Testosterone and Depression in Aging Men

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In men, testosterone secretion affects neurobehavioral functions such as sexual arousal, aggression, emotional tone, and cognition. Beginning at approximately age 50, men secrete progressively lower amounts of testosterone; about 20% of men over age 60 have lower-than-normal levels. The psychiatric sequelae are poorly understood, yet there is evidence of an association with depressive symptoms. The authors reviewed 1) the physiology of the hypothalamic-pituitary-gonadal axis and its changes with age in men; and 2) the evidence linking testosterone level and major depression in men. Data on this relationship are derived from two types of studies: observational studies comparing testosterone levels and secretory patterns in depressed and nondepressed men, and treatment studies using exogenous androgens for male depression. The data suggest that some depressed older men may have state-dependent low testosterone levels and that some depressed men may improve with androgen treatment.
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Testosterone secretion in adult men has multiple determinants, and this androgen has actions that are neurobehavioral, somatic, and metabolic.[1] Central nervous system (CNS) effects include organizing and activating actions on male sexual arousal and behavior and some influence on energy and mood.[2] Moreover, in animal models, testosterone plays a role in regulating some male social behaviors, particularly those related to male–male competition, dominance, and submission. Because of such effects, the relationship between testosterone secretion and major depression and the use of androgens to treat male depression or male "climacteric," have long been issues of speculation and anecdotal reports. Yet very few studies have systematically addressed these issues, and those doing so have produced inconsistent results. Furthermore, in aging men, specifically, among whom the prevalence of clinically significant hypogonadism may be 20%,[3] there have been no published studies addressing the psychiatric implications of this endocrinologic hypofunction.

In this article, we will first describe the physiology of testosterone secretion in men, with a focus on the changes that occur with aging, and the complicated interaction between testosterone and behavior. Then we will explore the following clinically relevant questions regarding the relationship between testosterone and depressive illness in men:

1. What is the relationship between testosterone level and male depressive illness? Specifically, do men who have a low testosterone level have an increased risk of developing major depression? Do

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men who are depressed develop a state-dependent impairment in testosterone secretion?

2. What is the relationship between testosterone administration and male depressive illness? a) Does testosterone replacement (i.e., for men with below-normal levels) lead to improvement in depressive symptoms or to remission of major depressive disorder? b) Does administration of testosterone to depressed men who have normal testosterone levels lead to remission of the depressive illness?

TESTOSTERONE PHYSIOLOGY

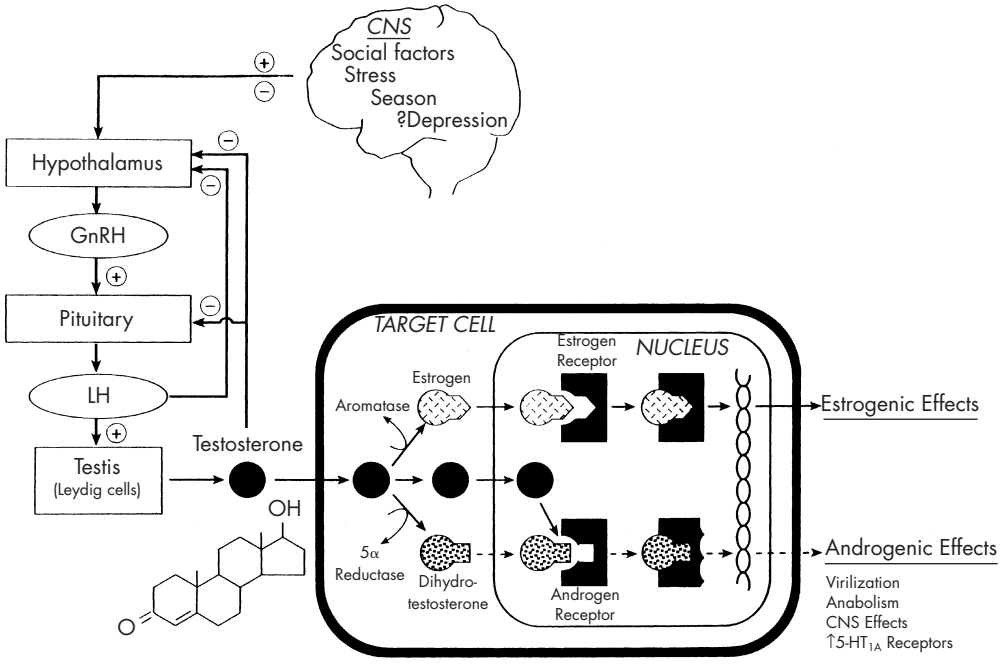
Secretion

The testes and adrenals secrete several male sex hormones, called androgens. All are steroid hormones—that is, derived from cholesterol and containing a basic skeleton of four fused carbon rings (Figure 1). Testosterone is the primary androgen—by far the most abundant and most potent. It binds to the intranuclear androgen receptor, which is distributed widely throughout the body and the central nervous system (CNS), including limbic and cortical tissue.[4,5] Dehydroepiandrosterone (DHEA) is an adrenal androgen that may play a protective role in many aspects of cellular functioning (particularly age-related deficits),[6] although it has a relatively minute amount of male androgenic activity.

Neural activity in the medial basal hypothalamus controlled by adrenergic, dopaminergic, serotonergic, and endorphinergic inputs—and the surrounding hormonal milieu—stimulates the pulsatile release of gonadotropin-releasing hormone (GnRH), a decapeptide, into the hypothalamic-hypophysial portal system. GnRH promotes anterior-pituitary release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the interstitial cells of Leydig in the testes to synthesize and secrete testosterone. Secretion occurs in pulsatile bursts, about six per day, with a morning peak and an early-evening trough; in total, approximately 7 mg of testosterone is secreted daily. Secretion is regulated through a negative feedback on the hypothalamus and pituitary.[1,4,5]

In the bloodstream, testosterone is about 98% protein-bound: of this, just over half is weakly bound to albumin, and the remainder is tightly bound to sex-hormone–binding globulin (SHBG).[1,4,5] SHBG, a β-globulin produced in the testes and the liver, consists

FIGURE 1. Male hypothalamic-pituitary-gonadal axis physiology



Note: CNS = central nervous system; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.

of different protein subunits, and one androgen binding site. Circulating free testosterone, the fraction that dissociates readily from albumin, and the fraction that dissociates less readily from SHBG (i.e., through molecular configuration changes in the capillaries), all diffuse into the target cell and bind to the androgen receptor.[4,5] This receptor is a typical steroid receptor: it contains an N-terminal domain, a DNA-binding domain, and a hormone-binding domain.[1,4,5] The steroid-receptor complex binds to specific sequences of genomic DNA, and thereby influences the production of messenger RNA, which modulates protein synthesis in the cell.[4,5]

In target cells, testosterone is converted to two active metabolites: dihydrotestosterone (DHT) and estradiol (E_2). There is tissue variability in the concentration of the cytoplasmic enzymes required for this conversion (5α-reductase and aromatase, respectively) and differential tissue sensitivity to each of these metabolites. Both testosterone and DHT bind to the androgen receptor; some androgen-responsive genes respond preferentially to intracellular DHT, making it the more potent androgen. For example, DHT is required for testosterone's effects on external genitalia and accessory sex glands; 5α-reductase enzymes are, therefore, abundant in reproductive tissues and skin. Estradiol binds to the estrogen receptor, and is required for some of testosterone's CNS and metabolic effects. Aromatase is most abundant in CNS, liver, and adipose tissue.[1,4,5]

Psychological, social, seasonal, and biological factors affect testosterone secretion transiently: levels are elevated at times of decisive victory in competition, when social status is enhanced, during REM sleep, during cigarette smoking, after sexual activity, after exercise, and during the autumn. They are decreased at times of defeat or submission, during physical or emotional stress, during heavy alcohol use, and in the spring.[7–9] Testosterone level typically reverts to baseline soon after such stimuli, although there is some evidence from nonhuman primates that an aggression-induced low testosterone level can persist for weeks.[10] It is unknown whether a chronic or prolonged stimulus (such as the stress occurring during a major depressive episode) can lead to a new testosterone setpoint.

Testosterone Levels Through Life

Testosterone secretion varies through life. Prenatally, the genital ridge, and then testes, are stimulated by chorionic gonadotropin from the placenta to produce testosterone. Such secretion begins about the seventh week of embryonic life, peaks from Weeks 9–14, and continues until the first few weeks after birth.[4] Then, there is very little testosterone secretion until about age 10, when nocturnal, pulsatile LH secretion begins. Between ages 11 and 14, testosterone secretion increases until adult male levels are achieved. It peaks at age 20, and slowly declines thereafter, although not significantly until about age 50.[3–5,8]

Free and total testosterone concentration are generally measured from serum or salivary samples by use of radioimmunoassay (RIA). In young-adult men, evening testosterone levels are about 25% lower than morning levels; and the reliability (*r*) of testosterone measurements is 0.64 from day to day, and 0.50 over 1–4 years;[11,12] among middle-aged men, the reliability is greater because of decreased diurnal and seasonal variability.[3,13] For example, Vermeulen and Verdonck[14] measured morning plasma-testosterone level in 169 middle-aged and elderly men on eight occasions over 1 year; correlation between the first sample and the mean of the next seven samples was 0.85.

The father–son heritability of total testosterone concentration in adulthood is about 30%.[11,12] Large epidemiologic studies have found body mass index and smoking status to be consistent predictors of testosterone level: obese men have relatively lower levels, smokers have higher levels.[3] The other known positive predictor of testosterone level is SHBG level. SHBG level increases with age and smoking, and decreases with obesity. The net age effect, as determined from large, cross-sectional studies is that 1) through adult life, free testosterone declines at a rate of 1.2% per year; and 2) total testosterone remains steady until about age 50, and then declines approximately 0.4%–0.8% per year (Figure 2).[15,16]

In a comprehensive meta-analysis, Gray and colleagues[15] used 44 studies that met stringent criteria for reporting the relationship between mean testosterone level and age. Mean testosterone level for adult men was 479(±115) ng/dl. They demonstrated that the age-related decline in testosterone level is particularly pronounced among healthier men, compared with men who have any illness: healthier men's testosterone level starts higher and falls faster. In a multiple-regression model, the best predictors of both testosterone level and the slope of the age-related decline were good general health status and morning serum sampling (both of which predicted higher levels and steeper slopes).[15]

The decreasing testosterone levels in older men is due primarily to a reduction of Leydig cell functioning: testosterone synthesis is impaired, responsiveness to LH is reduced, and the circadian early-morning peak is blunted.[4,5,13] Also, end-organ responsiveness may change with age. For example, the penis apparently becomes less responsive to testosterone, and the prostate becomes more responsive.[4,5]

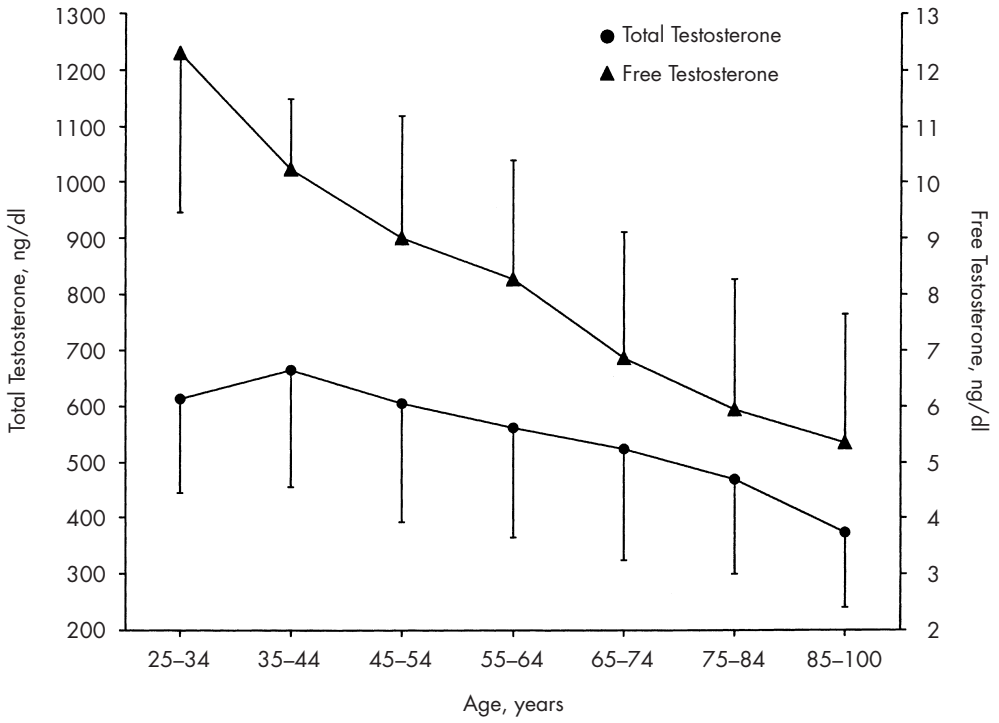
With regard to clinical significance, it is not known whether the lower limit of "normal" testosterone level should be fixed, or should vary with age. Symptomatic hypogonadism apparently develops only when the total testosterone level drops below a certain threshold, typically set between 200 and 300 ng/dl. This threshold has generally been used and defined in order to assess for HPG dysfunction in relatively young men. For example, young men with testosterone levels below 250 ng/dl often have symptoms of sexual dysfunction, such as impaired nocturnal erections and low libido.[17] In contrast, standards for determining the relevance of decreasing testosterone levels among healthy aging men—that is, "normative" gonadal hypofunction—may need to account for other age-related phenomena, such as changes in end-organ responsiveness and changes in HPG secretory patterns.[13,18] Particularly regarding the psychiatric sequelae of gonadal hypofunction, it is not known where clinical significance begins. Thus, determination of an absolute lower threshold (or threshold relative to baseline) with respect to psychiatric impairment is an open question.

TESTOSTERONE ACTIVITY

Metabolic Effects

The metabolic effects of testosterone are varied. During the embryonal stage, testosterone is responsible for the growth of the penis and scrotum, development of the prostate and seminal vesicles, descent of the testes, and suppression of the development of female genitalia.[1,4,5] The testosterone surge of puberty causes the

FIGURE 2. Serum testosterone levels in 250 healthy men, by age-group



Note: There were 21–48 subjects per age-group. Subjects were 250 men living in an industrial area who were nonsmokers, nonobese (i.e., BMI = 20–26), not taking medication or excessive alcohol, and in good health by clinical and laboratory exam. Testosterone levels were determined by radioimmunoassay from blood samples obtained between 8 A.M. and 10 A.M. Data used by permission from Vermeulen and colleagues.[16]

genitalia to enlarge about eightfold, promotes the development and maintenance of secondary sexual characteristics, and supports anabolic activity. Testosterone affects hair distribution (including baldness); stimulates prostatic secretion and growth; masculinizes the larynx and the skin (e.g., promoting thickening, increased melanin, and increased sebaceous secretion); promotes protein anabolism, leading to muscular development, bone growth, calcium retention, and an increase in basal metabolic rate; and increases red blood cell production and hemoglobin synthesis.[1,4,5] Exogenous testosterone, in addition to these effects, elevates serum prostate-specific antigen (PSA) and reduces HDL cholesterol.[19]

Neurobehavioral Effects

Perinatal androgens. It has been established in many mammalian species, that testosterone, acting during a brief developmental critical period, permanently alters brain structure and function.[7,20] Such "organizing" effects lead to behavioral predispositions in the setting of later reexposure to testosterone. This has been demonstrated most clearly in rodents. For example, perinatal exposure of a female rat to testosterone leads to masculinized sexual, aggressive, and exploratory behavior postpubertally (particularly when activated by testosterone), and loss of the female pattern of gonadotropin secretion.[7,21] Perinatal castration of male rats leads to impaired inter-male aggression when treated postpubertally with testosterone; this impairment is prevented by perinatal testosterone replacement.[7,20] Some evidence suggests that perinatal testosterone organizes later serotonergic transmission in limbic and striatal areas of the brain.[22]

The evidence for such perinatal effects among primates is less dramatic. In nonhuman primates, although male fetuses do secrete testosterone, there is only limited evidence that sex hormones organize later behavioral potential.[7] In humans, prenatal exposure of female fetuses to excessive androgens (as a consequence of congenital adrenal hyperplasia) is associated with the development of male-like play behavior during childhood, male-like sexual imagery and preferences in adulthood, and more aggressive behavior compared with female relatives.[23,24]

Postpubertal androgens. In most mammals, males are more socially aggressive than females.[21] The ancient practice of castration as a way to control the sexual and aggressive behavior of animals (including humans) reflects the long-held recognition that there is a relationship between the male gonads and behavior. The active agent in this relationship is clearly testosterone, and a strong relationship between testosterone and behavior has been found in a wide range of vertebrate species, particularly birds and mammals.[2,7,10,21] Among mammals, there is strong evidence that testosterone regulates the sexual, aggressive, and social behaviors of rodents and ungulates (e.g., cows and goats).[2,7,21] The relationship between testosterone secretion and these behaviors among primates (including humans) is less direct, and more complicated by social factors and learning.[2,7,10,21]

Among primates, testosterone secretion is powerfully stimulated or suppressed in response to the social/sexual context. In isolated groups of male talapoin monkeys, testosterone levels do not discriminate male status or aggression. However, if receptive females are introduced, the dominant male increases testosterone secretion until his is the highest. Subordinate males can develop a testosterone "boost" in the presence of a receptive female only in the absence of other males.[2,7,10,21] Dominant olive baboons increase testosterone secretion when stressed, whereas submissive baboons decrease testosterone secretion.[7,21] Administration of exogenous testosterone to cynomolgus monkeys leads to increased dominant behaviors and elevated heart rate among dominant males; it has the opposite effect on submissive males.[17] Finally, among rhesus monkeys, testosterone level has been found to directly correlate with aggressive and dominant behaviors in some,[10,25] but not all studies.[21] Notably, it has been shown that the changes in testosterone level that follow aggressive experiences in rhesus monkeys can last for weeks after the event.[7,10,21] In summary, among nonhuman primates, testosterone appears to play an important yet highly variable role in sexual, social, and aggressive behaviors.[2,7,10,21,25]

In human males, testosterone has been associated with sexual activity and libido, antisocial behavior, dominance, sensation-seeking, educational and occupational achievement, marital discord and divorce, and the experiences of success and failure.[2,7,12,21] Such associations may be mediated through androgenic effects on sexual arousal, emotionality, cognition, and aggression. In multiple large cohorts of young men (particularly in college, in jail, and in the military), Dabbs and col-

leagues[26] have demonstrated that low testosterone level is associated with intellectually oriented, friendly, docile behavior, whereas high testosterone level is associated with what they have termed "rambunctious" behavior—that is, behavior that is impulsive, aggressive, gregarious, and generally unfriendly (e.g., they report that "high testosterone men" rarely smile socially).[11,12,26]

Testosterone level decreases in response to stress and to failure; and increases after victory or a rise in social status.[7] These relationships have been demonstrated in studies of the change in testosterone levels among male tennis players in competition, of men in Officer Candidate School, and men during medical internship.[7] Some studies suggest that increased testosterone levels in young males is associated with low frustration tolerance, irritability, and impatience[27]—factors that may be markers of affective tone. Again, causal inferences cannot be drawn from these studies: testosterone secretion is both a cause and an effect of social interactions, and should be appreciated as part of a system rather than as a dependent or independent variable.[2,21] For example, the change in testosterone level after competition is altered by previous success in competition, dominance relationships, and perception of victory.[2] Affect and cognition may be the mediators of such interactions, although these aspects have been the least investigated.

The best-established testosterone–behavior relationship in human males is with sexual function: testosterone replacement in hypogonadal men leads to a dramatic increase in sexual desire and sexual activity;[28] suppression of testosterone secretion in eugonadal men leads to reduced sexual desire and activity, and a decrease in spontaneous erections.[29] There appears to be a threshold (which varies from person to person) below which sexual function is impaired.[30] Even so, some data suggest that testosterone administration to men who have clearly normal testosterone levels leads to an increased arousability and sexual interest,[28] although this finding is contradicted by other studies.[31]

Numerous correlational studies have examined the relationship between plasma-testosterone level and measures of aggression in human males.[7,12,21] Interpretation of these studies is limited by the known increase in testosterone that occurs as a result of aggressive encounters.[7,12,21] Furthermore, these studies are not easily summarized because they have used different measures of aggression—for example, some focus on actual behavior, others on aggressive traits—and different sample populations. Some have reported positive correlations between testosterone level and some aspects of aggression, especially among subjects selected on the basis of violent behavior (i.e., male prisoners). Others have not found any correlation between testosterone level and multiple aspects of aggression. In a comprehensive review of the topic, Archer[21] concludes that: 1) consistent evidence suggests that violent male offenders have significantly higher testosterone levels than less violent individuals; and 2) there is a small but statistically significant correlation between testosterone level and hostility in a variety of male populations, which is stronger when aggressiveness is rated by others in the person's social environment vs. ratings by self-assessment.

In summary, the testosterone–behavior relationship is complicated and modulated by experience. In humans, testosterone may act by setting affective "tone" rather than by directing specific behaviors. Testosterone secretion and action are part of a neurochemical context that determines the emotional, cognitive, and behavioral effects of a wide range of neuromodulators.[2] Such a context may have implications for the study and manipulation of affective states or syndromes.

Aging Men

It has been noted that the effects of testosterone deficiency are similar to those of the aging process itself: decreased musculoskeletal mass, increased adipose deposition, decreased hematocrit, decreased facial hair growth, as well as decreased appetite, decreased libido, and impaired memory.[16,18,19] Testosterone replacement consistently reverses these sequelae in younger hypogonadal men (i.e., ages 20–60): body weight, fat-free muscle mass, muscle size, and strength increase; continued bone loss is prevented; sexual function and secondary sex characteristics (e.g., facial hair) are restored and maintained; and hematocrit increases.[1,19,28,32–34] The application of a testosterone replacement strategy for older men with low or low normal testosterone levels is thought by some investigators to be especially promising for reversing the aging effects on bones and muscle mass, as well as for enhancing mood, cognition, and libido.[16,18,19,32] In fact, some anecdotal reports of testosterone replacement in hypogonadal older men suggest that such treatment leads to improved mood, energy, libido, and sense of well-being; better sleep and appetite; and decreased frailty, with gains in muscle

strength and lean body mass.[16,18,19,32] Yet there are only limited controlled data on the effects of testosterone replacement in men older than 60, and none that address psychiatric symptoms in this age-group.

Despite the completion of numerous controlled testosterone replacement trials over the past three decades, none have described the prevalence of pre-replacement psychiatric illness followed by systematic monitoring of psychiatric symptoms during testosterone replacement. It is unlikely that all hypogonadal men develop major depression, because there is no apparent increase in major depression among epidemiologic cohorts of aging men that parallels the increase in hypogonadism.[35] Yet, the suggestion that testosterone replacement has salutary effects on specific components of the major depressive syndrome, such as mood, appetite, and cognition, may be of relevance to the study and treatment of depression in aging men. Specifically, it is conceivable that comorbid depression in the setting of the "normative" hypogonadism of aging may remit or improve after testosterone replacement therapy or that a "hypogonadal depression" may respond less well to conventional antidepressant treatment if testosterone is not replaced. Such possibilities are entirely speculative because there are no specific studies addressing testosterone replacement and psychiatric symptoms in older depressed or nondepressed men.

TESTOSTERONE AND DEPRESSIVE ILLNESS IN MEN

Overview

Research into the relationship between testosterone and major depression is complicated by diagnostic and etiologic uncertainties. For example, in the setting of comorbid low testosterone level and depressive illness, it is not known whether hypogonadism is primary, depression is primary, or the conditions are unrelated. Despite these difficulties, a growing body of evidence suggests some association between testosterone level and male depression. This evidence comes from studies of: 1) the relationship of testosterone level to depressive symptoms and depressive illness; and 2) the antidepressant actions of androgen administration.

Testosterone Level and Depression in Men

A. Hypogonadism. Hypogonadal men commonly complain of loss of libido, dysphoria, fatigue, irritability, and appetite loss.[2,7,28,30] These symptoms are generally reduced after testosterone replacement.[32–34] Although such apparent psychiatric sequelae of hypogonadism overlap with signs and symptoms of major depression, it is not known what proportion of hypogonadal men meet criteria for major depression, and when they do, which dysfunction is primary. Furthermore, it is unclear what testosterone level might be associated with psychiatric symptoms.

There are only two epidemiologic studies that assessed both testosterone level and depressive symptoms: the Massachusetts Male Aging Study (MMAS)[36] and the Veterans' Experience Study (VES).[37,38] The MMAS was a population-based survey of 1,709 men age 40–70 that included monitoring of morning testosterone level and a self-report depression instrument, the Center for Epidemiologic Studies Depression Scale (CES-D). There was no correlation between CES-D–determined "depression" (using a cutoff of 16) and testosterone level (odds ratio [OR] 0.9; 95% confidence interval [CI] = 0.75–1.1).[36] Yet, because fewer than half of those identified by this CES-D cutoff likely had major depression,[39] it is not clear whether a different cutoff or a more accurate diagnosis would have demonstrated a relationship between testosterone level and major depression. Moreover, the cohort of men with a low testosterone level was not analyzed specifically to determine whether they were more likely to have depressive symptoms.

The VES included a representative sample of 5,236 Vietnam-era veterans (median age, 37 years; 95% age range: 33–42), and included: multiple morning testosterone samples; a structured interview for depression, the Diagnostic Interview Schedule (DIS); and a self-report personality inventory, the MMPI.[37,38] Testosterone level was correlated most strongly with antisocial personality, substance abuse, and gambling ($r = 0.13$–0.18, $P < 0.001$); and very weakly with depression, mania, obsessionality, and anxiety ($r = 0.03$–0.05, $P < 0.01$).[37] The relationship with markers of deviance was strongest among men of low socioeconomic status. Notably, whereas the diagnosis of depression from the DIS was positively associated with testosterone level ($r = 0.04$; $P < 0.01$), in the MMPI clinical scale, the affect "depression" was negatively (and nonsignificantly) associated with testosterone level ($r = -0.02$).[37,38] Such low correlations are unlikely to be clinically meaningful. And again, analysis of the cohort of men with a testosterone level below a certain threshold might have been

informative regarding the possibility of a "hypogonadal" psychiatric syndrome.

Focusing specifically on men who present clinically with low testosterone level, Woodman and Williams[40] reviewed the records of 173 hypogonadal men being treated in an endocrinology clinic. They found that 39% were being treated with medication for a psychiatric illness (although the specific medications and illnesses were not reported). This is far in excess of what would be expected from the general, or even medically ill, male population, and suggests that psychiatric sequelae of hypogonadism may be substantial. Clearly there is a need for a further descriptive psychiatric epidemiology of male hypogonadism.

B. Major depression. Neuroendocrine studies of the HPG axis among men with well-diagnosed major depression have been few and contradictory. Most psychiatric investigators have focused on basal testosterone level alone. Yet, basal testosterone level is a limited indicator of HPG functioning: LH level and pattern of secretion, testosterone pulse amplitude and frequency, conversion to active metabolites, and end-organ responsivity may all play some role in affective symptoms. None of these other areas has been extensively studied by psychiatric researchers, although there is little evidence of impaired gonadotropin secretion among depressed men.[41–43]

In general, two types of observational studies have been done: studies comparing the mean testosterone levels of groups of depressed men with those of nondepressed control subjects (Table 1) and studies comparing the mean testosterone level of cohorts of depressed men during acute illness to the mean testosterone level after remission (Table 2). Findings from such studies have been inconsistent. In comparing cohorts of depressed men with nondepressed, age-matched control subjects, some investigators report that depressed men have lower mean testosterone levels,[44,45] although most report that there is no difference.[42,46–49] Multiple studies have reported a negative correlation between testosterone level and age among depressed men but not among age-matched control subjects, suggesting blunted secretion among older depressed men.[46,47] Isolated studies have demonstrated a negative correlation between testosterone level and severity of depressive symptoms,[48,50,51] melancholia,[47] anxiety,[48] and sexual activity;[47] these relationships, however, were not found in other studies.[42,44–46,49] Finally, studies that determined testosterone level during acute illness compared with level after remission have also been inconsistent: of five studies (*N*s of 6–15), acute mean testosterone levels were lower in three, higher in one, and no different in one.[45,49,52–54]

The discrepancies between the various studies that have assessed testosterone levels in depressed men may be caused by the diurnal, seasonal, situational, and age-related variability in testosterone secretion; generally small sample sizes; and/or heterogeneity in depressed samples. The earliest studies that included well-diagnosed unipolar depressed men used one or two serum samples, usually obtained in the morning, to determine basal testosterone concentration. In the first such study, Sachar and colleagues[52] determined testosterone levels of a heterogeneous group of 15 unipolar and bipolar depressed men (mean age, 63 years) before and after treatment with ECT. They found that mean testosterone level in the untreated phase was in the mid-normal range (550 ng/dl), and did not change significantly with remission.[52]

Levitt and Joffe[46] measured afternoon testosterone levels in 12 men with RDC-diagnosed major depression and 12 age-matched control subjects. They found that there was no difference in testosterone levels between these groups. However, although there was no correlation between testosterone levels and Ham-D scores in the depressed cohort, there was a significant negative correlation between testosterone level and age ($r = -0.70$, $P < 0.01$) that was not found in the control group.

The authors suggest that depressed men may be more sensitive (i.e., symptomatic) to the age-related decline in testosterone level.[46] Because it is known that testosterone level declines with age, it is unusual that in three studies this relationship has been demonstrated only among depressed men ($r = -0.70$, -0.70, and -0.40) and not among age-matched control subjects ($r = -0.10$ in one study[47] and not reported in others). Such evidence suggests that blunted testosterone secretion might be demonstrable among older depressed (compared with nondepressed) men.

Vogel et al.[44] compared testosterone levels of 27 men with unipolar depression (mean age, 39.5 years) and 13 nondepressed control subjects (mean age, 38.0 years). Mean testosterone level was 30% lower in the depressed cohort (448 ng/dl vs. 682 ng/dl, respectively, $P < 0.01$). Yesavage and colleagues[50] obtained testosterone levels on three consecutive mornings from 18 men

TABLE 1. Testosterone level (*T*) at baseline in men with major depression and age-matched control subjects

Reference	Depression Diagnosis	*n*	Mean Age ± SD, years	Sampling Time (# samples)	Mean *T* (SE), ng/dl	Comment
Levitt[46]	MDD	12	31.9 ± 8.0	1–5 P.M. (1)	440 (115)	*T* correlated with age ($r = -0.70$; $P<0.01$), not with severity
	Control	12	31.4 ± 6.0	1–5 P.M. (1)	489 (138)	*T* not correlated with age (*r* not reported)
Vogel[44]	MDD	27	39.5 ± 7.8	9 A.M. (1)	448 (191)*	
	Control	13	38.0 ± 8.6	9 A.M. (1)	682 (272)	
Yesavage[50]	MDD	18	NR	8 A.M. (3)	NR	*T* correlated with Ham-D ($r = -0.56$) and age ($r = -0.40$)
Rubin[47]	MDD	16	39.5 ± 8.0	3–7 A.M. (8)	590 (median)	*T* correlated with DSM-III melancholia ($r = 0.58$) and age ($r = -0.70$); not correlated with Ham-D or BDI items
	Control	16	31.9 ± 8.0	3–7 A.M. (8)	620 (median)	
Amsterdam[42]	Unipolar depressed	12	37.2 ± 3.5	8–9 A.M. (1)	736 (53)	
	Bipolar depressed	11	35.5 ± 3.5	8–9 A.M. (1)	609 (71)	
	Control	18	33.2 ± 2.8	8–9 A.M. (1)	629 (71)	
Unden[49]	MDD	14	46.9 ± 3.1	8 A.M. (2)	581 (63)	
	Control	9	37.4 ± 4.0	8 A.M. (2)	615 (81)	
Wexler[51]	Affective disorder[a] CLV+	9	42	9 A.M. (1)	297 (41)*	*T* negatively correlated with BPRS sum ($r = -0.67$); thinking disorder, hostile-suspiciousness, activation
	Affective disorder[a] CLV−	9	42	9 A.M. (1)	450 (32)	*T* positively correlated with BPRS sum ($r = 0.64$); thinking disorder, hostile-suspiciousness, activation
Rupprecht[45]	MDD melancholic	6	42 ± 15.4	7 A.M., 4 P.M. (2)	NR	Mean *T* level lower than control ($P<0.07$); *r* not reported
	Control	20	37 ± 9.7	7 A.M., 4 P.M. (2)	NR	

Note: SD = standard deviation; SE = standard error of mean; MDD = major depressive disorder; CLV is a combined laterality variable constructed to measure right-ear advantage on word compared with nonsense dichotic tests, which had been validated as a reliable marker of information-processing.

[a]includes unipolar, bipolar, and schizoaffiective.

*$P<0.01$.

TABLE 2. Testosterone levels (*T*) in men with major depression during acute illness and after remission

Reference	Depression Diagnosis	*N*	Mean Age ± SD, years	Sampling Time (# Samples)	T-acute (± SD), ng/dl	T-remission (± SD), ng/dl	Comment
Sachar[52]	unipolar, bipolar	15	63.0 (range: 46–78)	8 A.M. (1)	550	500	severe, inpatient, some psychotic; 13 received ECT; *T* correlated with severity ($r = -0.18$)
Steiger[53]	MDD	12	46.4 ± 11.3	11 P.M.–3 A.M. (5)	371 (128)	456 (141)*	mean time to remission, 36 weeks; cortisol level decreased after remission
				3 A.M.–7 A.M. (5)	450 (127)	493 (133)	
Rupprecht[45]	MDD melancholic	6	42 ± 15.4	7 A.M.–4 P.M. (2)	NR	NR	*T* level lower during acute depression
Mason[54]	MDD melancholic	7	37.3 ± 7.0	9 A.M.	363 (54)	292 (58)	*T* level lower when discharged ($P<0.08$)
Unden[49]	MDD, DST−	8	49.5 ± 4.3	8 A.M. (2)	NR	NR	*T* level unchanged
	MDD, DST+	6	43.5 ± 4.3	8 A.M. (2)	NR	NR	*T* level lower in acute than after remission ($P<0.03$)

Note: DST− = negative dexamethasone suppression test; DST+ = positive dexamethasone suppression test.

*$P<0.05$.

with RDC-diagnosed major depression but not from control subjects. They found that testosterone level was negatively correlated with age ($r = -0.40$), negatively correlated with Ham-D score ($r = -0.67$, controlling for age); and positively correlated with a sexual activity score ($r = 0.48$); this correlation became nonsignificant after controlling for age and Ham-D score ($r = 0.09$, $P > 0.05$).[50]

Davies and colleagues[48] used salivary samples to compare free testosterone levels among 11 men with melancholic depression and 10 age-matched control subjects. There was no significant difference between the groups in mean free testosterone level. Yet in the depressed group alone, free testosterone level was significantly negatively correlated with severity of depression and with anxiety.[48]

Mason and colleagues[54] determined morning testosterone levels on admission and every 2 weeks thereafter for seven men hospitalized with RDC-diagnosed endogenous depression (mean age, 37 years) and for other male psychiatric inpatients. The mean testosterone level of this depressed cohort was in the low-normal range (363 ng/dl), significantly lower than in the schizophrenic cohort but not different from the bipolar cohort.[54] Mean testosterone level actually decreased after recovery only in the depressed cohort, though this decrease was not statistically significant ($P = 0.08$).[54]

In more elaborate neuroendocrine studies, investigators have attempted to control for diurnal variability in hormone levels by using indwelling catheters to obtain multiple serum samples over many hours. Such labor-intensive methods have, however, had limited numbers of subjects. In one of the largest and most rigorous, Rubin et al.[47] enrolled 16 RDC-diagnosed depressed men (mean age, 39 years) and 16 paired, age-matched control subjects. They assessed multiple measures of HPG functioning (i.e., LH, FSH, estradiol, and testosterone levels, and response to TRH, LHRH, and dexamethasone) over 26 hours, with serum sampling every 30 minutes, and found that testosterone level was significantly more negatively correlated with age among depressed men ($r = -0.70$) than among control subjects ($r = -0.10$), and was positively correlated with DSM-III–diagnosed melancholia ($r = 0.58$).[47] Yet, despite extensive factor analyses with Beck and Hamilton depression scales, there were no significant correlations between testosterone level and depressive symptoms.[47] This study provides some evidence that testosterone secretion may be blunted among older depressed men.

Similar methods were used in two smaller studies that support the tentative conclusion that blunted testosterone secretion is a state marker of depression in some men. Rupprecht and colleagues[45] found lower testosterone levels among six men during an acute episode of melancholic depression compared with levels after their recovery, and compared with 20 control subjects. Steiger and colleagues[53] studied 12 men hospitalized with DSM-III-R major depression (mean age, 46 years) with hourly serum sampling while they were sleeping. They demonstrated that nocturnal testosterone secretion—particularly between 11 P.M. and 3 A.M.—was significantly lower during the acute phase than after remission, whereas cortisol secretion increased after remission.[53] In fact, testosterone blunting during depression may parallel the hypothalamic-pituitary-adrenal (HPA) axis activation of depression: Unden and colleagues[49] demonstrated a lower basal testosterone level only among the 8 of 14 depressed men who had a non-suppressing dexamethasone suppression test (DST–).

Some evidence from neuropsychiatric studies of cerebral laterality supports the possibility that HPG function may vary by a still poorly defined depressive subtype. In a study of 18 men hospitalized with affective illness (mostly major depression, but including bipolar and schizoaffective disorders), Wexler and colleagues[51] divided them into two equal subgroups on the basis of subjects' responses to language-related dichotic listening tests of cerebral laterality. A combined laterality variable (CLV) was constructed to measure the extent to which subjects exhibited right-ear advantage (REA) on word compared with nonsense dichotic tests, which had been validated as a reliable marker of information-processing. The group with high CLV had significantly lower testosterone levels than the group with low CLV, with little overlap. Furthermore, among the high-CLV group, testosterone level was negatively correlated with BPRS symptom severity—particularly on measures of activation, anxiety, and suspiciousness. Among men in the low-CLV group, testosterone level was positively correlated with these measures of symptom severity. In the combined group, there was no correlation between testosterone level and symptom severity.[51] These intriguing findings have not been replicated and should therefore be considered tentative. They are, moreover, methodologically limited by the inclusion of bipolar and

schizoaffective patients. Yet, if supported, the interaction between testosterone level and depressive "subtype" might help explain why the demonstration of a relationship between testosterone level and depressive symptoms has been so inconsistent.

In summary, data suggest, though do not demonstrate, that among some men with major depression, testosterone secretion may be reduced. The studies are mostly small and cross-sectional, and have been unable to adequately control for the multi-determined variability in testosterone level found among normal subjects. It is possible that a subgroup of depressed men in these studies are symptomatic because of hypogonadism alone—that is, that their depressive symptoms are sequelae of low testosterone levels. Finally, in some cases, blunting of testosterone secretion may be a response to a depressive symptom, such as caloric restriction (a known inhibitor of GnRH), sleep disturbance, stress, or the experience of "defeat." Thus, it remains unclear whether lower testosterone levels among some depressed men represent state-dependent HPG dysfunction.

The research questions for geriatric psychiatry remain: Does major depression have an impact on HPG functioning, and does "normative" gonadal hypofunction result in a depressive syndrome? Currently available data are too limited to answer these questions. We require studies that address 1) the specific endocrinologic status (i.e., HPG axis) of older depressed men; 2) the psychiatric status of older hypogonadal men; and 3) the relationship between measures of HPG functioning and psychiatric symptoms in representative samples of aging men.

For clinicians, there are few "take-home" messages regarding the role of testosterone level in the psychiatric management of older men because it remains entirely unclear what the significance of a low testosterone level is in the setting of depressive illness. Yet, because testosterone level is easy to check with a routine blood test, it is advisable to check testosterone level in men who complain of persistent low libido (with or without loss of morning erections), irritability, and low energy. If hypogonadism appears likely, consultation with an endocrinologist or urologist is then indicated for further medical evaluation and consideration of the benefits vs. the potential risks of replacement. Although psychiatric symptoms may respond dramatically to testosterone replacement, the clinician should be mindful of the possibility of nonspecific placebo effects.

Exogenous Testosterone Administration and Depression

Androgen administration to eugonadal men. Exogenous androgens clearly have direct behavioral effects. In animal models, they stimulate sexual activity, aggressive behavior, and dominance.[2,7,10,21,25] In humans, studies of testosterone administration to eugonadal young men have demonstrated changes in sexual arousal, cognition, and mood,[1,2,28–30,55,56] although not consistently in sexual behavior. Generally, such effects are not easily demonstrated, and may be subtle. For example, one study demonstrated a significant increase in optimism in predicting psychomotor task performance after testosterone administration to 30 eugonadal men.[57] Most large studies in which moderately supraphysiologic doses of testosterone were administered to eugonadal men have demonstrated that it is relatively safe and has few obvious psychiatric effects.[58–60] In the most rigorous such study that followed psychiatric symptoms, Tricker and colleagues[60] randomized 43 eugonadal men ages 19–40 to double-blind treatment with testosterone enanthate 600 mg or placebo weekly for 10 weeks. They found no change in self-reported or observer-reported scales of hostility, anger, and mood during testosterone treatment. Similarly, Matsumoto[58] administered 100 mg and 300 mg of testosterone enanthate weekly for 6 months to 20 eugonadal men ($n = 10$ in each group). He demonstrated that compared with a 4- to 6-month pretreatment placebo phase, supraphysiologic testosterone was associated with an increased hematocrit; weight gain; mild truncal acne; and reduced LH, FSH, and sperm count. No significant psychiatric effects were detected. In contrast, use of massive doses of synthetic androgens by bodybuilders has consistently been reported to induce mood changes such as anger, hostility, irritability, and euphoria.[61–63]

There are a few well-controlled studies of testosterone administration to eugonadal men with erectile dysfunction.[30,31,64] In general, they have demonstrated that administration of testosterone is no more effective than placebo for erectile dysfunction, that it leads to a modest increase in sexual interest, and does not lead to an increase in self-reported measures of mood. For example, Schiavi and colleagues[31] enrolled 18 eugonadal men (age range: 46–67 years) who presented with the chief complaint of erectile dysfunction in a double-blind, placebo-controlled, crossover study of testosterone 200 mg or placebo every 2 weeks for 6 weeks. They

found that during the testosterone vs. placebo phase: ejaculatory frequency doubled; other measures of sexual arousal also increased, but this finding was not statistically significant; erectile function and sexual satisfaction were unaffected; and mood, assessed by self-report instruments, was also unaffected.[31] Most subjects could not correctly identify the phase in which they received testosterone, and they felt it was not helpful. The authors were unable to demonstrate that this schedule of testosterone administration led to an increase in circulating levels 2 weeks after each intramuscular injection—which suggests that this dose may have been too low to override the compensatory feedback mechanisms operating in eugonadal men. Furthermore, the number of subjects in this trial was likely too small to allow detection of significant mood effects.

Androgen administration to hypogonadal men. Numerous testosterone replacement studies provide consistent support for its safety and efficacy in hypogonadism: replacement increases body weight, fat-free muscle mass, muscle size and strength; prevents continued bone loss; restores and maintains sexual function and secondary sex characteristics (e.g., facial hair); and increases hematocrit.[1,4,5,28,33,34] Yet in the endocrinologic literature, only rarely has rigorous attention been paid to psychiatric symptoms. In most such studies the effects on sexual function (i.e., consistently improved libido and arousal, and restoration of sleep-related erections and ejaculatory capacity) are described most systematically; other psychiatric symptoms are noted anecdotally or not at all.[30,32–34] No testosterone replacement trial has included a systematic determination of pretreatment psychiatric diagnosis with adequate longitudinal monitoring of psychiatric symptoms. Yet, despite such methodologic flaws with regard to the psychiatric effects of hormonal replacement, investigators consistently note that such patients report enhanced relaxation, cheerfulness, "well-being," and energy; and reduced irritability, anger, and tension.[30,32–34,65]

In the most systematic study of the mood effects of testosterone replacement, Wang and colleagues[65] followed 51 hypogonadal men age 22–60 years during 2–6 months of testosterone replacement. Testosterone level at baseline was below 250 ng/dl, and many of the subjects had been withdrawn from testosterone replacement for 6 weeks to enter the study. Self-reported mood ratings were compared from pre-replacement baseline to Weeks 3, 6, and 8 of testosterone replacement. On positive mood scales, there was a significant increase in self-reported friendliness, energy level, and well-being, usually evident by the first visit (Treatment Week 3), and persisting through 6 months of replacement. On negative mood scales, there was a significant decrease in self-reported nervousness, irritability, sadness, and anger.[65]

Androgen administration to depressed men. The psychiatric effects of androgen administration in men (hypogonadal or eugonadal) who have well-diagnosed major depressive illness have not been systematically investigated. What evidence exists includes mostly anecdotal reports from the 1940s and '50s (without syndromal diagnoses), the more recent clinical trials of oral androgen treatment of depressed men,[44,66–68] and testosterone treatment of mild-to-moderately depressed HIV-positive men.[69]

Reports from the older psychiatric literature on the "antidepressant" effects of testosterone, conducted mostly between 1935 and 1960, without standardized, syndromal psychiatric diagnoses or baseline testosterone levels, suggested that a substantial proportion of "depressed" men responded immediately and dramatically, and relapsed when treatment was discontinued.[70–72] For example, Rieter[73] reported his experiences from London in the 1950s with 240 middle-aged men in whom he implanted intramuscular testosterone crystals (800 mg–2,400 mg [along with small doses of estradiol (20 mg)]), which he claimed gave a steady dose of 4 mg–12 mg per day over 6 months. He rated men with an eight-point depression scale, with 8 defined as "complete loss of confidence in carrying on the activities of living, a tendency to abandon any occupation, and even the danger of self-destruction" at baseline, and 2 and 4 months post-implantation. He began his studies by administering lower testosterone doses (800 mg–1,800 mg), and noted that treated men had moderate decreases in depression scores. Later, after he began administering higher doses (2,000 mg–2,400 mg), he reported that treated men had substantial and sustained reductions in their depression scores, from the 5–8 range to the 1–3 range.[73] However, lack of any control group limits interpretation of these data.

In the past two decades, we know of only seven androgen treatment trials for depression in men in which investigators used DSM diagnoses of major depression and systematically followed depressive symptoms (e.g., with the Hamilton Depression Rating Scale

[Ham-D]). Most used the oral androgen mesterolone, which is a derivative of DHT and therefore lacks testosterone's non-DHT actions (i.e., testosterone-specific and estrogenic activity).[5]

Itil et al. performed three mesterolone trials.[67,68] First, they administered variable doses of mesterolone to 17 depressed men openly for 3 weeks, and found that 8 (47%) improved, particularly in mood and anxiety level.[68] Then, in a randomized, double-blind, 4-week trial, low-dose mesterolone (i.e., 75 mg/day) or placebo was administered to 38 dysthymic men. They reported that treatment led to improvement in symptoms such as anxiety, lack of drive, lack of desire, and impaired satisfaction.[68] Finally, they administered high-dose mesterolone (i.e., 450 mg/day) or placebo in a 6-week randomized trial to 52 men (mean age, 40 years) with dysthymia, unipolar depression, and bipolar depression.[67] Both the mesterolone and placebo groups improved significantly, and there was no statistically significant difference demonstrable between the two.[67] Mesterolone treatment led to a significant decrease in LH and testosterone levels. Notably, of those patients who improved on mesterolone (initial drug responders, and placebo nonresponders who were crossed over and responded), improvement in psychopathology was positively correlated with the decrease in testosterone levels during Weeks 3–6 of treatment.[67]

Vogel et al.[44] administered mesterolone openly for 7 weeks to 13 eugonadal men (mean age, 39 years) with refractory chronic unipolar depression. Eleven responded, most by the second week, with a mean Ham-D decrease (in these 11) from 21.1 to 5.6 ($P<0.001$). The same investigators, in a 12-week randomized, double-blind trial, gave mesterolone or amitryptyline to 34 chronically depressed, eugonadal men age 27–62 years.[66] Mesterolone was as effective as amitriptyline in reducing depressive symptoms: mean Ham-D score decreased by 8 in both groups.[66]

Rabkin and colleagues[69] administered testosterone openly to 52 HIV-positive men who had testosterone levels below 450 ng/dl and a depressive disorder (42% with major depression, the remainder with a minor depressive syndrome). Twenty-eight patients (64%) improved, with mean Ham-D decrease from 13.6 to 4.1 at Week 8.[69] Notably, neither baseline nor final testosterone levels were associated with antidepressant response.

Finally, Seidman and Rabkin[74] administered testosterone openly to five men who had SSRI-refractory major depression and testosterone level below 350 ng/dl. In this 6-week trial, all five achieved remission, with a mean Ham-D decrease from 19.2 to 7.2 by Week 2, and to 4.0 by Week 8. In an ongoing randomized trial, Seidman and colleagues are treating depressed, hypogonadal men with testosterone vs. placebo.

One additional report bears consideration, in which five men hospitalized with major depression were given methyltestosterone 15 mg/day orally along with imipramine 75 mg–150mg/day.[75] All five patients improved, with a mean Ham-D decrease in the first week from 28.2 to 13.4, and full remission by the third week in four patients. However, the authors report that within 1–4 days of beginning testosterone treatment, four men developed an agitated psychosis, with mostly persecutory and guilty delusions. The psychotic episodes were not apparently associated with delirium and did not include hallucinations; the episode was manic-like in only one patient. Methyltestosterone was stopped immediately, and these "episodes" all resolved within 1 day; the antidepressant response was maintained with continued imipramine treatment. These "paranoid reactions" have never been adequately explained, nor has anything like it been described in the treatments with mesterolone or with the esterified androgens used almost exclusively today.

In summary, androgens have psychoactive properties. There is limited, though suggestive, evidence that exogenous androgen treatment has antidepressant effects in some male depressed patients. Such effects may be more prominent among men who are hypogonadal, although this effect is not well established. In general, the evidence is too limited to evaluate whether the presumed antidepressant efficacy is related to testosterone replacement, symptomatic improvement (e.g., increased libido or energy), or nonspecific placebo effects.

Therapeutic Limitations of Androgen Administration in Aging Men

A note of caution must be raised regarding the potential risks of testosterone replacement in aging men, especially regarding erythropoiesis, cardiac disease, and prostate disease. Specifically, exogenous androgen treatment is known to stimulate erythropoiesis, reduce plasma HDL cholesterol, and stimulate the growth of established prostate adenocarcinoma. The theoretic risks of inducing polycythemia, worsening coronary ar-

tery disease, exacerbating asymptomatic benign prostatic hypertrophy, and/or promoting the development of precursor prostatic lesions into cancer have never been demonstrated.[76] Most clinicians consider the risk of prostate cancer the most worrisome possibility and do not administer testosterone to men who have an abnormal digital rectal exam of the prostate or an elevated PSA (i.e.,>4.0 ng/ml).[77] Because these risks have not been adequately evaluated, testosterone therapy should currently be considered potentially harmful.

CONCLUSION

Testosterone is a hormone of social interaction: it is secreted in response to social, sexual, and psychological factors, and, in turn, acts on the brain as a target organ to affect mood and behavior. Mason and colleagues[54] have suggested that because the testosterone system is linked to a psychological "mastery–failure" axis, certain subtypes of depression (i.e., those in which the experience of defeat is prominent) might be better delineated by following testosterone secretion, and perhaps better treated with exogenous testosterone.

Because there are no published studies examining the role of testosterone in late-life depression in men, we have by necessity examined the data regarding the relationship of testosterone action to male depressive illnesses, irrespective of age. Caution should be exercised in extrapolating these data to aging men. Moreover, this deficiency in the literature highlights the need for specific studies in this area of geriatric psychoendocrinology.

We have evaluated two lines of evidence regarding the relationship between testosterone and depression: the association between testosterone level and depression; and the association between testosterone administration and antidepressant action. Some evidence suggests that testosterone secretion is impaired in some depressed men and that androgen administration may have specific antidepressant actions. Further research is needed, including epidemiologic studies of the relationship of testosterone level to psychiatric symptoms and syndromes and randomized clinical trials to assess testosterone's antidepressant efficacy in different subgroups. Until such studies are done (and given the potential danger of testosterone treatment), no recommendation can be made regarding treatment of depression with testosterone.

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