LEADING ARTICLE

Drugs Aging 2004; 21 (6): 361-376
1170-229X/04/0006-0361/$31.00/0

Depression in Aging Men
The Role of Testosterone

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Abstract

Age-related decline in testosterone levels is associated with a number of mild, nonspecific symptoms, including depressive symptoms. The relationship between depressive symptoms and testosterone levels is confounded by numerous factors, including medical illness, obesity, smoking, alcohol use, diet and stress, and is thus complex. Studies have not consistently supported an integral role of reduced testosterone levels in major depressive disorder, although levels may often be reduced in men with treatment-refractory depression and older men with dysthymia. Low testosterone levels may also increase the risk of incident depression in older males, although this may depend upon androgen receptor genetic polymorphisms. Testosterone replacement has demonstrated short-term tolerability and efficacy in augmenting antidepressants to alleviate treatment-refractory depression in adult males. Case studies support the potential need for maintenance therapy to maintain response. In a placebo-controlled trial, testosterone monotherapy was not effective in treating major depressive disorder in men with hypogonadism. However, in an open-label, noncomparative study, testosterone monotherapy appeared effective in treating late-onset but not early-onset major depressive disorder in older males. Testosterone therapy is not without potential for adverse effects, the most worrisome of which is the worsening of pre-existing prostate carcinoma. Oral, short- and long-acting parenteral, and transdermal patch and gel formulations are available. Testosterone has demonstrated usefulness in the treatment of a number of depressed populations, but further studies are needed to fully elucidate its role in the treatment of depressive syndromes in the aging male.

Depression in elderly males is a significant public health problem. It is under-recognised and undertreated in this population.[1] The most striking statistics reflecting this problem are suicide rates. In the US, the highest rates of suicide are in men over 65 years of age. The rate continues to increase beyond age 65 years, doubling by age 85 years.[2] This problem is not unique to the US. Men over the age of 75 years had the highest rates of suicide in all but one country reporting suicide data to the WHO.[3] In contrast, the highest rates of suicide in women occur between the ages of 45 and 54 years. Rates in age

groups above 65 years are 4–10 times higher in men than in women, and the rates in women remain fairly stable beyond age 65 years.[2] This begs the question – what occurs as males age that predisposes them to depressive syndromes and suicide? It is likely the answer is complex, with a myriad of factors contributing to the problem. Hypogonadism can lead to depressive syndromes and other psychological problems, including anxiety, irritability, insomnia, memory impairment and reduced cognitive function.[4] Physical manifestations of hypogonadism can include weakness, fatigue, osteoporosis, reduced muscle mass and sexual dysfunction in the form of oligospermia, diminished libido and impotence.[4] These problems may resolve with the initiation of testosterone replacement therapy.[4] More pertinent to this review is the question of whether the age-related gradual decline in bioavailable testosterone levels contributes to the high rate of depressive syndromes and suicide in elderly males. Is there a subpopulation of depressed males that may benefit from testosterone replacement therapy or antidepressant augmentation with testosterone? The aim of this review is to assess the literature pertinent to the role of testosterone in the treatment of late-life depression, such that an evidence-based recommendation on its use can be made.

A MEDLINE search was conducted (January 1966–June 2003) combining the terms 'testosterone' and 'depression' or 'depressive disorder'. Citations were limited to articles about humans and written in English. Studies were included if they involved the assessment of testosterone levels and depressive symptoms, or testosterone was administered and depressive symptoms monitored. Case reports were included if they added information beyond that found in larger or controlled trials. For background information, a MEDLINE search was conducted (January 1996–June 2003) using the terms 'testosterone' and 'aging'. Articles providing relevant information were included and article reference lists were used to identify studies published prior to 1996 or not found in our searches and that were important to this manuscript.

1. Testosterone and Aging

1.1 Testosterone Metabolism

The hypothalamic-pituitary gonadal (HPG) axis controls testosterone production in men. Gonadotropin-releasing hormone (GnRH) secreted from the hypothalamus stimulates the pituitary gland to release luteinizing hormone (LH), which in turn stimulates testicular Leydig cells to produce testosterone. Testosterone is metabolised to dihydrotestosterone by 5α-reductase, and aromatase converts dihydrotestosterone to estradiol. Further secretion of GnRH is inhibited by increasing levels of testosterone. Approximately 80% of testosterone is bound to sex-hormone-binding globulin (SHBG). Testosterone also binds to other serum proteins, including albumin. Ultimately, about 2% exists unbound as free testosterone. Testosterone that is not bound to SHBG, including that bound to albumin, is referred to as bioavailable testosterone. This is generally considered the biologically active portion of testosterone. Testosterone production follows a circadian rhythm in younger males, with peak levels occurring at approximately 8.00am.[5,6]

1.2 Changes in Testosterone Levels with Aging

The aging process results in a lowering of total, especially free and bioavailable, testosterone levels. Free testosterone levels decline at a rate of approximately 1% per year between the age of 40 and 70 years.[7] Concurrently, total serum testosterone levels decline at an approximate rate of 0.4% per year.[7] Levels of SHBG increase at a rate of approximately 1.2% per year during this time period and the resultant increased binding of testosterone to SHBG provides an explanation for a substantial portion of the decline in free testosterone levels.[6,7] This decline is reputed to result in a change in body

composition manifested as increased body fat and reduced muscle mass.[8] Aging is associated with reduced Leydig cell function and HPG axis sensitivity. Thus, aged men have more difficulty compensating for the reduction in testosterone levels.[9] The circadian rhythm of testosterone production is also reduced as men age. Levels seen in elderly men throughout the entire day are similar to the nadir levels seen in younger men at around 8.00pm.[10] Androgen receptor genetics appear to modify the effect of age on testosterone levels. Men with shorter androgen receptor CAG repeat lengths had a more rapid decline in testosterone levels in one longitudinal study, the Massachusetts Male Aging Study.[11] The sample included 882 men with a mean baseline age of 53 years. The average follow-up period was 8 years. This modifying effect on testosterone levels may be due to the modulation of androgen receptor sensitivity by the CAG repeat length polymorphism, leading to more negative feedback on testosterone release at the same level of testosterone in men with shorter CAG repeats.

The most commonly cited lower limit of normal for total plasma testosterone levels is 350 ng/dL. However, testosterone assays differ among laboratories and it has been suggested that each laboratory should establish its own normal range.[9] There is also some debate as to what becomes 'normal' as a man ages, since this cut-off is based upon levels seen in middle-aged men. The prevalence of total testosterone levels <350 ng/dL has been estimated to be 7% in men aged 40–60 years, 20% in men aged 60–80 years and 35% in men over 80 years of age.[12] When considering free testosterone, 60% of very healthy men between the age of 60 and 80 years, evaluated by one laboratory, were hypotestosteronemic when compared with the normal range for young males.[13] With these prevalence rates it is obvious why some authorities may feel that it is inappropriate to label a low testosterone level in an aged male pathologic. Total testosterone levels in males decline slowly with aging, in contrast to female menopause, which represents a rapid decline in hormone levels. Because of this the physiological and emotional effects of declining testosterone levels may not be as obvious as the effects of menopause. This has caused some to prefer the term 'climacteric', which refers to climbing down the rungs of a ladder, as opposed to 'andropause' or 'viropause', which suggests a process analogous to menopause. The terms 'low-testosterone syndrome', 'partial androgen deficiency in the aging male (PADAM)', and 'androgen decline in the aging male (ADAM)' have also been used. The current authors prefer ADAM as it is least dependent upon defining low testosterone levels in aging males as a syndrome and is simply descriptive of the aging process. The validity of ADAM as a clinical syndrome depends upon the strength of the relationship between low testosterone levels and the clinical pathology of the syndrome, and the ability of the testosterone replacement therapy to alleviate the pathology. The decrease in testosterone levels associated with aging may not be considered pathologic, as menopause is not pathologic, but hormone replacement therapy may be considered for its potential benefits in overall health and quality of life. The aging course is clearly associated with a reduction in testosterone levels and an increase in the prevalence of sub-normal levels.

2. Testosterone and Factors Other Than Aging

Testosterone secretion can be affected by a multitude of factors, including medical illness, obesity, smoking, alcohol use, diet and stress. Some researchers argue that the relationship between low testosterone levels and the nonspecific physical, sexual and emotional states attributed to testosterone deficiency is actually due to worsening health, which leads to reduced testosterone levels. It is true that causation is very difficult to establish, as testosterone affects, and is affected by, so many things. Arguments inevitably resemble those of whether the chicken or egg came first. It is not the place of this review to argue for or against the existence of a

testosterone deficiency syndrome in aged males. In fact, the clinical relevance of whether testosterone deficiency is the absolute cause of the symptoms could even be questioned, unless the underlying causes were readily reversible by other means. Ultimately, the utilitarian questions for clinicians are whether testosterone replacement therapy results in a resolution of the described symptoms and in whom the therapy is likely to be of benefit. Regardless, it is important to understand the many factors that can affect testosterone levels.

2.1 Medical Illness

Medical illness is the most important confounder in the relationship between mild testosterone deficiency and the symptoms it is purported to cause. The relationship between testosterone and medical illness was characterised most clearly in a cross-sectional study of 1709 men aged 39–70 years.[7] Subjects were classified as either healthy or unhealthy. Subjects considered unhealthy comprised 1294 patients who were obese, alcoholic, taking at least one prescription medication and/or chronically ill. At each level of age, testosterone levels were approximately 10% lower in the unhealthy group than the healthy group. The rate of reduction in levels associated with age in each group was similar – approximately 1% per year of age. Thus, health status was associated with lower levels of testosterone, but not an acceleration of the rate of decline in levels. The unhealthy group in this study was not homogenous. Alcohol use, obesity, and some prescription medications can affect testosterone production and may have accounted for some of the differences in testosterone levels, apart from the medical illness of patients. An alternative hypothesis that cannot be ruled out due to the cross-sectional nature of this study is that lower testosterone levels predisposed some of the unhealthy men to being unhealthy. As is usual with testosterone, the relationships are complex and it is likely that no single answer is sufficient.

In another study,[14] patients were evaluated after myocardial infarction. In younger patients, testosterone levels were significantly reduced early after myocardial infarction, then rebounded as the patients recovered. Elderly patients did not experience this fluctuation in testosterone levels. Cortisol levels remained the same through this period in younger and older patients, suggesting that testosterone secretion was not suppressed by cortisol.[14] The mechanism by which myocardial infarction leads to reduced testosterone levels is unclear;[14] however, it is notable that testosterone administration can reduce myocardial ischaemia.[15,16]

2.2 Obesity

Obesity may be related to testosterone levels through multiple mechanisms. The most obvious is through increased aromatase activity. Aromatase is located in fatty tissue; thus, increased fat mass results in increased aromatase and, consequently, conversion of testosterone to estrogen. The resultant hormone balance is thought to favour visceral fat deposition, worsen the hypogonadal-obesity cycle, and contribute to the development of the CHAOS complex (coronary artery disease, hypertension, adult-onset diabetes mellitus [type 2 diabetes], obesity and/or stroke).[8]

In a study of 696 British men, Allen et al.[17] found, on average, 30% lower total testosterone, 45% lower SHBG and 5% lower free testosterone levels among men with a body mass index (BMI) $\geq$30 kg/m^2 in contrast to men with a BMI <20 kg/m^2. A high waist circumference was associated with 12% lower testosterone and SHBG levels, but no difference in free testosterone levels. Glass et al.[18] reported that total testosterone levels were reduced by 63% in a group of 10 massively obese men (200–380% of ideal bodyweight) compared with control subjects. SHBG levels were also reduced substantially, such that free testosterone levels were decreased by only 21% compared with control subjects. In a group of mildly obese men (>20% over ideal bodyweight) who were free of concomitant

disease states, free and total testosterone levels were reduced by 25% and 19%, respectively.[7] Thus, reductions in total testosterone appear to correlate with the degree of obesity. In contrast, free testosterone levels are reduced in obesity, but do not necessarily correlate with the degree of obesity due to changes in SHBG levels. Obesity may be an important confounder due to the vascular component in some cases of late-life depression.[1]

2.3 Smoking

Smoking is usually associated with an increase in total testosterone levels, when subjects are matched for age and bodyweight.[14,19] English et al.[20] found increased levels of total and free testosterone, as well as SHBG, in smokers compared with nonsmokers, matched for age and BMI, but no difference in bioavailable testosterone levels. The study of 696 British men by Allen et al.[17] reported that smoking ten or more cigarettes per day was associated with 15% higher testosterone levels and 22% higher SHBG levels. Thus, it was not surprising that there was no difference in free testosterone levels, compared with men who had never smoked. The mechanism by which smoking might affect testosterone levels is unclear.[12] The clinical importance of the effect of smoking on testosterone is not apparent.

2.4 Alcohol

Alcohol consumption in chronic alcoholics resulted in dose-dependent reductions in testosterone levels ranging from 19% to 27%. Discontinuation of alcohol consumption resulted in a return to normal testosterone levels.[21]

2.5 Diet

A vegetarian diet (versus conventional) did not affect testosterone levels, nor did residency in a care facility (versus home care).[14] Allen et al.[22] found that vegan men had higher SHBG and testosterone levels than vegetarians and meat-eaters, but there were no differences between diet groups in free testosterone levels.

2.6 Physical and Mental Stress

Compared with no exercise, vigorous exercise for 3 or more hours per week was associated with 11% higher testosterone and 16% higher SHBG levels, but no difference in free testosterone levels.[17] Strength training causes an age-dependent increase in testosterone levels immediately after exercise, but men engaging in regular strength training have not shown increased testosterone levels relative to controls (sedentary men).[23] During ultramarathon competitions, decreased testosterone and increased cortisol levels have been observed in competitors versus controls (medical team that observed the race).[24] Physical stress and overtraining result in elevated cortisol levels with stimulation of the hypothalamic-pituitary adrenal axis. Mental stress also increases cortisol levels. Decreased testosterone level has been observed under periods of both mental and extreme physical stress,[23] and in men reporting high psychological stress compared with their counterparts who have reported low psychological stress.[25] Reduction of stress has been associated with an increase in testosterone levels.[23] The exact nature of any potential relationship between cortisol and testosterone secretion has not been elucidated. In general, testosterone is reduced and cortisol is increased under periods of mental or extreme physical stress. Testosterone rises and cortisol levels decrease when stress subsides.[23] The importance of stress in any relationship between testosterone and depression is unclear.

3. Testosterone and Depression

Studies examining the relationship between testosterone and depression in men have found conflicting results. It is likely that the relationship is quite complex, with genetic, environmental and personality factors playing a role. It is unclear whether hypogonadism causes major depression or depressive states, increases stress vulnerability or leads to

resistance to standard treatments. Due to the cross-sectional nature of most studies, one cannot also rule out the hypothesis that depression leads to low testosterone levels in some individuals due to complex interactions between hormones and emotion. However, it does seem that mildly reduced testosterone levels are not sensitive or specific in predicting any type of depression.

3.1 Longitudinal Studies in Major Depressive Disorder

Studies of testosterone in major depressive disorder in males have been inconclusive. Sachar et al.[26] studied 15 men aged 46–78 years with psychotic, neurotic, or manic depression that, in most cases, was associated with decreased libido or aggressive behaviour. Most of these men received electroconvulsive therapy and no antidepressants. The investigators observed no significant change in total plasma or urinary testosterone levels during illness until recovery. Levels were similar to those seen in healthy controls. Testosterone levels were not associated with cortisol production rates. Shaw et al.[27] studied 14 men and women of unreported age with depression and found no change in total testosterone levels during illness until following recovery. Cortisol levels were elevated during illness and after recovery. Steiger et al.[28] evaluated nocturnal secretion of testosterone and cortisol in 12 male inpatients with major endogenous depression, aged 21–66 years, during depression and following remission. During illness, patients had reduced night-time testosterone and elevated night-time cortisol secretion in contrast to the remission period. No clear pattern of testosterone changes throughout the course of depression has been identified.

3.2 Cross-Sectional Studies in Major Depressive Disorder or Dysthymia

Vogel et al.[29] observed lower total (4.48 vs 6.82 μg/L) and free indices (2.36 vs 3.30 μg/L) of testosterone in 27 outpatient males with primary, unipolar, neurotic depression and a mean age of 39.5 years compared with 13 nondepressed controls of comparable age. The investigators also found increased metabolic clearance of testosterone, but no difference in testosterone production rate, in 15 men with depression with a mean age of 40.9 years compared with 12 nondepressed controls of similar age. Yesavage et al.[30] reported that testosterone levels were inversely correlated with severity of depression in 18 men with endogenous depression, whose demographic characteristics were otherwise poorly defined. Swinden et al.[31] studied 30 men with rheumatoid arthritis between 25 and 65 years of age and found no relationship between depression and testosterone levels, although there was a nonsignificant trend towards higher free testosterone levels in patients with more anxiety and depressive symptoms. Schweiger et al.[32] studied testosterone, pulsatile LH secretion, follicle-stimulating hormone (FSH) and cortisol in 15 male inpatients (mean age 48 ± 15 years; mean BMI 24.3 ± 4.2 kg/m^2) with moderate-to-severe depression, and 22 healthy controls of similar age and BMI. The investigators observed significantly lower night-time (5.3 vs 8.2 nmol/L) and 24-hour mean testosterone (5.7 vs 8.0 nmol/L), lower LH pulse amplitude, and higher 24-hour mean cortisol in the men with depression compared with healthy controls. There was a trend towards lower daytime testosterone in the men with depression versus healthy controls (6.0 vs 7.8 nmol/L; $p = 0.09$). Kaneda and Fujii[33] found no difference in total testosterone levels between 11 patients with depression and 11 age-matched healthy males aged ≥50 years. They also found no relationship between depressive symptoms and testosterone levels in either group. Seidman et al.[34] studied men aged at least 60 years with dysthymia ($n = 32$), major depressive disorder ($n = 13$) and without depression ($n = 175$). Median total testosterone levels were lower in the men with dysthymic disorder (295 ng/dL) compared with men with major depressive disorder (425 ng/dL) or no depression (423 ng/dL). Testosterone abnormalities in major depressive disorder are not consistent or obviously detectable and

any relationship with the disorder needs further clarification and exploration of the importance of depressive subtypes. However, it appears possible that some older men with dysthymic disorder are displaying symptoms of ADAM.

3.3 Population-Based, Cross-Sectional Studies of Testosterone and Depressive Symptoms

Barrett-Connor et al.[35] studied testosterone and depressive symptoms in a cross-sectional, population-based study of 856 men aged 50–89 years. Bioavailable testosterone was significantly and inversely associated with scores on the Beck Depression Inventory (BDI), independent of age, weight change and physical activity. Both low bioavailable testosterone and high BDI scores were associated with weight loss and lack of physical activity.

Booth et al.[36] conducted the largest published study to date to evaluate the association between testosterone and depression. The investigators analysed a random sample of 4393 Vietnam veterans aged 30–48 years, raising question as to the applicability of the findings to older males. Morning total testosterone levels were measured. The Diagnostic Interview Schedule items from the Diagnostic and Statistical Manual of Mental Disorders, third edition, were assessed, including items related to appetite, sleep, fatigue, interest in sex, feelings of worthlessness, trouble thinking and thoughts of death. These investigators also assessed the impact of psychosocial factors on the relationship between testosterone level and depression. They found a curvilinear relationship between testosterone level and depression. In patients with total testosterone levels <590 ng/dL, increasing testosterone levels were associated with fewer depressive symptoms. No psychosocial factors affected this relationship. Among men with levels >590 ng/dL, higher testosterone levels were associated with more depressive symptoms. After adjustment for psychosocial risk factors (antisocial and risk behaviours) and protective factors (marriage and employment), the relationship between testosterone levels and depression in the men with higher testosterone disappeared.[36] Whether high levels of testosterone are caused by, or are a cause of, antisocial or risk-taking behaviour is not clear.

Perry et al.[37] studied the relationship of bioavailable testosterone with anxiety and depressive symptoms, among other things, in a group of 78 males aged 55–75 years. Bioavailable testosterone decreased with age, and lower bioavailable testosterone was associated with fewer depressive symptoms. The investigators actually found that increasing age was associated with fewer anxiety and depressive symptoms and greater emotional well-being. This study highlights the many complexities that contribute to a person's mood and sense of well-being. While testosterone and mood may affect one another, a multitude of other factors modifies any potential relationship.

Seidman et al.[38] studied the relationship between testosterone levels, androgen receptor polymorphism and depressive symptoms in 1000 men aged 48–79 years (mean 62.6 years). They identified 110 men with 'depression' defined by scores on the Center for Epidemiologic Studies-Depression Scale. They found no crude relationship between testosterone level and depression; however, when subjects were stratified into tertiles by androgen receptor CAG repeat length and quintiles by testosterone levels, a relationship was found in the tertile with the shortest CAG repeat lengths. In this group, lower total testosterone levels were associated with more depression. The prevalence of depression was 21.6% in the quintile with the lowest and 4.2% in the quintile with the highest total testosterone levels. Thus, a shorter androgen receptor may increase vulnerability to depression in the face of hypogonadism. The investigators suggested that this may be due to a more reactive testosterone-androgen receptor system, as shorter CAG repeat lengths have been associated with increased transcriptional activity, i.e. more androgen receptor production. This increased reactivity may also mean increased sensitiv-

ity to negative feedback by testosterone. Another potential explanation for the finding would be that because men with shorter CAG repeat lengths experience a faster decline in testosterone levels,[11] they experience more symptoms associated with the decline. This seems less likely since testosterone levels decline slowly with age regardless of androgen receptor genotype.

3.4 Testosterone and Risk of Depression

Only one study to date has evaluated the risk of depression associated with hypogonadism with a longitudinal design.[39] A group of 1456 older men (mean age 65 years) were followed-up for 2 years. Those with untreated hypogonadism were two to three times more likely to develop depression compared with men with eugonadism and men receiving testosterone replacement therapy.[38,39]

3.5 Testosterone, Impulsive Aggression and Suicide Attempts

Suicide may be perceived as an aggressive behaviour directed towards oneself. As suggested in the study of Vietnam veterans presented in section 3.3,[36] elevated levels of testosterone have been associated with a repetitive pattern of aggressive behaviour beginning early in life and a repetitive pattern of aggressiveness while intoxicated with alcohol. This was the conclusion of Virkkunen et al.[40] when they reviewed the literature on this topic. They also examined cerebrospinal fluid (CSF) testosterone levels in alcoholic impulsive offenders with antisocial personality disorder and concluded that high levels of CSF testosterone may be associated with outward directed aggressiveness or interpersonal violence. Other authors noted that the association between elevated testosterone and aggression has only been found when study populations were chosen based upon a history of outwardly directed violent behaviour.[41]

CSF testosterone levels were measured in 43 males who attempted suicide, with the hypothesis that elevated testosterone may be associated with inwardly directed aggressive behaviour.[42] In contrast to the studies of testosterone and outwardly directed aggression, they did not find associations between high levels of testosterone and deviant aggressive impulses, impulsiveness or substance use disorder. They did find positive correlations between CSF testosterone levels and ratings of irritability and verbal aggression in patients with cluster B (antisocial, borderline, narcissistic and histrionic) personality disorders. This seems an intuitively obvious finding since these patients with lifelong histories of impulse control difficulties and aggressive behaviour are the most predictable personality in whom to expect this relationship to exist. Overall, this group of males who attempted suicide had lower CSF testosterone levels than the previously studied group of impulsive alcoholic offenders with antisocial personality disorders.[40,42] The investigators did not feel that this study supported their hypothesis that elevated testosterone level is associated with inwardly directed aggressive behaviour. They concluded that any relationship between high testosterone level and impulsive aggression was more likely to apply to aggression directed at others.[42]

4. Effects of Testosterone Administration on Depression

4.1 Testosterone Replacement in Males with Hypogonadism not Selected for Depression

Hypogonadism in a group of men aged 25–40 years who had never been treated was associated with more depression, fatigue, confusion and anger compared with healthy controls. Testosterone replacement therapy for 1 year in the same hypogonadal men improved some of these parameters, but not depression. The experience of drastically delayed puberty in these men may have contributed to their continued depression.[43] A case study of a similar male whose chronic testosterone deficiency was not discovered until the age of 31 years described improvement in mood symptoms over 4 years of testosterone replacement therapy. He start-

ed out as actively suicidal, the cause of which seemed to be his identity struggles from knowing he had not developed like other males. As his physical puberty developed and he received concurrent psychotherapy, he experienced sustained psychological improvements in ego strength, self-confidence, social presence and libido. It is difficult to apply these observations to older males as the untreated patients with hypogonadism are a different type of patients, but they do lend some support to the hypothesis that testosterone replacement therapy can improve depression.[44]

The largest studies focusing on mood changes with testosterone replacement therapy in younger males with hypogonadism were conducted by Wang et al.[45] The studies almost exclusively included men who had been treated before, eliminating the confounding effects of delayed puberty. Firstly, they studied 51 males with hypogonadism, aged 22–62 years, in whom testosterone replacement therapy was discontinued for at least 6 weeks. At the baseline, untreated condition, all men had total testosterone levels <250 ng/dL. While untreated, serum testosterone (area under the curve) correlated positively with friendliness and sense of well-being, and correlated negatively with nervousness, irritability and tiredness. These correlations were weak, but consistent across positive and negative mood parameters. Testosterone replacement therapy for 60 days led to decreases in anger, irritability, sadness, tiredness and nervousness, and improvements in energy level, friendliness and sense of well-being. Correlations between testosterone and mood parameters disappeared after testosterone replacement therapy, suggesting that these relationships are not noticeable within the normal range of testosterone levels. They followed-up this study by evaluating the effects of 6 months of testosterone replacement therapy in 30 males with hypogonadism aged 20–59 years. During the 6-month treatment period the patients were less nervous, more alert and energetic, and friendlier compared with the baseline, treatment-free period. While the results of open-label trials must be interpreted with caution, these studies suggest that low testosterone levels can lead to negative mood symptoms and testosterone replacement can improve mood-related parameters in men with hypogonadism.

4.2 Testosterone Replacement Therapy for the Treatment of Depression in Hypogonadism

Seidman and Rabkin[46] studied testosterone replacement to augment treatment with selective serotonin reuptake inhibitors (SSRIs) in five men with hypogonadism. All had major depression refractory to at least 2 months of a maximum tolerated dose of an SSRI. The mean age at baseline was 40 years (range 34–50 years) and the mean total serum testosterone level at baseline was 277 ng/dL (range 223–320 ng/dL). The median duration of SSRI therapy at baseline was 3 months and the median duration of the current depressive episode was 12 months. Patients were treated with testosterone enantate 400mg intramuscularly every 2 weeks for 8 weeks. Depression in all patients remitted rapidly with testosterone replacement therapy. The mean Hamilton Depression Rating Scale (HAM-D) score decreased from 19.2 at baseline to 7.2 by week two. Total testosterone levels during treatment ranged from 980 to 1215 ng/dL, which were mostly above the laboratory's normal range of 300–990 ng/dL. After the 8-week study, four patients entered a 6-week maintenance phase. At the end of this period, these four patients received placebo injections under single-blind conditions and continued SSRI treatment. Three of the four patients relapsed within the next 2 weeks, with the mean HAM-D score worsening from 2.7 to 11.3 over the 2-week period. This study supports the use of testosterone replacement therapy for the augmentation of SSRI therapy in men with hypogonadism with treatment-refractory major depressive disorder, and suggests that some degree of maintenance therapy may be necessary to sustain the benefits on mood.[46] The

small sample size and open-label nature of the study are major limitations.

In another study, Seidman et al.[47] studied testosterone replacement as monotherapy for major depressive disorder in men with hypogonadism (total testosterone level ≤350 ng/dL). This was a 6-week, randomised, double-blind trial in which 13 men received testosterone enantate 200mg intramuscularly weekly and 17 received placebo injections. The mean age of patients was 52 years (range 35–71 years). The mean total serum testosterone level at baseline was 266.1 ng/dL and the mean baseline HAM-D score was 21. The mean testosterone level in the treatment group at endpoint was in the upper-normal range (981.3 ng/dL). HAM-D scores improved to means of 10.1 in the treatment group and 10.5 with placebo. In the treatment group, 38.5% (5/13) of patients responded, defined by ≥50% reduction in HAM-D score, compared with 41.2% (7/17) in the placebo group. The only identifiable difference between these treatment groups was a small improvement in sexual functioning in the treatment group. This study suggests that testosterone monotherapy is not an efficacious treatment for major depressive disorder, even in hypogonadism.[47] It may be efficacious in treating depressive syndromes in men with hypogonadism, but once major depression is present, an antidepressant may also be needed.

Most recently, testosterone gel supplementation was studied to augment antidepressant therapy in men with a low or borderline morning total serum testosterone level (100–350 ng/dL) and treatment-refractory depression.[48] Of 56 treatment-refractory patients aged 30–65 years who were screened, 24 (42.9%) patients had total morning testosterone levels ≤350 ng/dL. This observation alone is important in that it suggests a high rate of hypogonadism in men with treatment-refractory depression, even in a non-elderly patient population. Twelve patients were randomly assigned to 1% testosterone gel (10 g/day) and ten to placebo gel. All patients continued their previous antidepressant regimen. Mean baseline HAM-D scores were 21.8 in patients treated with testosterone gel and 21.3 in those who received placebo. Patients treated with testosterone gel had a mean total testosterone level of 789 ng/dL after 1 week of treatment compared with 249 ng/dL in patients treated with placebo. One patient treated with testosterone gel did not return after the baseline visit. Three patients treated with testosterone gel actually had increases of <70 ng/dL in testosterone levels, suggesting the possibility of noncompliance. These patients had little improvement in their depressive symptoms. Despite this, the patients treated with testosterone gel improved at a faster rate than the patients treated with placebo on the HAM-D. Testosterone was superior to placebo in the treatment of both vegetative and affective symptoms, showing that improvements were not solely in somatic symptoms such as fatigue and libido. With regard to degree of response, three patients treated with testosterone gel had improvements of >50% on the HAM-D and three had improvements from 36% to 43%. No patient treated with placebo had an improvement of >30% on the HAM-D. Changes in the BDI scores were not significantly different between the groups, but the trend favoured testosterone enough to suggest a type II error caused by limited sample size. Clinical Global Impression-Severity scores improved at a faster rate in the patients treated with testosterone gel than the patients treated with placebo. Overall, the response to testosterone supplementation was not particularly robust; however, it was clinically significant, especially as it was in treatment-refractory patients. One patient treated with testosterone gel developed increased nocturia and difficulty with urination, suggesting an exacerbation of benign prostatic hyperplasia (BPH). He also had no improvement in depression and was thus withdrawn from the study after 4 weeks. No other adverse events were attributed to testosterone.[48]

4.3 Testosterone Treatment for Late-Life Depression in Eugonadal Males

The only study to examine testosterone therapy for the treatment of depression in eugonadal males was an open-label study of 15 males with major depressive disorder who were >50 years of age.[49] Eugonadal was defined as having a free testosterone level within the normal range for men of their age. Patients were antidepressant-free for at least 1 year before and during the study. There was a 2-week placebo lead-in period followed by randomisation to receive either a physiologic (100mg) or supraphysiologic (200mg) dose of testosterone cipionate intramuscularly on a weekly basis for 6 weeks.

Overall, the mean HAM-D score decreased from 20.1 to 11.9, which was significant. There was no difference by dosage group in response to testosterone cipionate or in testosterone levels achieved during treatment. The most interesting finding of this study was that the ten patients with late-onset depression (first episode at age ≥45 years) had a much greater response than the five with early-onset depression. The mean HAM-D scores in those with late-onset depression decreased from 19.8 to 9.3 compared with a decrease from 20.8 to 17.0 in those with early-onset depression. These group differences were statistically significant ($p = 0.011$). Six of ten patients with late-onset depression responded, defined by a HAM-D score reduction of ≥50%, compared with none of the five patients with early-onset depression. Five of ten patients with late-onset depression experienced remission, defined by a final HAM-D score of ≤7, compared with none with early-onset depression. Correlations between testosterone levels and HAM-D score changes suggested that higher doses were not beneficial in improving response.

This study suggests that testosterone monotherapy may be effective in the treatment of late-onset depression in older, eugonadal males.[49] A placebo-controlled follow-up study that also compares testosterone therapy to conventional antidepressants is needed.

5. Special Populations

5.1 Testosterone in Parkinson's Disease

Testosterone replacement therapy in Parkinson's disease has recently been evaluated. In one Parkinson's disease registry, 24 of 68 patients (35%) had total testosterone levels <325 ng/dL. Improvement in nonmotor symptoms that were consistent with ADAM was described in a series of five patients treated with testosterone replacement therapy.[50]

This finding was followed by an open-label study of testosterone replacement therapy in ten men with Parkinson's disease and testosterone deficiency, defined by a free testosterone level <80 ng/L, who also displayed symptoms consistent with ADAM. Each man applied testosterone gel 5g daily (equivalent to testosterone 5mg). Patients were ≥45 years of age (mean 70.8 years) and had a Mini-Mental State Examination score ≥26 (mean 28.2). A battery of tests that included the St Louis Testosterone Deficiency Questionnaire, the HAM-D and the Hamilton Anxiety Questionnaire (HAM-A) were administered.

At baseline, the mean number of symptoms reported on the St Louis Testosterone Deficiency Questionnaire was 7.9, compared with 5.6 at 1-month follow-up, which was a significant change. Six patients were evaluated after 3 months of treatment and the mean number of testosterone deficiency symptoms was 5.8. This change from baseline was of borderline significance ($p = 0.08$). There were mild improvements on most of the measured symptoms. The mean HAM-D and HAM-A scores were 13.6 and 17.9 at baseline and did not show significant improvement after 1 or 3 months. There was a trend towards significant improvement on the HAM-A with a mean score of 15.0 at 1 month ($p < 0.1$), but this was lost after 3 months of treatment. It is notable that these scores do not reflect severe symptoms of anxiety and depression, thus a robust effect would be difficult to observe. The investigators noted that only four of ten patients had

a doubling of free testosterone level, suggesting that a higher dose might have been more helpful for some patients. To date, the evidence for the use of testosterone in Parkinson's disease with comorbid depressive and other symptoms of ADAM is not compelling, but the strategy deserves evaluation in a placebo-controlled trial.[51]

5.2 Testosterone in HIV Infection

A number of mechanisms may lead to hypogonadism in patients with HIV infection. Approximately 15–20% of patients receiving potent antiretroviral therapy and 50% of patients with AIDS are hypogonadal. Testosterone deficiency contributes to loss of lean body mass, insulin resistance, anaemia, osteoporosis, dyslipidaemia, increased truncal fat and increased depressive symptoms in men infected with HIV. In placebo-controlled trials, testosterone replacement therapy has been shown to increase weight, lean body mass, libido and energy, and decrease depressive symptoms.[52] Currently, these findings are only indirectly relevant to non-HIV-infected older males, as the hypogonadal symptoms are similar in HIV-infected and older populations. However, with more effective HIV treatment regimens, the population of older HIV-infected men will undoubtedly grow in years to come. Testosterone replacement therapy may be an important treatment modality in these men.

6. Adverse Effects and Monitoring of Testosterone Therapy

Acne, gynaecomastia, oedema and local reactions to injections or patches are the most commonly reported adverse effects seen with testosterone replacement therapy.[6] Polycythaemia may also occur and periodic haematologic assessments are recommended, although men with hypogonadism may be anaemic and an increase in haematocrit within the normal range might be considered beneficial for some.[53] Evidence is beginning to suggest that androgens may actually be beneficial in coronary artery disease.[15,16] However, the effects of androgens on lipids and cardiovascular risk are still not clear. Thus, it is prudent to obtain a fasting lipid profile at baseline and at least yearly thereafter if maintenance testosterone therapy is administered. Androgens also occasionally cause fluid retention, which may affect cardiovascular risk. Liver toxicity has also been attributed to testosterone therapy, although the alkylated forms are almost exclusively responsible. These are not recommended. Regardless, it is also prudent to check liver function tests at baseline, quarterly for the first year, and yearly thereafter if maintenance therapy is employed.[54]

Obstructive sleep apnoea is a potential problem with testosterone replacement therapy that has not been well characterised. In one series of five men with hypogonadism who were administered testosterone replacement therapy for 6 weeks, obstructive sleep apnoea developed in one man and markedly worsened in another. Both had reductions in oxygen saturation, increased haematocrit, and developed cardiac dysrhythmias during sleep. All patients had a decrease in hypoxic ventilatory drive when on testosterone therapy.[55] Paradoxically, nocturnal testosterone secretion is reduced in men with obstructive sleep apnoea, even after adjusting for obesity and age. Sleep fragmentation and hypoxia had the greatest association with decreased testosterone.[56] The development of dysrhythmias also contrasts the evidence that testosterone administration can reduce myocardial ischaemia in men with coronary artery disease and chronic stable angina, probably due to coronary vasodilation.[15,16,57] There is not enough evidence at this time to recommend routine monitoring for sleep apnoea in patients receiving testosterone replacement therapy, but clinicians should be aware of the potential problem.

Prostate carcinoma is the most worrisome potential problem with testosterone therapy. Pre-existing prostate carcinoma is an absolute contraindication to testosterone; however, testosterone therapy does not cause prostate carcinoma, but only accelerates an existing carcinoma. Also, testosterone therapy does not cause BPH,[53] although at least one study de-

scribed a worsening of BPH symptoms with testosterone therapy that resolved upon discontinuation of the testosterone therapy.[48] Antiandrogen agents can also treat BPH.[53] Regardless, BPH is not a contraindication to testosterone therapy unless bladder outlet obstruction is severe. Overall, evidence suggests that testosterone therapy may result in small increases in prostate size and prostate specific antigen (PSA) levels, but that these generally stay within the normal range.[53]

Because testosterone therapy can worsen prostate carcinoma, the prostate should be assessed at baseline. Total PSA levels should be measured and digital palpation of the prostate should be performed. If these are abnormal then a free PSA should be considered and if the levels are under 15%, a transrectal ultrasound and biopsy of the prostate is indicated. If PSA is normal, levels should be monitored regularly, at least every 3 months for the first year and yearly thereafter.[54] One potential problem with this strategy is that these tests may not be sensitive enough in men with hypogonadism. One study found a 14% rate of adenocarcinoma of prostate determined by needle biopsy in men with low free testosterone levels, normal PSA levels and digital rectal examinations.[58] This reduced sensitivity of PSA levels in predicting prostate cancer in the face of hypogonadism supports the use of needle biopsy or transrectal ultrasound at baseline, although these studies may be considered excessive and impractical due to morbidity and expense. It is not entirely clear whether PSA becomes a more sensitive monitoring tool once testosterone replacement therapy is instituted. If this were the case then frequent monitoring of PSA levels would likely unmask existing prostate cancer that was undetected by baseline studies. For the time being, most experts do not recommend that transrectal ultrasound and needle biopsies be performed universally at the inception of testosterone replacement therapy.

7. Testosterone Formulations

7.1 Oral Formulations

Oral formulations are convenient from the standpoint of dosage flexibility, the ability to immediately discontinue therapy, and that they can be self-administered. However, fluoxymesterone and methyltestosterone are not recommended because of extensive first-pass metabolism by the liver and their association with liver toxicity. Mesterolone, an oral dihydrotestosterone derivative, is a poor choice because it is not aromatisable and, thus, cannot be converted to estrogen, therefore it only has a partial androgenic effect. Testosterone undecanoate is the only oral testosterone formulation that is well tolerated and effective for testosterone replacement. It bypasses first-pass liver metabolism and is free of liver toxicity. It must be administered with meals because it is liposoluble. The usual dose of testosterone undecanoate for testosterone replacement is 120–200 mg/day, although it has not been studied for the treatment of depression. Oral formulations do not mimic the normal circadian rhythm of testosterone, although the timing and amount of doses can be adjusted to do so. However, the clinical significance of mimicking circadian rhythms is not clear.[54]

7.2 Parenteral Formulations

Parenteral testosterone esters are inexpensive and well tolerated, but have disadvantages. These include the requirement for injections at least every 2–3 weeks and large variations in testosterone levels that may result in swings in mood and well-being. Intermittent supraphysiologic levels may also lead to breast tenderness and gynaecomastia. Testosterone propionate is short-acting and requires injections every other day. The enantate and cipionate esters are commonly-used longer-acting formulations that can be administered every 10–21 days; however, the aforementioned shortcomings apply. There is a formulation that combines short- and

long-acting esters (propionate, phenylpropionate, isocaproate and decanoate) that is supposed to have a longer duration of action (Sustanon®, N.V. Organon, The Netherlands)[1].[54]

7.3 Transdermal Formulations

Transdermal testosterone formulations include scrotal and non-scrotal patches, as well as a gel. These formulations best mimic circadian rhythms and offer a fairly non-intrusive, convenient form of therapy. Scrotal patches require shaving of the scrotal skin and often poorly stay in place. The high levels of 5α-reductase in the skin also cause them to produce abnormally elevated dihydrotestosterone levels. Thus, these have fallen out of favour. Non-scrotal patches produce normal levels of estrogen, dihydrotestosterone and testosterone, and are good treatment options. Their major drawback is that skin reactions to absorption-enhancing agents are common and can be as severe as chemical burns. The testosterone gel has the same advantages as the patches, but does not cause frequent skin reactions. The main concerns are that others may be exposed to the gel through skin-to-skin contact and that there are no long-term studies of its use.[54]

8. Conclusion

The exact role of testosterone in depression has yet to be clarified. Evidence supports a relationship, although perhaps weak, between low levels of testosterone and depressive symptoms in elderly males. Androgen receptor polymorphisms appear to be important, with shorter CAG repeat lengths associated with a greater risk of depression in the face of hypogonadism.[38] The relationship becomes less clear when factors such as medical illness come into play, as some of these factors are related to both testosterone levels and depression.[6,59] Hypogonadism does not seem to be an integral part of major depressive disorder, but it may play a role in dysthymia in elderly males.[34] Clinical trials are necessary to evaluate the efficacy of testosterone in alleviating dysthymia in this population. Hypogonadism may be especially common in men with treatment-refractory depression.[48] Low testosterone levels may also increase the risk of incident depression in elderly males.[39] Randomised studies of testosterone for the prevention of depression in males with hypogonadism have not yet been conducted, but may provide important information.

A double-blind, placebo-controlled trial supports the short-term use of testosterone supplementation to augment antidepressants in males with hypogonadism with treatment-refractory depression.[48] This is the best evidence to date for the use of testosterone in depression. Case studies suggest that maintenance therapy may be necessary for some men.[46] Testosterone replacement also appears to reduce the psychiatric symptoms of ADAM, including depressive symptoms;[45] however, testosterone monotherapy has not yet proved useful in men with hypogonadism and major depressive disorder.[47] It is likely that antidepressants need to be used concurrently for many of these men. An open-label study has suggested that testosterone may be useful for the treatment of late-onset (at or after the age of 45 years) depression in older males, but perhaps not useful if their depressive disorder had an early onset (before the age of 45 years).[49] A double-blind, placebo-controlled trial is needed to test this theory and also compare the efficacy of this treatment strategy to that of standard antidepressants. The tolerability of long-term testosterone replacement in males with hypogonadism has been demonstrated,[6] but long-term treatment with testosterone of patients with depression needs to be studied more thoroughly. Future studies of testosterone replacement therapy in depression should evaluate androgen receptor polymorphisms and their importance to response. ADAM may be an important public health problem, the negative impact of which may be reduced by androgen replacement therapy; however, much

1 The use of trade names is for product identification purposes only and does not imply endorsement.

work is still needed to clearly define the role of testosterone and its pharmacologic replacement in the prevention or treatment of depressive syndromes and overall health in aging males.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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