone replacement therapy in young and older men was associated with lower serum total cholesterol and LDL concentrations and no effect on HDL concentrations.³⁵ Even supra physiologic doses of testosterone (600mg every week for 10 weeks) did not cause an increase in the serum cholesterol or LDL concentration.³⁶ And, testosterone supplementation decreases subjective and objective markers of coronary artery disease in older men. In a randomized, placebo-controlled, cross-over trial in older men with documented coronary artery disease, testosterone replacement markedly improved anginal symptoms and may have improved ECG evidence of ischemic events.³⁷ In support of this testosterone effect on anginal symptoms, testosterone withdrawal and replacement has a strong correlation with pain threshold in the rat.³⁸

Although more data will be published in the near future, two rigorous trials of testosterone replacement in older men support a beneficial treatment effect. The first, a randomized, placebo-controlled trial of testosterone 100mg im for 3 months, demonstrated that lean body mass increased, urinary hydroxyproline (a marker of bone breakdown) decreased, and both cholesterol and LDL decreased.³⁹ However, there was a worrisome rise in the serum PSA concentration. More recently, Sih et al. reported the results of a 12-month randomized, controlled trial of testosterone 200mg im every 2 weeks in older men.⁴⁰ They found that testosterone improved grip strength, hemoglobin, and decreased serum leptin concentrations. And, there was no effect on serum lipoproteins or PSA. Taken together, these studies suggest that testosterone supplementation in older relatively hypogonadal men is safe and likely beneficial.

If a clinician decides to pursue testosterone supplementation in an older male patient, the decision should be based on multiple serum free-testosterone concentrations within or below the lower third of the normal range and the absence of contraindications. Absolute contraindications include prostate or breast cancer and symptomatic untreated BPH. The testosterone replacement dose for older men is slightly lower than the dose for younger men. Specifically, testosterone 75mg im weekly appears to maintain the midweek serum testosterone concentration within the normal range. In addition to the parenteral route of administration, testosterone can be given transdermally and orally. However, some formulations of transdermal testosterone have not met with widespread success. For example, the scrotal patch (Testoderm by Alza) requires that the scrotum be shaved, and is, therefore, somewhat inconvenient. One of the patches which can be applied to the chest or other non-scrotal areas (Androderm by SmithKline Beecham) is convenient but is associated with contact dermatitis. Recently, another non-scrotal patch has been released (Testoderm TTS by Alza) which has a lower incidence of contact

dermatitis, but data on long-term use are not yet available. Finally, transdermal testosterone gel is now available (AndroGel by Unimed), and has met with greater acceptance. Transdermal testosterone may be an improvement over weekly injection of testosterone because they approximate the circadian fluctuations in serum testosterone concentration. But, no product is yet able to mimic the ultradian rhythms of serum testosterone concentration. Although intuitively we might expect that the best form of testosterone supplementation would approximate both the circadian and ultradian rhythms, scientific data are not yet available to support this hypothesis. While on replacement therapy, patients should be monitored approximately every six months to make certain of a treatment effect and the absence of urinary obstructive symptoms, rising PSA, or excessive elevations of the hemoglobin concentration.⁴¹

REFERENCES :

- ¹ Reyes-Fuentes A, Veldhuis JD. Neuroendocrine physiology of the normal male gonadal axis. *Endocrinol Metab Clin North Amer* 1993; 22:93-124.
- ² Veldhuis JD, Iranmanesh A, Johnson ML, Lizarralde G. Twenty-four-hour rhythms in plasma concentrations of adenohipophyseal hormones are generated by distinct amplitude and/or frequency modulation of underlying pituitary secretory bursts. *J Clin Endocrinol Metab* 1990;71:1616-23.
- ³ Tenover JS, Matsumoto AM, Plymate SR, Bremner WJ: The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. *J Clin Endocrinol Metab* 1987; 65:1118-26.
- ⁴ Gray A, Feldman HA, McKinlay JB, Longcope C: Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. *J Clin Endocrinol Metab* 1991; 73:1016-25.
- ⁵ Mooradian AD, Morley JE, Korenman SG: Biological actions of androgens. *Endocr Rev* 1987; 8:1-28.
- ⁶ Rudman D, Drinka PJ, Wilson CR, Mattson DE, Scherman F, Cuisinier MC, Schults S: Relations of endogenous anabolic hormones and physical activity to bone mineral density and lean body mass in elderly men. *Clin Endocrinol* 1994; 40:653-61.
- ⁷ Jackson JA, Riggs MW, Spiekerman AM: Testosterone deficiency as a risk factor for hip fractures in men: a case-control study. *Am J Med Sci* 1992; 304:4-8.
- ⁸ Harman SM, Blackman MR. Male menopause, myth or menace? *Endocrinologist* 1994; 4:212-7.
- ⁹ Phillips GB, Pinkernell BH, Jinh TY: The association of hypotestosteronemia with coronary artery disease in men. *Arteriosclerosis & Thrombosis* 1994; 14:701-6.
- ¹⁰ Janowsky JS, Oviatt SK, Orwoll ES: Testosterone influences spatial cognition in older men. *Behav Neurosci* 1994; 108:325-32.
- ¹¹ Urbanski HF, Doan A, Pierce M, Fahrenback WH, Collins PM: Maturation of the hypothalamo-pituitary-gonadal axis of male Syrian hamsters. *Bio Reprod* 1992; 46:991-6.
- ¹² Gruenewald DA, Matsumoto AM: Age-related decrease in serum gonadotropin levels and gonadotropin-releasing hormone gene expression in the medial preoptic area of the male rat are dependent upon testicular feedback. *Endocrinol* 1991; 129:2442-50.
- ¹³ Kalra SP, Sahu A, Kalra PS: Ageing of the neuropeptidergic signal in rats. *J Reprod Fertil* 1993; 46:11-9.
- ¹⁴ Martinez de la Escalera G, Choi ALH, Weiner RI: β_1 -adrenergic regulation of the GT1 gonadotropin-releasing hormone (GnRH) neuronal cell lines: stimulation of GnRH release via receptors positively coupled to adenylate cyclase. *Endocrinology* 1992; 131:1397-1402.
- ¹⁵ Steger RW, De Paolo LV, Shepherd AM: Effects of advancing age on hypothalamic neurotransmitter content and on basal norepinephrine-stimulated LHRH release. *Neurobiol Aging* 1985; 6:113-6.

-
- ¹⁶ Kaufman JM, Giri M, Deslypere JM, Thomas G, Vermeulen A: Influence of age on the responsiveness of the gonadotrophs to luteinizing hormone-releasing hormone in males. *J Clin Endocrinol Metab* 1991; 72:1255-60.
- ¹⁷ Veldhuis JD, Urban RJ, Lizarralde G, Johnson ML, Iranmanesh A: Attenuation of luteinizing hormone secretory burst amplitude as a proximate basis for the hypoandrogenism of healthy aging in men. *J Clin Endocrinol Metab* 1992; 75:707-13.
- ¹⁸ Miyamoto A, Maki T, Blackman MR, Roth GS: Age-related changes in the mechanisms of LHRH-stimulated LH release from pituitary cells in vitro. *Experimental Gerontology*. 1992; 27:211-9.
- ¹⁹ Coiro V, Volpi R, Bertoni P, Marcato A, Vourna S, Bocchi R, Bianconi L, Marchesi M, Buonanno G, Chiodera P: Restoration of normal gonadotropin responses to naloxone by chronic bromocriptine treatment in elderly men. *Horm Res* 1991; 36:36-40.
- ²⁰ Feng Y, Shalts E, Xia L, Rivier J, Rivier C, Vale W, Ferin M: An inhibitory effect of Interleukin-1 α on basal gonadotropin release in the ovariectomized rhesus monkey: reversal by a corticotropin-releasing factor antagonist. *Endocrinology* 1991; 128:2077-82.
- ²¹ Shalts E, Feng Y, Ferin M: Vasopressin mediates the interleukin-1 α -induced decrease in luteinizing hormone secretion in the ovariectomized rhesus monkey. *Endocrinology* 1992; 131:153-8.
- ²² Thind KK, Boggan JE, Goldsmith PC: Interactions between vasopressin-and gonadotropin-releasing hormone-containing neuroendocrine neurons in the monkey supraoptic nucleus. *Neuroendocrinol* 1991; 53:287-97.
- ²³ Snyder PJ, Reitano JF, Utiger RD: Serum LH and FSH responses to synthetic gonadotropin-releasing hormone in normal men. *J Clin Endocrinol Metab* 1975; 41:938-45.
- ²⁴ Winters SJ, Troen P: Episodic luteinizing hormone (LH) secretion response of LH and follicle-stimulating hormone to LH-releasing hormone in aged men: evidence for coexistent primary testicular insufficiency and an impairment in gonadotropin secretion. *J Clin Endocrinol Metab* 1982; 55:560-5.
- ²⁵ Zwart AD, Urban RJ, Odell WD, Veldhuis JD: Contrasts in the gonadotropin-releasing hormone dose-response relationships for luteinizing hormone, follicle-stimulating hormone and alpha-subunit release in young versus older men: appraisal with high-specificity immunoradiometric assay and deconvolution analysis. *Eur J Endocrinol* 1996; 135:399-406.
- ²⁶ Deslypere JP, Kaufman JM, Vermeulen T, Vogelaers D, Vandalem JL, Vermeulen A: Influence of age on pulsatile luteinizing hormone release and responsiveness of the gonadotrophs to sex hormone feedback in men. *J Clin Endocrinol Metab* 1987; 64:68-73.
- ²⁷ Urban RJ, Veldhuis JD, Blizzard RM, Dufau ML: Attenuated release of biologically active luteinizing hormone in healthy aging men. *J Clin Invest* 1988; 81:1020-9.
- ²⁸ Veldhuis JD, King JC, Urban RJ, Rogol AD, Evans WS, Kolp LA, Johnson ML: Operating characteristics of the male hypothalamo-pituitary-gonadal axis: pulsatile release of testosterone and follicle-stimulating hormone and their temporal coupling with luteinizing hormone. *J Clin Endocrinol Metab* 1987; 65:929-41.
- ²⁹ Bremner WJ, Vitiello MV, Prinz PN: Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab* 1983; 56:1278-81.

-
- ³⁰ Liao C, Reaven E, Azhar S: Age-related decline in the steroidogenic capacity of isolated rat Leydig cells: a defect in cholesterol mobilization and processing. *J Steroid Biochem Molec Biol* 1993; 46:39-47.
- ³¹ Hagenfeldt Y, Linde K, Sjoberg HE, Zumkeller W, Arver S: Testosterone increases serum 1,25-dihydroxy vitamin D and insulin-like growth factor-1 in hypogonadal men. *Int J Androl* 1992; 15:93-102.
- ³² Weissberger AJ, Ho KKY: Activation of the somatotrophic axis by testosterone in adult males: evidence for the role of aromatization. *J Clin Endocrinol Metab* 1993; 76:1407-1412.
- ³³ Urban RJ, Bodenbun YH, Gilkison C, et al: Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. *Am J Physiol* 1995; 269:E820-6.
- ³⁴ Ajayi AAL, Mathur R, Halushka PV: Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses. *Circ* 1995; 91:2742-7.
- ³⁵ Zgliczynski S, Ossowski M, Slowinska-Srzednicka J, et al: Effect of testosterone replacement therapy on lipids and lipoproteins in hypogonadal and elderly men. *Atherosclerosis* 1996; 121:35-43.
- ³⁶ Bhasin S, Storer TW, Berman N, et al: The effects of supra physiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 1996; 335:1-7.
- ³⁷ Wu SZ, Weng XZ: Therapeutic effects of an androgenic preparations on myocardial ischemia and cardiac function in 62 elderly male coronary heart disease patients. *Chinese Med J* 1993; 106:415-8.
- ³⁸ Pednekar JR, Mulgaonker VK: Role of testosterone on pain threshold in rats. *Indian J Physiol Pharmacol* 1995; 39:423-4.
- ³⁹ Tenover JS: Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab* 1992; 75:1092-8.
- ⁴⁰ Sih R, Morley JE, Kaiser FE, Perry HM, Ping P, Ross C: Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab* 1997; 82:1661-7.
- ⁴¹ Morales A, Bain J, Ruijs A, Chapdelaine A, Tremblay RR: Clinical practice guidelines for screening and monitoring male patients receiving testosterone supplementation therapy. *Int J Impot Res* 1996; 8:95-7.