Endocrinology of the Aging Male

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Abstract

The endocrinology of the aging male is complex, with multiple hormones along the hypothalamic-pituitary-testicular (HPT) axis interacting with one another in feedback. As men age, there is a small and progressive (not precipitous, as in women) decline in several sex hormones, in particular testosterone and dehydroepiandrosterone, and related increases in luteinizing hormone, follicle-stimulating hormone, and sex hormone-binding globulin. The importance of these changes is wide-ranging because of the ubiquitous role of sex hormones in male physiology. This chapter discusses the endocrinology of the aging male. We provide an overview of the regulation of the HPT axis with an emphasis on the changes that occur with aging and the measurement of gonadal steroids, including hormone pulsatility, within-subject and circadian variations. The difficulties of assessing the symptoms of late-onset hypogonadism are highlighted. There is a comprehensive discussion of the epidemiology of sex hormone changes, including their age associations, prevalence of symptomatic hypogonadism, secular changes, risk factors, and the association of sex hormones with outcomes.

Keywords

Aging; androgens; hormones; hypogonadism; men; testosterone

II. Introduction

Aging is associated with degenerative changes in multiple organ systems. The rate and extent to which these occur depend on genetics, the presence of other disease processes, and the accumulated effects of socioeconomic, lifestyle, and environmental factors. Although there is no equivalence in men of the abrupt cessation of cyclical ovarian activity that occurs in women, a variable and inconsistent decrease in testosterone with increasing age is observed, albeit that even at very advanced age, sexual and reproductive function may be

within normal limits. The age-related decrease in testosterone is primarily due to testicular dysfunction, at least in the absence of disorders that affect the hypothalamic-pituitary testicular (HPT) axis, for example obesity, although some reduction in central responsiveness of the HPT axis may also occur. The extent to which an age-related decrease in testosterone has direct consequences for physical or cognitive function as well as mood and overall quality of life, and the level of testosterone at which these occur remains incompletely resolved, as does the role of the testosterone supplementation.

This chapter discusses the endocrinology of the aging male, with particular focus on the biology and central regulation of the HPT axis, and the epidemiology of sex hormone changes, with implications for diagnosis and management of hypogonadism in aging men. Since testosterone is the most important androgen from a biological perspective and assays are widely available, this chapter focuses on testosterone, with attention paid to other androgens and other sex hormones as appropriate.

III. Biology and Central Regulation of the Hypothalamic-Pituitary-Testicular (HPT) Axis in Men

a. Gonadotrophin-releasing hormone

In a normal adult male, neurons in the preoptic area and the medial basal region of the hypothalamus secrete gonadotrophin-releasing hormone [GnRH] in a pulsatile manner. The periodicity and amplitude of GnRH secretion determine the pattern of secretion of the gonadotrophins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), from the gonadotroph cells of the anterior pituitary.

It has been suggested, but not proven, that neuronal GnRH outflow in healthy men is reduced by 33–50% between the second and eighth decades of life. Feedback from testosterone induces a slowing of the hypothalamic pulse generator and consequently a decrease in the frequency of the LH pulsatile release, 1 but independent of this phenomenon testosterone has a role in maintaining physiological LH pulse frequency and incremental LH pulse size. In the face of eugonadal concentrations of testosterone, young and older men exhibit remarkably similar LH responses to a 300-fold dose range of exogenous GnRH, 2 an observation that implies an absence of a direct effect of aging on gonadotroph function. 2 GnRH dose shortens LH but not FSH secretory bursts and it has been reported that age elevates basal FSH but not LH secretion. [2] Nevertheless data from the European Male Aging Study (EMAS) demonstrates a clear elevation of basal LH with age. [3]

Estrogen-dependent mechanisms also mediate testosterone negative feedback on GnRH expression, although there is no effect of targeted disruption of the estrogen receptor on the central regulation of reproductive function in males. Possible increases in circulating estrogen levels with increasing age, not be because of age per se, but as a result of increased body fat and aromatase activity, may lead to a decline in testosterone. In older men, aromatase inhibition increases testosterone levels. [4]

Three peptides, kisspeptin, NKB, and dynorphin (DYN), colocalize in a single subpopulation of neurons in the hypothalamic arcuate nucleus (ARC). [5] The inputs from these neurons regulate pulsatile GnRH secretion and, importantly integrate signals relating to nutrition, photoperiod, stress, 6 and inflammation. 7 Accordingly, changes concomitant with aging that affect any of these homeostatic mechanisms may lead to changes in pulsatile GnRH release and testosterone production. The kisspeptins are a family of proteins encoded by the Kiss-1 gene. Kisspeptins and the kisspeptin receptor, GPR54, are pivotal to the central control of reproduction in rodents, primates and humans throughout the lifecycle, 8

and integrate gonadal steroid feedback, environmental and metabolic signals. There is evidence that leptin is a regulator of the hypothalamic KiSS-1 system. [9]

Neurokinin B (NKB) and its receptor, NK3R, mediate a predominant effect on LH secretion. [10] NKB induces multiple-unit activity (MUA) bursts in the medial basal hypothalamus that relate directly to LH pulses. [11] One pulse per hour of GnRH sustains gonadotrophin synthesis and secretion. Slower pulse frequencies result in a decline in LH secretion but a rise in FSH secretion. [12] Impaired NKB signaling may specifically slow GnRH pulse frequencies. Dynorphin (DYN), like NKB, may be involved in generating changes in the rhythm of GnRH pulses, but in contrast to NKB inhibits bursts of multiple-unit activity in the medial basal hypothalamus. [11]

b. Pituitary gonadotrophs and the gonadotrophins LH and FSH

GnRH is delivered to the anterior pituitary via the hypophyseal portal circulation where it binds to a 7-transmembrane domain, G-protein coupled, receptor (GnRHR) on the surface of gonadotrophs triggering the synthesis and secretion of the gonadotrophins FSH and LH. The gonadotrophins are composed of distinct hormone-specific β subunits paired with a common α subunit (αGSU). LH production is favored by fast pulse frequencies (> 1 pulse per h) and FSH favored by slow pulse frequencies (< 1 pulse per 2–3 h).

LH binds to the LH receptor on the plasma membrane of Leydig cells in the testis resulting in the synthesis of the enzymes of testosterone biosynthesis. LH is also required for Leydig cell differentiation and gonadal growth. A moderate decline in testosterone synthesis capacity may not necessarily be compensated completely by increased LH secretion even in young men, [13] suggesting that there is some tolerance within the system to fluctuating levels of gonadal steroids. FSH regulates spermatogenesis following its binding to the FSH receptor in the basal aspect of the plasma membrane of Sertoli cells in the testis. Deletion of the FSHβ gene does not cause infertility in male mice but does reduce testicular tubule size, sperm number and motility. FSH secretion is modulated by activin and inhibin. [14, 15]

Activin is a homodimer produced by the Sertoli cells, peritubular and interstitial cells as well as the pituitary and hypothalamus, where it mediates effects on a purely paracrine basis. Activin binds to activin receptor type II in the gonadotroph cells in the pituitary and stimulates the secretion of FSH. Increase in FSH secretion is also thought to be via activin stimulation of GnRH in the hypothalamus. [16]

Inhibin B is a heterodimeric glycoprotein that is predominantly produced in the Sertoli cells and it shows a diurnal rhythm parallel to that of testosterone. Inhibin's production is stimulated by FSH and it in turn, inhibits the secretion of FSH via a negative feedback mechanism. Inhibin has also been shown to bind to activin receptor type II, reducing activin binding to the receptor and therefore activin's stimulation of FSH secretion. [17, 18] FSH levels increase with the loss of germinal elements in the testis [19] and FSH has been used as a marker of spermatogenesis. Inhibin B used in combination with FSH is a more sensitive marker of spermatogenesis. [20]

c. Gonadal- and tissue-derived sex steroids

Steroidogenic acute regulatory protein (StAR), rapidly synthesized in response to LH actively transports cholesterol from the outer to the inner mitochondrial membrane. The translocator protein (TSPO) mediates the StAR-induced cholesterol transport. Cytochrome P450 enzyme, CYP11A is located on the inner mitochondrial membrane and catalyses the rate limiting step of pregnenolone synthesis. The combined actions of the cytochrome P450 enzyme CYP17 and the HSD enzyme HSD3B2 convert pregnenalone into DHEA and then androstenedione. The enzyme 17β-HSD-3 converts androstenedione to testosterone, and

DHEA into 5-androstene-3β,17β-diol which is in turn a substrate for HSD3B2 to form testosterone. [21] All steps beyond the formation of pregnenolone take place in the smooth endoplasmic reticulum.

Stress induced increases in glucocorticoids can suppress testosterone levels in adult males via a direct effect on the testis. Leydig cells express 11 β-HSD-1, an oxidoreductase, and 11 β-HSD-2, a unidirectional oxidase. Under normal physiological conditions, generation of NADPH, a byproduct of glucocorticoid metabolism by 11 β-HSD-1 potentiates testosterone biosynthesis, as NADPH is the cofactor used by steroidogenic enzymes such as 17β-HSD-3. The NAD+ generated drives 11 β-HSD-1 oxidase activity. Accordingly, it is only under stressful conditions when high input amounts of cortisol exceed the capacity of oxidative inactivation by 11 β–HSD that testicular cortisol levels increase to the extent that testosterone synthesis is inhibited. [21] With aging there is an increase in the cortisol production rate and free cortisol levels are increased [22] but whether this mediates age-related decreases in testicular function has not been established. At least in rats, there is an age related decline in 11 β-HSD-2 which therefore limits the degree of protection afforded from increasing glucocorticoid levels. [23]

d. Testosterone and SHBG

Testosterone controls sexual differentiation (stabilization of the Wolfian ducts) and is active on skeletal muscle, libido and sexual function. Testosterone is present in plasma as free (unbound testosterone), albumin-bound and sex hormone-binding globulin [SHBG]-bound. SHBG is a plasma glycoprotein produced by hepatocytes and secreted into the blood.

The fraction of testosterone bound to SHBG in serum is proportional to the SHBG level. SHBG production in the liver is regulated by a number of hormones. Estrogen and related steroids, thyroid hormone and insulin increase SHBG levels. SHBG decreases in response to androgens, and in the presence of hypothyroidism, and insulin resistance. Hepatocyte nuclear factor-4 (HNF-4) recruits the transcription initiating complex to the human SHBG promoter. Lipogenesis induced by glucose or fructose inhibits hepatic SHBG expression by reducing cellular HNF-4 levels. [24]

SHBG expression indirectly via thyroid hormone-mediated decreases de-novo synthesis of palmitate in the liver and consequently HNF-4 levels increase. [25] The human SHBG promoter also contains a PPAR-response element.

Plasma SHBG levels tend to increase with increasing age but remain inversely associated with plasma insulin and triglyceride levels irrespective of age. [26]

The apparent metabolic clearance rate of testosterone is decreased in elderly as compared to younger men. Possible reasons for this include age-related changes in body composition, SHBG, hepatic blood flow, and presumably a range of other factors yet to be identified. [27]

e. Dihydrotestosterone (DHT)

In certain target tissues testosterone is converted to 5α-dihydrotestosterone (DHT), which has a higher affinity than testosterone for both SHBG and the androgen receptor (AR). A 10-fold higher concentration of testosterone is required to achieve the AR mediated transcriptional effects of DHT. [28] Testosterone is converted to DHTby a membrane protein, steroid 5α-reductase (5αR). There are two types of 5αR each coded by a separate gene. The expression of 5αR1 is highest in hair follicles, sebaceous glands of the skin, and the liver, although its expression is widespread. 5αR2 is located primarily in the prostate, epididymis and seminal vesicles. DHT increases the expression of both 5αR1, 5αR2. Type 3 3α-hydroxysteroid dehydrogenase (HSD) (*AKR1C2*) catalyzes the reduction of 5α-DHT to yield

the inactive androgen 3α-androstanediol (3α-diol), which can be oxidized back to DHT, at least in prostate stromal cells. [29] Type 3 3β-HSD reduces DHT to 3β-androstanediol, a potent ligand for ERβ. [29] DHT (and its precursor testosterone) can also be formed in bone, muscle, and the prostate from the circulating adrenal androgen DHEA, a pathway which may be of increasing importance with age.

f. Estrogen

Estrogen in the male can be synthesized locally from testosterone, by aromatase enzymes, in many tissues. [30, 31] This includes the brain, where estrogen may act via its classic nuclear receptors, or via rapid membrane actions. [32–34] The rate of whole body aromatization is higher in older men, [35] but the precise mechanisms are unclear.

In the presence of inactivating mutations in the *CYP19* gene, several physiological disturbances have been identified in men, including skeletal, metabolic, and reproductive impairments. [30, 31] Studies in aromatase knockout mice generally recapitulate these sequelae. [36, 37]

Estradiol suppresses LH and FSH to exogenously administered GnRH in GnRH-deficient men and aromatase inhibition increases LH and FSH indicating a role for estrogens in negative feedback. These effects are blocked by a GnRH agonist indicating the changes in hypothalamic GnRH secretion are responsible. In males, estrogen-dependent mechanisms also mediate testosterone negative feedback on GnRH expression and secretion. [38]

IV. Measurement Issues

Proper assessment of HPT axis functioning relies critically on accurate assessment of analytes in human serum, and to a lesser extent and for specific syndromes (e.g., hypogonadism), on medical history or patient self-report.

Testosterone circulates predominantly bound to the plasma proteins SHBG and albumin, with high and low affinity respectively. A small and variable fraction is said to circulate as free testosterone. One or another of these circulating fractions of testosterone have been used as outcome measures in different studies, with various investigators attributing greater biological relevance to one measure as opposed to another. There is general consensus that the most relevant fraction to measure for both clinical and epidemiological purposes is total testosterone. The precision of many platform-based assays is suboptimal and there is limited standardization of processes both in terms of specimen collection and analysis. [39] Although liquid chromatography-tandem mass spectrometry (LC-MS/MS) is considered to be considerably more sensitive and precise, similar technical issues in relation to sample collection apply, and there are quite considerable variations in assays, which are technically difficult to undertake. While LC-MS/MS methodology represents a considerable advance, and in the case of some sex steroids, for example estrogen, permits reliable assessment of the very low plasma levels that are otherwise at the limits of detection of more conventional assays, harmonization of LC-MS/MS assays is required. [40] In the clinical setting, it generally accepted that a high-quality radioimmunoassay or chemiluminescence assay will provide sufficient information on testosterone levels in aging men. In obese men, free testosterone levels may also need to be measured.

Testosterone is secreted in a pulsatile fashion. [41] Since the pulse frequency is so rapid and the amplitude relatively low, a single blood sample is generally considered sufficient for most clinical or epidemiologic studies.[42] Nonetheless, testosterone and other serum hormones exhibit considerable variability within subjects over time. [43] Current clinical guidelines suggest at least two measurements.

In adult men, there is a well-documented diurnal variation (particularly in younger subjects) in testosterone levels, which are highest in the early morning and progressively decline throughout the day to a nadir in the evening. [44] In older men, the diurnal variation is blunted. [45] Data on the clinical implications of keeping a consistent time window for the drawing of serum for testosterone assessment have been reported. [46] Thus, it is standard practice for samples to be obtained between 0800 and 1100 h.

The most substantial challenge to developing valid instruments to assess for symptoms attributable to hypogonadism, particularly with aging, is the non-specificity of these symptoms, [47] reflected in the low specificity of screening instruments for hypogonadism. [48–50] A recent publication showed that the presence of 3 sexual symptoms (decreased morning erections, erectile dysfunction, and decreased frequency of sexual thoughts) best predicted the presence of low testosterone, providing the first empirically-derived approach to defining hypogonadism. [51] The main limitation of this algorithm is the relatively high prevalence of these symptoms in the general population, making its use as a screening device especially challenging. We have previously shown that the relative percentages of low libido, ED, and two or more non-specific symptoms (e.g., fatigue, depressed mood) were elevated in men with low testosterone levels compared to men with testosterone levels in the normal range and that with increasing age, the specificity of symptoms for low testosterone appeared to increase [52] Zitzmann and colleagues have shown that some symptoms of hypogonadism might appear at higher concentrations of androgens than others, [53] with variations between individuals,[54] perhaps related to genetic differences that affect androgen sensitivity.

V. Epidemiologic and Clinical Research

a. Age Trends

Because of the complex interrelations of the sex hormones with other hormone systems, common chronic diseases of aging (cancer, CVD, diabetes, depression, hyperlipidemia, arthritis), and associated risk factors for chronic disease (obesity, sedentariness, nutritional deficiency, smoking), there is still little consensus to what constitutes a normal sex hormone profile for an aging male. There is no male equivalent of the menopause, and even in very old men with healthy active lifestyles plasma testosterone levels and sexual function may be well within the range of normal. Nevertheless, it is well established that several of these sex hormone levels – though not all – undergo, on average, a gradual shift with age. Testosterone and DHEA decline, whereas LH, FSH, and SHBG rise.[55] DHT remains constant despite the decline of its precursor testosterone (Figure 1). [55] It is by no means clear whether these shifts are universal, inevitable, or deleterious.

i. Testosterone—Longitudinal studies show an average annual decline of 1–2% total testosterone levels, with decline in free testosterone more rapid because of increases in SHBG with aging (Figure 1). [55–57] Nonetheless, the decline in testosterone observed in population studies is by no means universal and testosterone levels may be stable or even increase with age in some men (Figure 2). [58]

ii. DHEA—Studies agree that levels of the adrenal steroid DHEA and its sulfate (DHEAS), the most plentiful steroid in serum, decline with age more markedly than other hormones.[59, 60] The adrenal steroid androstenedione (Ae) follows a similarly sharp decline.[60] Massachusetts Male Aging Study (MMAS) data show DHEA, DHEAS, and Ae declining at 2–3% per year, both cross-sectionally [61] and longitudinally (Figure 1). [55]

iii. DHT—DHT showed no cross-sectional age trend in MMAS [55] or other studies [60, 62–64] but increased within subjects between MMAS visits. [55]. Androstanediol glucuronide

(AAG) declined cross-sectionally with age in the MMAS sample, at 0.6% per year (but not longitudinally) and appeared to be related to prostate cancer [65] but the functional consequences of declines in AAG are not completely clear.

iv. Estrogen—The age trends of estrogen levels have been reported variously as declining [66] or remaining steady. [67] Estrogens were invariant with age in MMAS. [61]

v. Gonadotrophins and regulation of the HPT axis with aging—There is general agreement that the pituitary gonadotrophins, LH and FSH (the function of which in men is to stimulate respectively testosterone secretion by Leydig cells and sperm production by Sertoli cells in the testes), increase in serum concentration with age in men. In MMAS, LH and FSH increased longitudinally at 1.1% and 3.5% per year, respectively. [55]

The rise in FSH and LH with increasing age is consistent with the decline in testosterone, assuming normal operation of the feedback pathway by which low testosterone level signals the hypothalamic-pituitary axis to release FSH and LH.[68] This has been further shown in a publication from the European Male Aging Study (EMAS), a cross-sectional survey on 3,200 community-dwelling men aged 40–79 yr in eight European countries. [3] The EMAS data show that, consistent with the longitudinal findings of MMAS (Figure 1), the core hormonal pattern with increasing age is suggestive of incipient primary testicular dysfunction with maintained total testosterone and progressively blunted free testosterone associated with higher LH. They also observed that obesity impairs hypothalamic/pituitary function, which is consistent with the observation that plasma INLS3 levels decrease with increasing age but are not related to obesity and are largely independent of LH levels. [69] The implication of this is that aging effects on testicular function may be compensated by increases in LH, but since obesity impairs hypothalamic/pituitary function independent of age, there should be no compensatory mechanism.

b. Prevalence

Most elderly men have testosterone levels within the normal range, with prevalence estimates of "low" (e.g., < 300 ng/dL (10.4 nmol/L)) serum testosterone generally between 10% and 25%. [66, 70] More appropriate prevalence estimates also account for presence of clinical symptoms. Data from the MMAS indicate that the prevalence of symptomatic hypogonadism is between 6%–12%, [71] which is similar to prevalence in the Boston Area Community Health (BACH) Survey (5.6%), [52] suggesting that there could be up to 4.7 million men American men 30–79 years with symptomatic hypogonadism.

Wu and colleagues [51] estimated the prevalence of hypogonadism in the EMAS, defined as the presence of at least 3 sexual symptoms (loss of morning erections, low sexual desire, and erectile dysfunction), total testosterone < 320 ng/dL (11 nmol/L), and free testosterone < 64 pg/mL (220 pmol/L). Using this definition, the overall prevalence of hypogonadism in the EMAS study population was 2.1% and increased with age from 0.1% for men 40 to 49 years of age to 5.1% for those 70 to 79 years.

c. Secular Trend

We published [72] results from the MMAS showing the first evidence of an age-independent secular decline in testosterone levels over the past three decades. The analyses indicated a 1% per year decrease in total testosterone. Because the secular effect is age independent (Figure 3), its existence is evidence that time-variant factors other than the aging of the population are having an effect on the distribution of testosterone in the general population. This finding was robust to control for secular changes in some of these factors, e.g., the increased prevalence of obesity and reduced prevalence of smoking. These observations are

consistent with others showing population-level declines in sperm counts and increasing incidence rates of certain reproductive disorders in men. [73] The finding has been replicated in Denmark. [74]

d. Risk Factors

In addition to aging, modifiable lifestyle factors that are associated with testosterone levels, and therefore might have a role in modulating the decline with age, include tobacco and alcohol use, [75] caffeine intake, [76] social behavior mood, and severe psychosocial stress, [77] exercise, [56] obesity, [78] type 2 diabetes mellitus, [76] and the presence of obstructive sleep apnea and medication use. The MMAS has shown that comorbid conditions (e.g., diabetes, hypertension) and lifestyle influences may be as strongly associated with declining testosterone levels as is aging itself over the short- to mid-term. [58] This has implications for clinical practice. Diet and exercise have also shown influences on SHBG, thereby affecting the bioavailable pool of testosterone. [79]

e. Association of Low Testosterone with Outcomes

The importance of a decline in testosterone is wide-ranging because of its ubiquitous role in male physiology, regulating sexual function and mood, muscle mass, secondary sex characteristics, liver function, lipid regulation, bone formation, erythropoiesis, and immune function. [68] In recent years, there has been an increasing interest in the role low testosterone levels or testosterone therapy may have with regard to important health outcomes, including not only the role of testosterone in sexual function or libido, but also its involvement in bone and muscle, metabolic disease, and survival. This has been highlighted by the Institute of Medicine report on testosterone in aging men. [80] The National Institutes of Health have initiated a coordinated series of 4 short-term randomized clinical trials examining the efficacy of testosterone administration for physical, sexual, and cognitive function, as well as vitality. Results from that series of trials will be available in the next 5 years.

Chapters 8, 9, 10 of this issue discuss the role of androgens in bone, metabolic/cardiovascular disease, and prostate health, respectively. Thus, this section only briefly touches on these issues, with more in-depth discussion of other targets.

i. Sexual Function—Low testosterone levels are associated with reduced libido. [81] There is debate regarding the effect of testosterone on erectile function in mildly hypogonadal men, [82] with studies showing no effect [83] or subgroup effects.[84], [85] The confusion could stem from inadequate specification of androgen effects on sexual function. MMAS data show that the relationship between testosterone and ED is conditional on gonadotrophin level; testosterone is associated with ED only among men with high LH levels. [86] Some studies suggest that the testosterone concentration required for sexual activity is very low and that testosterone may affect sexual function only at markedly decreased testosterone levels [83] which is supported by a meta-analysis of 17 randomized placebo-controlled trials. [84] In summary, androgens exert weak (or even threshold) effects on erectile function, but probably play a more important role in libido. [87]

ii. Body Composition, Muscle Strength, Physical Function, and Falls—Studies consistently show a significant relationship between low testosterone levels and body composition. [88], [89] The mechanisms linking sex hormones with body composition are not completely understood, but possible biological mechanisms include the effects of testosterone on regulation of mesenchymal stem cell differentiation [90] and muscle protein synthesis [91] through androgen receptor-mediated pathways, [90] activation of inflammatory pathways [92], [93] or increases in cortisol. [22]

The relationship between aging, testosterone, muscle strength and overall physical function remains unclear. Low testosterone levels were not associated with 3-year declines in muscle strength or physical performance in two independent samples of older men. [94] In contrast, prospective data from the Framingham Offspring Study [95] showed an association between low free testosterone levels and a greater risk of incident or worsening mobility limitation in older men (Figure 4). In the Osteoporotic Fractures in Men (MrOS) cohort, [96] lower bioavailable testosterone levels were associated with increased fall risk, even with adjustment for physical performance, suggesting that the effect of testosterone on fall risk is mediated by other androgen actions (e.g., vision, coordination). At least one other study has related testosterone level to fall risk, [97] whereas another study did not. [98]

Interventional data show that testosterone administration improves body composition, including increasing lean mass and decreasing fat mass. [89] Despite its role in improving body composition, evidence in support of the concept that testosterone administration improves muscle strength and physical function is limited. In a meta-analysis that estimated the effect of testosterone therapy on men with hypogonadism, [99] the changes in muscle strength were inconsistent across trials. These findings have been replicated in recently-conducted dose-response studies [100, 101] and interventional trials. [102, 103] Bhasin has discussed limitations of physical function efficacy studies to date, which include the inclusion of men with low-normal testosterone levels or without functional limitations, failure of some studies to increase testosterone levels into the target range, the conceptual and practical difficulties in defining the indication for inclusion in a clinical trial, and the difficulty in measurement of functional endpoints. These limitations were addressed in a recently-published clinical trial of testosterone in elderly men with low testosterone levels (total testosterone 100–350 ng/dl or free testosterone <50 pg per ml) and limitations in mobility. [104] Despite a preliminary finding that testosterone improved leg-press and chest-press strength and ability to climb stairs while carrying a load, the trial was stopped because testosterone-treated men had 23 cardiovascular-related adverse events compared with only 5 such events in the placebo group.

iii. Bone metabolism, osteoporosis and fractures—In normal aging men, endogenous testosterone levels have been related to bone turnover markers, BMD, and hip structural geometry [105] although these findings are by no means universal. [67] Prevalence of osteoporosis is higher in men with low (12.2%) vs. normal (6.0%) testosterone levels. [106] The primary mechanism by which testosterone influences bone appears to be through aromatization to estradiol. [107] The limited data on endogenous testosterone levels and fracture are inconsistent, with low testosterone being associated with fractures in some studies [108] but not others. [109] The majority of studies of testosterone in association with bone outcomes have focused on BMD as assessed by dual x-ray absorptiometry (DXA). The limitations of DXA are known, with most fracture patients not meeting the WHO criterion for osteoporosis, [110] suggesting that other features of bone strength are relevant to fracture risk. Studies have shown that bone structural parameters (e.g., cortical and trabecular BMD, bone microarchitecture) are impaired in men with hypogonadism [111, 112] and that administration of exogenous testosterone may improve these parameters. [113]

Two separate meta-analyses of testosterone trials in older men have shown significantly greater increases in lumbar spine BMD in testosterone-treated men than in those receiving placebo. [89, 114] The improvement in lumbar spine BMD was approximately 8%. [114] In general, trials that used intramuscular testosterone showed greater increment in vertebral BMD than those using transdermal testosterone delivery systems. [114]

iv. Metabolic and Cardiovascular Disease Outcomes—Studies of induced hypogonadism have shown significant effects on glucose metabolism. Androgen deprivation

in men with prostate cancer has been associated with increased insulin resistance, worse glycemic control, and a significant increase in risk of incident diabetes. [115] Low serum testosterone is associated with the development of metabolic syndrome [116, 117] and type 2 diabetes. [118] SHBG has been inversely correlated with type 2 diabetes. [119, 120]

Improvement in insulin sensitivity with testosterone treatment has been reported in healthy [121] and diabetic [122] adult men. In studies conducted in men with central adiposity, testosterone has been shown to inhibit lipoprotein lipase activity in abdominal adipose tissue leading to decreased triglyceride uptake in central fat depots. [123]

Testosterone may have direct effects on vascular reactivity and cardiac muscle. [124, 125] Although cross-sectional studies have shown an inverse correlation between sex steroids and CVD, most longitudinal studies have not. [126] There is evidence that the beneficial effects (if any) of testosterone, at least at the level of the endothelium, is mediated by conversion of testosterone to estradiol. [126, 127]

Intervention studies of testosterone replacement on symptomatic coronary artery disease show some beneficial effects, [126, 128] but randomized controlled studies are relatively rare. A recent meta-analysis of incident cardiovascular events from 6 clinical trials of testosterone treatment showed a pooled odds ratio of 1.82 (95% CI 0.78, 4.23), indicating a non-significant increased risk among men on testosterone. The authors highlighted the heterogeneity of results across studies and the small number of events (14 events among men who received testosterone and 7 among placebo). [129]

iv. Cognitive Function, Mood, and Quality of Life—Studies have also shown associations between androgens and quality of life outcomes such as cognitive function [130] and depressed mood or dysthmic disorder [62, 131]. While the efficacy data are relatively weak, in some studies testosterone treatment significantly improved energy, mood, and subjective well-being. [132, 133]

v. Mortality—Men with low testosterone levels are more likely to die prematurely, as reported in most [134–147] but not all [148–153] studies. It is not clear from these observational studies whether testosterone represents a causative factor or merely a risk marker, [154] although nearly every positive study reported that in sensitivity analyses excluding early deaths, results were fundamentally unchanged.

VI. Treatment

In men with classical hypogonadism, treatment is clearly indicated and men should be monitored appropriately. See Chapter X (Bhasin). There is considerable debate about the appropriateness of testosterone in aging men. The long-term safety or efficacy of testosterone replacement in aging men with late-onset hypogonadism has not been established, but as noted above, small-scale clinical studies suggest that testosterone may have beneficial effects.

VII. Practice Points

- On average there is a small (1–2%) annual decrease in total testosterone levels with aging but the age-related change varies between individuals.

- Factors related to disease, medication use, lifestyle behaviors, environmental exposures and psychosocial stress may be as important as age per se in leading to a testosterone declines, which implies that alternatives to testosterone therapy may be viable treatment options.

- The diagnosis of hypogonadism must be based on at least two unequivocally low levels of testosterone on morning blood samples together with compatible symptoms.

- Significant hypogonadism may occur at any age, and treatment with testosterone may be beneficial, but requires careful monitoring.

VIII. Research Needs

- Assessment of the effects of aging on estrogen is required using well-validated assays with the requisite sensitivity.

- Additional longitudinal studies to determine the interrelationships between sex steroid levels and physical and psychological function, disease, lifestyle factors, medication use, environmental factors, and psychosocial stress.

- The factors underlying a possible secular decline in testosterone.

- Appropriately constructed and validated questionnaires to empirically assess androgen action.

- Understanding of the relationship between various sex steroids and specific symptoms attributable to hormonal deficiency in relation to age and health status.

- Detailed study of the molecular physiology of the regulation of sex steroid production, action, and metabolism, with aging in relation to health outcomes.

- The most appropriate circumstances for treatment with testosterone and quantifiable risks and benefits in each case.

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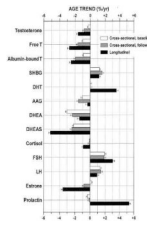
Figure 1.
Cross-sectional and 8-year longitudinal trends of testosterone, other androgens and metabolites, and related hormones in middle-aged men. Abbreviations: AAG, androstanediol glucuronide; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; LH, Luteinizing hormone; T, testosterone. Source: MMAS, Feldman et al, J Clin Endocrinol Metab 2002; 87(2):589–598. [55] Copyright 2002, The Endocrine Society. Used with permission.
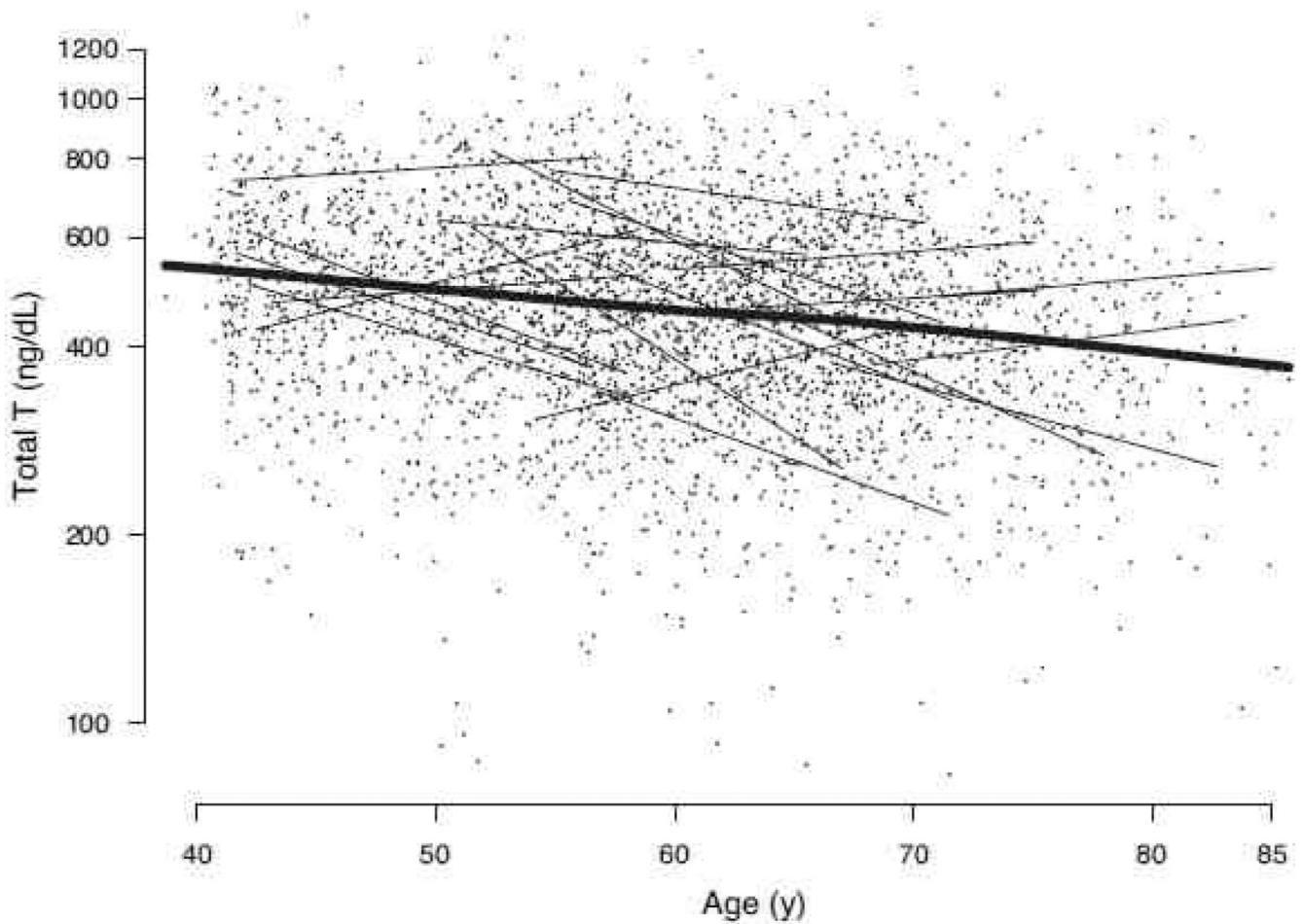
Figure 2.
Total testosterone vs. age (natural log scale for all observations). Linear trajectories for 20 randomly chosen subjects are plotted (thin lines), demonstrating the substantial inter-subject variation in testosterone trends over time. A nonparametric, locally weighted regression smooth (thick line) depicts the linear decline in log testosterone values with age over all observations, which is generally outstripped by within-subject longitudinal decline. To convert total testosterone from nanograms per deciliter to nanomoles per liter, multiply by 0.0347. Source: MMAS, Travison et al, J Clin Endocrinol Metab 2007; 92(2):549– 555. [58] Copyright 2007, The Endocrine Society. Used with permission.
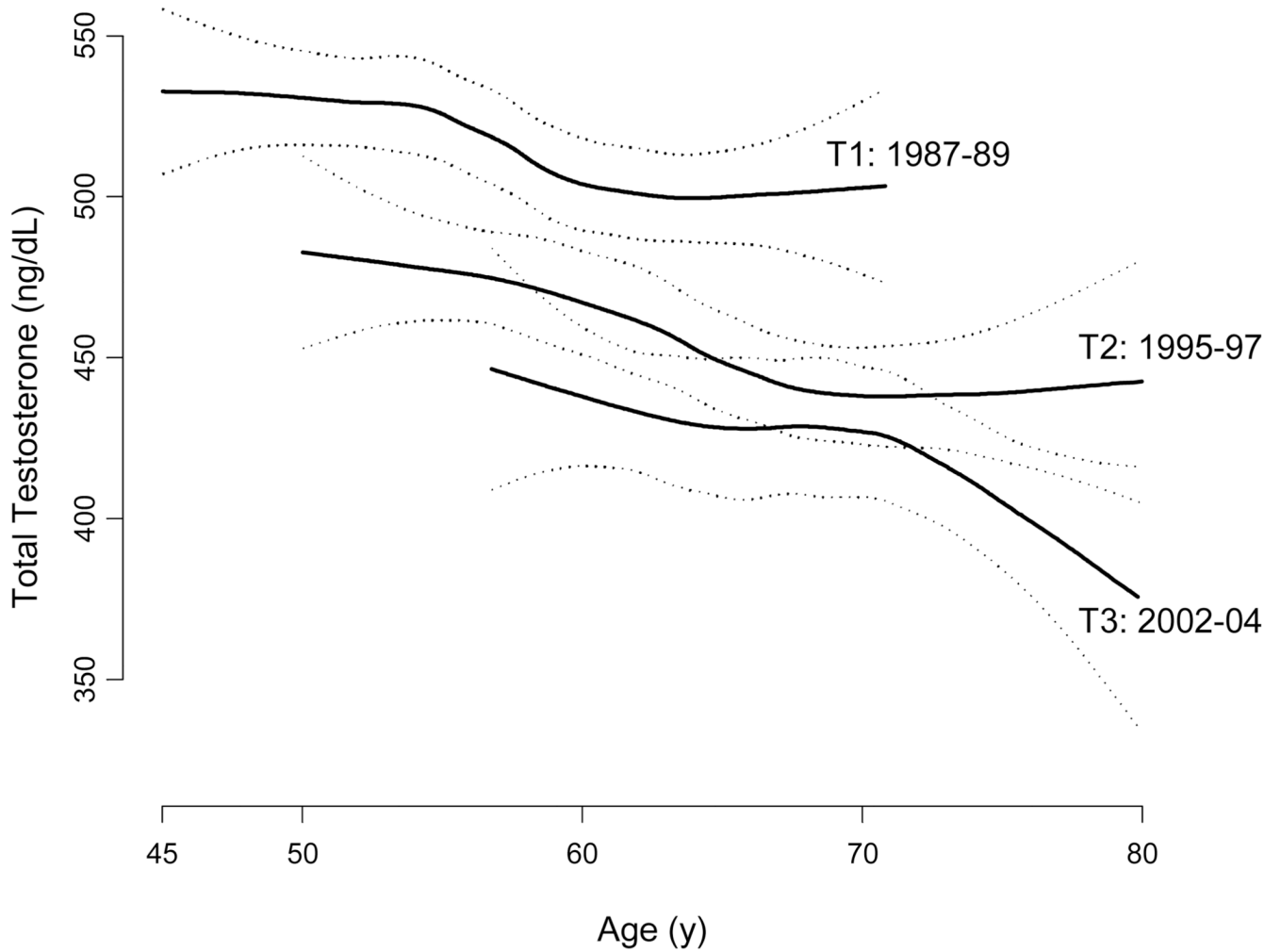
Figure 3.
Crude mean total testosterone concentrations, by MMAS study wave (T1, T2, T3), with confidence bands (dotted lines). Estimates are obtained from a generalized additive model with a lowess smoothing term. Source: MMAS, Travison et al., J Clin Endocrinol Metab 2007; 92(1):196–202. [72] Copyright 2007, The Endocrine Society. Used with permission.
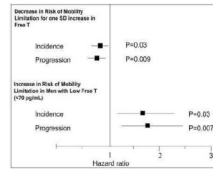
Figure 4.
Longitudinal analyses of incident mobility limitation. Hazard ratios are for 1 SD increase in hormone levels, adjusting for age, BMI, smoking, and comorbidities (cardiovascular disease and cancer). As shown in the upper panel, each SD increase in free testosterone level was associated with 22% (OR 0.78; 95% CI 0.62–0.97) decrease in the risk of developing mobility limitation and 25% decrease n the risk of worsening mobility limitation (progression). The lower panel shows the association of low free testosterone (<2.5th percentile (<70.0 pg/ml)) at baseline examination 7 with the risk of developing (incident) mobility limitation at examination 8 or of reporting worsening mobility limitation (progression) at examination 8. The squares indicate point estimates for hormones, and the lines indicate 95% CI. Source: Framingham Offspring Study, Krasnoff et al., J Clin Endocrinol Metab 2010. [95] Copyright 2010, The Endocrine Society. Used with permission.