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PATIENTS WITH TESTOSTERONE DEFICIENCY SYNDROME AND DEPRESSION

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Summary.- Prevalence of depression in men increases with age, so does the prevalence of hypogonadism. Depression and anxiety are the most common psychopathological symptoms associated with male hypogonadism. The question is whether the age-related gradual decline in testosterone levels contributes to the rising rate of depression in older men.

Many studies have demonstrated the improvement in depressive symptoms in hypogonadal men with testosterone supplementation. However, a subpopulation of hypogonadal men appear to be better responders to TRT when treated for depression.

Testosterone deficiency is associated with numerous non-specific symptoms including decline in libido, erectile dysfunction, increased fat deposition, decreased muscle mass, decreased energy and depression. The relationship between increased depressive symptoms and declining testosterone levels is complex because many conditions are independently associated with depression and testosterone deficiency. These conditions include medical illnesses, such as HIV/AIDS, and obesity, stress, smoking, and alcohol abuse.

While the literature does not support a consistent relationship between testosterone levels and depressive symptoms most studies do suggest that lower testosterone levels are associated with depressive symptoms. Furthermore, TRT has been shown to improve depressive symptoms in most men. This could be due to the fact that testosterone is a modulator of GABAA receptors and inhibits 5-HT3 receptors centrally. However there appears to be a subpopulation of depressed male patients that tend to respond best to TRT. These patients include men who have HIV/AIDS, mild depression, more severe testosterone deficiency, use transdermal testosterone as opposed to IM testosterone, and those not responding to SSRIs. However, patients taking SSRIs also experience a significant improvement in depressive symptoms once treated with TRT.

Men with depressive symptoms and testosterone deficiency syndrome should be given a trial of testosterone replacement therapy for at least 3 months as TRT alone may improve clinical symptoms of depression. Furthermore, men already on SSRIs may also experience further improvement in depressive symptoms after initiating TRT.

Keywords: Depression. Testosterone deficiency syndrome. Testosterone replacement therapy.
Resumen.- La prevalencia de depresión en hombres aumenta con la edad, al igual que la del hipogonadismo. Depresión y ansiedad son los síntomas psicopatológicos más comunes asociados con el hipogonadismo masculino. La cuestión es si la disminución gradual de los niveles de testosterona relacionada con la edad contribuye al aumento de las tasas de depresión en ancianos. Muchos estudios han demostrado la mejoria de los síntomas depresivos en varones con hipogonadismo con el suplemento de testosterona. Sin embargo, una subpoblación de varones con hipogonadismo parecen ser mejores respondores al tratamiento sustitutivo con testosterona (TST) cuando reciben tratamiento para la depresión. El déficit de testosterona se asocia con numerosos síntomas inespecíficos incluyendo disminución de la libido, disfunción eréctil, aumento de los depósitos de grasa, disminución de la masa muscular, disminución de la energía y depresión. La relación entre aumento de los síntomas depresivos y la disminución de testosterona es compleja porque muchas condiciones tienen una asociación independiente con la depresión y el déficit de testosterona. Éstas condiciones incluyen enfermedades médicas, como VIH/SIDA, y obesidad, estrés, tabaquismo y abuso del alcohol. Mientras que la literatura no respalda una relación consistente entre los niveles de testosterona y los síntomas depresivos la mayoría de los estudios sugieren que los niveles bajos de testosterona se asocian con síntomas depresivos. Además, el TST ha demostrado que mejora los síntomas depresivos en la mayoría de los hombres. Esto puede ser debido al hecho de que la testosterona es un modulador de los receptores de GABAA e inhibe los receptores de 5 HT3 centrales. Sin embargo parece haber una subpoblación de pacientes varones con depresión que tienden a responder mejor a TST. Estos pacientes incluyen varones con VIH/SIDA, depresión leve, déficit de testosterona más severo, uso transdérmico de testosterona en oposición a testosterona intramuscular, y los que no responden a inhibidores selectivos de la recaptación de serotonina (SSRI). Sin embargo, los pacientes que toman SSRIs también experimentan una mejoria significativa de los síntomas depresivos una vez tratados con TRT. Los varones con síntomas depresivos y SDT deberían hacer una prueba con TST durante al menos tres meses porque el TST solo puede mejorar los síntomas clínicos de depresión. Además, los varones que ya están en tratamiento con SSRIs también pueden experimentar una mejoria adicional de los síntomas depresivos después de iniciar el TST.

Palabras clave: Depresión. Síndrome de déficit de testosterona. Tratamiento sustitutivo con testosterona

INTRODUCTION

Depression is a leading cause of disability throughout the world and affects approximately 2% to 5% of the population (1, 2). While depression is generally twice as common in females as in males (8.3% vs. 4.6%), studies have found no gender difference between older men and women in the prevalence of clinically significant depression (8.6% vs. 7.9%) (3, 4).

While the prevalence of depression in men increases with age, so does the prevalence of hypogonadism. It has been reported that roughly 39% of men over the age of 45 years suffer from androgen deficiency and roughly 8% of men over the age of 50 years suffer from symptomatic androgen deficiency (5, 6). Depression and anxiety are the most common psychopathological symptoms associated with male hypogonadism (7). The question is whether the age-related gradual decline in testosterone levels contributes to the rising rate of depression in older men.

Several studies suggest an association between low testosterone levels and depressive symptoms (8, 9). However, this relationship between low testosterone and depression appears to be complex and associated with many factors, such as androgen receptor genetic polymorphisms. Many studies have also demonstrated the improvement in depressive symptoms in hypogonadal men with testosterone supplementation (8, 9). However, a subpopulation of hypogonadal men appear to be better responders to TRT when treated for depression.

CLINICAL SCENARIO-THE REAL STORY

Personal background

The patient is a 65-year-old Caucasian male with a past medical history significant for HIV, diabetes, hypertension, osteoporosis, and back pain. He reports two years of significant decrease in libido, energy, and quality of erections. He is moderately obese and has smoked 1 pack of cigarettes a day for the past 27 years. He drinks alcohol on occasion and does not take any drugs. He has a long history of depression and has taken SSRIs for the past 15 years with only mild improvement in his depressive symptoms. He has not been screened for testosterone deficiency syndrome in the past.

The patient has never had surgery and has a family history significant for a paternal uncle with prostate cancer. The only medications he takes
PATIENTS WITH TESTOSTERONE DEFICIENCY SYNDROME AND DEPRESSION

Besides venlafaxine (SSRI) are metformin, metoprolol, and opioids for his chronic back pain.

On physical examination he appears depressed. He is obese and has mild muscle wasting. His wife states that he regularly snores when he sleeps. Laboratory values include a morning total testosterone of 150ng/dl and a free testosterone of 30ng/dl. He has a PSA of 1.5ng/dl and a hematocrit level of 50 g/dl.

Relevant clinical data

This patient has low testosterone and many risk factors for low testosterone including metabolic syndrome, chronic opioid use, HIV, diabetes, and, possibly, obstructive sleep apnea. He is depressed and is not responding well to SSRIs. He has never been treated for low testosterone in the past.

Complementary tests

A validated depression questionnaire such as the Beck Depression Inventory or the Patient Health Questionnaire-9 (PHQ-9) questionnaire should be administered. An ADAM and/or an AMS questionnaire would also be helpful in assessing signs and symptoms of low testosterone. This patient should also have a repeat test of morning total testosterone values as well as a measurement of LH and prolactin levels. If the LH is suppressed or the prolactin is elevated, the patient should also have a pituitary MRI to evaluate for a pituitary adenoma.

Because this patient is obese and snores and has low testosterone, he should also undergo a sleep study to check for obstructive sleep apnea (OSA). It also would be appropriate to consider administering the Epworth Sleepiness Scale to screen for OSA.

Treatment and follow-ups

Attempts should be made to wean this patient off of chronic opioids as this is a factor contributing to his testosterone deficiency. Current literature would support the suggestion that testosterone supplementation should be considered to improve his signs and symptoms of hypogonadism, including his depressive symptoms. The literature would also support the use of a transdermal gel over an injectable testosterone to achieve maximal improvement in depressive symptoms. Follow-up should include reassessment with validated instruments for depression, such as the PHQ-9 or Beck Depression Inventory, to assess improvement in depressive symptoms. Any improvements in energy, libido, and sexual function should also be documented. Follow-up should also include reassessment of testosterone levels, biannual assessment of hematocrit and PSA, and a digital rectal examination.

Discussion- Review of the Literature

While many studies suggest that testosterone replacement therapy may have an antidepressant effect in depressed patients, the literature is conflicting. A recent meta-analysis explored the effect of TRT on depression using both a systematic review of the literature and a meta-analysis (10). Seven studies (N = 364) were identified that included control group receiving placebos in a double-blind design. Meta-analysis of the data from these studies demonstrated a significant improvement in depressive symptoms after initiation of TRT in hypogonadal men when compared to results in men receiving the placebo (z = 4.04, p < 0.0001). These authors concluded that TRT may have an antidepressant effect in depressed patients, especially those with hypogonadism or HIV/AIDS, and in elderly subpopulations.

Testosterone deficiency is associated with numerous non-specific symptoms including decline in libido, erectile dysfunction, increased fat deposition, decreased muscle mass, decreased energy and depression. The relationship between increased depressive symptoms and declining testosterone levels is complex because many conditions are independently associated with depression and testosterone deficiency. These conditions include medical illnesses, such as HIV/AIDS, and obesity, stress, smoking, and alcohol abuse.

The Use of TRT to Treat Depression

There have been many studies demonstrating the correlation between testosterone deficiency and depression. Furthermore, there is evidence to suggest that testosterone replacement in these patients improves depressive symptoms. Almeida et al demonstrated a significant increase in depressive symptoms when eugonadal men underwent androgen deprivation therapy (ADT) for prostate cancer (11). Moreover these men experienced a significant improvement in depressive symptoms once ADT was discontinued. Several studies have also demonstrated that major depressive disorder can lead to blunting of testosterone levels in older men (12, 13).

Pope et al conducted an 8-week randomized, placebo-controlled trial with testosterone transdermal gel in men who had refractory depression and low or borderline testosterone levels (9). Twenty-two hypogonadal depressed men were evaluated at the end of the study and were randomly assigned to
receive 1% testosterone gel (10 g/day) or a placebo. Each patient continued his existing antidepressant regimen. Ten men receiving testosterone and nine receiving placebo completed the 8-week trial. Men receiving testosterone gel had significantly greater improvement in scores on the Hamilton Depression Rating Scale than subjects receiving the placebo. Although this was a small study, it was one of the first to demonstrate the potential benefits of TRT to treat depression.

A recent multi-center, 12-month observational registry included 849 hypogonadal men prescribed 1% testosterone gel and assessed for the effect of long-term testosterone replacement therapy (TRT) on symptoms of depression (8). These symptoms were measured with the Patient Health Questionnaire-9 (PHQ-9). Overall, 92.4% demonstrated some level of depressive symptoms, with 17.3% having moderately severe to severe symptoms. Subcohorts with significantly (p ≤ 0.03) more moderately severe to severe symptoms were those <60 years old, with TT levels <250 ng/dl (<8.68 nmol/l), HIV/AIDS-positive, or who used antidepressants or opioids. TT levels and PHQ-9 scores were improved significantly (p < 0.01) by 3 months of TRT. At 12 months after TRT, PHQ-9 scores were significantly improved with patients having moderately severe to severe symptoms decreased from 17.3% to 2.1%. Those patients taking SSRIs also experienced a significant improvement in PHQ-9 scores. The authors concluded that TRT may reduce symptoms of depression in hypogonadal men, including middle aged men and those using antidepressants.

Studies have found mixed results in evaluation of depressive symptoms in men already taking SSRIs. Several studies found that chronically depressed hypogonadal men refractory to SSRIs experienced significant improvements in depressive symptoms when given TRT (14, 15). Within just 12 weeks TRT in these men with low or borderline testosterone levels (200-350ng/dl) resulted in significant improvement in depressive symptoms (9, 14). However, when Pope et al sought to assess the antidepressant effects of testosterone augmentation of a serotonergic antidepressant in depressed, hypogonadal men they found different results (16). They enrolled 100 men with major depressive disorder who showed partial response or no response to an adequate serotonergic antidepressant trial. Men received testosterone gel or placebo gel in addition to their existing antidepressant regimen. Changes in depression were measured using the Hamilton Depression Rating Scale (HDRS) score and the Montgomery-Asberg Depression Rating Scale. They found no significant difference between TRT and placebo groups, although, in one analysis of treatment responders, they found a possible trend in favor of testosterone on the HDRS.

Finally, not all studies have demonstrated an association between depressive symptoms and testosterone levels. No association was reported in the Massachusetts Male Aging Study, a cross-sectional, population-based multidisciplinary survey of 1,709 men (17). It is noteworthy that, being a cross-sectional study, it was limited by confounding symptom overlap and could not comment on the incidence of depressive symptoms. In another study, T’Sjoen et al evaluated the prevalence of depression in a cohort of elderly men as assessed using a 30-item Geriatric Depression Scale (GDS) score (18). They also assessed the association between the GDS score and sex steroids, androgen receptor (AR) polymorphism, and general health status. They evaluated 428 men 70-years-old and older with serum levels of testosterone, estradiol, sex hormone binding globulin (SHBG), dehydroepiandrosterone-sulfate (DHEAS), cortisol, and the AR gene cytosine, adenine, guanine (CAG)-repeat length polymorphism. A GDS score of 11 or greater was found in 30 (12.7%) men. Age and GDS score were significantly interrelated (P<.01), as were all health-assessment scores. GDS scores were not related to (free) testosterone or AR polymorphism. These authors concluded that there was no role for testosterone in treating depression in elderly men as assessed using the GDS.

Central Neurological Effects of Testosterone

Testosterone acts as a positive modulator of GABAA receptors and inhibits 5-HT3 receptors (19). Both of these neurotransmitters act centrally and are involved in the physiopathology of anxiety and depression. Testosterone has short- and long-term α-aminobutyric acid (GABA)-ergic properties that can have an impact on mood in men (20). Testosterone has also been shown to increase both neurotransmitter function and metabolism (21-23). This further explains the anxiolytic and antidepressive effect of testosterone. Schutter et al demonstrated that in healthy young women testosterone increased the functional connectivity between left prefrontal and parietal cortices, areas considered important in the pathogenesis of depression (24). A common endocrine abnormality in depressed patients is hyperactivity of the hypothalamic–pituitary–adrenal axis and alteration of the growth-hormone and thyroid axes (25).

Androgen Receptor Sensitivity and Depression

Studies have demonstrated that androgen receptor (AR) polymorphism can explain why some men are more susceptible to depressive symptoms
(26, 27). Schneider et al assessed how sex hormone levels and AR polymorphism related to depressive symptoms in aging men (26). They conducted a cross-sectional study of 120 men from the Department of Psychosomatics and Psychotherapy, 76 men from an Andrologic Clinic, and 100 men from a community sample (CS). All men were asked to complete the Patient Health Questionnaire. Total and free testosterone, estradiol, and the AR CAG polymorphism were assessed in each of these men. They found that depression scores were positively correlated with the number of CAG repeats \(r = 0.20, p \leq 0.038\) in psychosomatic patients and with number of CAG repeats \(r = 0.27, p \leq 0.043\) and estradiol \(r = 0.31, p \leq 0.019\) in andrologic patients. In another study, Sankar and Hampson assessed salivary testosterone and androgen receptor gene (AR) polymorphism and their relation to depressive symptoms (27). They evaluated 150 depressed men between the ages of 17 and 27. These men were asked to complete the Center for Epidemiologic Studies Depression Scale and the Patient Health Questionnaire-9. They found that higher rates of sleep disorder and symptoms of depression were predicted by lower T concentrations and shorter CAG lengths. The association between T, CAG length, and sleep symptoms was seen in men who reported moderate to severe depression. In these men who reported moderate to severe depression, CAG repeats and T concentrations were also found to be significant predictors of negative affect scores, with the number of CAG repeats having the greatest impact. Finally, a study by Seidman et al demonstrated that the androgen receptor had a polymorphic CAG microsatellite coding for a variable length of glutamine residue. These authors found that men with shorter sequences of CAG repeats who have higher total testosterone levels were less likely to experience clinically significant improvements in depressive symptoms when treated with testosterone replacement therapy (28).

**Evaluation of Subpopulations of Depressive Patients**

Certain subpopulations of patients have been studied to assess the efficacy of TRT in improving symptoms of depression. The data supports the hypothesis that certain subpopulations are more inclined than others to experience beneficial improvements in depressive symptoms after initiation of TRT.

**A. Early vs Late Onset Depression**

There are conflicting results as to whether early-onset vs late-onset depression tends to respond better to TRT. Several studies have demonstrated that patients with late-onset depression tend to respond better to treatment with testosterone than those with early-onset depression. It is not clear if this effect is due to lower starting testosterone levels in older men (29-31). In a double-blind, placebo-controlled trial, Dehydroepiandrosterone (DHEA) was found to improve depressive symptoms in older men (32). However, there also are studies demonstrating improvement in depressive symptoms in younger men with early-onset depression. A study by Aydogan et al assessed the relationship between testosterone levels and psychological symptoms in young male patients with congenital hypogonadotrophic hypogonadism (CHH) (33). A total of 79 patients (39 with CHH and 40 age-matched controls) were evaluated with measurement of serum testosterone levels and validated instruments before and 6 months after initiation of TRT. The average age of the patients treated with TRT was 22 years old. The validated instrument used included the Short Form-36 (SF-36), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Arizona Sexual Experiences (ASEX). These investigators found that patients with CHH had significantly higher scores for BDI, BAI, and ASEX than control subjects at baseline \(p=0.011, p=0.036, p<0.001\), respectively. The ASEX and BDI scores significantly improved after the TRT \(p<0.001\). When compared to the control group, treatment naïve hypogonadal patients were found to have more severe symptoms of sexual dysfunction, anxiety, and depression, and poorer quality of life. After 6 months of TRT, there were significant improvements in sexual function, anxiety, depression and quality of life.

**B. Effect of Route of Administration of TRT to Treat Depression**

In a meta-analysis Zarrouf et al found that the route of TRT administration can affect the degree of symptomatic improvement in depressed men (10). In their investigation they performed four studies that administered testosterone IM injections \(n=159\), 2 studies that administered testosterone gel \(n=51\), and 1 study that used oral testosterone \(n=145\). They found a significant improvement in depressive symptoms in men treated with testosterone gel \(z = 2.32, p =0.02\), and an insignificant improvement in men receiving IM testosterone \(z = 1.88, p 0.06\). This result may be due to the steady, more consistent levels of testosterone being delivered with transdermal testosterone compared to variability in serum testosterone levels in patients receiving weekly testosterone injections.

**C. Metabolic Syndrome and Depression**

A randomized, placebo-controlled, double-blind, phase III trial by Gillay et al evaluated the effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men
with metabolic syndrome (34). The Beck Depression Inventory (BDIIA), Aging Males’ Symptoms (AMS) scale, and International Index of Erectile Function 5-item (IIEF-5) scale at baseline, 18, and 30 weeks were analyzed using multilevel analysis. A total of 170 men suffering from both the metabolic syndrome and hypogonadism were treated for 30 weeks with either parenteral testosterone undecanoate (TU) or placebo injections. There were significant improvements in BDIIA after 30 weeks. The mean difference from placebo was -2.5 points. Significant improvements were also seen in the results of the AMS and IIEF questionnaires in those men being treated compared with those receiving the placebo. The effects on the BDIIA, AMS, and IIEF-5 were strongest in men with baseline total testosterone levels <7.7 mmol/L.

D. Obstructive Sleep Apnea and Depression

Obstructive sleep apnea (OSA) has been associated with low testosterone and depressive symptoms. A study by Bercea et al assessed the relationship between serum testosterone and depressive symptoms in obese men with OSA (35). Forty patients diagnosed with severe OSA and forty aged-matched controls were enrolled in the study. The authors found that the serum testosterone levels in the OSA group were significantly lower than those in controls. In addition, OSA patients had significantly higher levels of depression than controls. A statistically significant inverse correlation has been found between serum testosterone levels and depressive symptoms. The serum testosterone level was shown to be the only independent variable significantly predictive of depression in OSA patients.

E. Treating Hypogonadal vs Eugonadal Patients with TRT for Depression

The question arises if eugonadal men receiving testosterone would also experience an improvement in depressive symptoms. A meta-analysis by Zarrouf et al found that TRT had no beneficial effect in improving depressive symptoms in eugonadal men (36). Of the 7 studies included in the meta-analysis, 5 studies enrolled patients with low TT levels at baseline (n = 252) while 2 enrolled eugonadal patients (n = 103). TRT had a significant effect on HAM-D response in the hypogonadal men (z = 3.84, p = 0.0001), but did not have a significant effect in the eugonadal men (z = 1.49, p = 0.14).

F. AIDS/HIV and Depression

Zarrouf et al also evaluated the effects of TRT in patients with HIV and AIDS when treated for depressive symptoms (36). In their meta-analysis of 7 studies, 3 studies enrolled men with HIV/AIDS (n=248) and 4 studies enrolled men without HIV (n=107). Meta analysis of these studies demonstrated that TRT had a significant improvement on HAM-D responses in HIV/AIDS patients (z = 3.33, p = 0.0009) and a smaller but still significant improvement in men without HIV/AIDS (z = 2.29, p = 0.02).

G. Treating Mild vs Major Depression with TRT

A recent double-blind randomized controlled study by Shores et al examined the effect of testosterone treatment in older, hypogonadal men with subthreshold depression (36). Men received either 7.5 g of testosterone gel or placebo gel daily for 12 weeks, followed by a 12-week open-label extension phase during which all men received 7.5 g of testosterone gel. At the end of the double-blind phase, men treated with testosterone had a greater reduction in depression (P < 0.05) and a higher remission rate of subthreshold depression (52.9% versus 18.8%, P < 0.05) than men treated with placebos. At the end of the open-label phase, men originally treated with testosterone had sustained improvement. Patients originally treated with placebo and then with testosterone also demonstrated improvement in depressive symptoms.

Message

While the literature does not support a consistent relationship between testosterone levels and depressive symptoms most studies do suggest that lower testosterone levels are associated with depressive symptoms. Furthermore, TRT has been shown to improve depressive symptoms in most men. This could be due to the fact that testosterone is a modulator of GABAA receptors and inhibits 5-HT3 receptors centrally. However there appears to be a subpopulation of depressed male patients that tend to respond best to TRT. These patients include men who have HIV/AIDS, mild depression, more severe testosterone deficiency, use transdermal testosterone as opposed to IM testosterone, and those not responding to SSRIs. However, patients taking SSRIs also experience a significant improvement in depressive symptoms once treated with TRT.

Proposed clinical algorithm-recommendations

Men with depressive symptoms and testosterone deficiency syndrome should be given a trial of testosterone replacement therapy for at least 3 months as TRT alone may improve clinical symptoms of depression. Furthermore, men already on SSRIs may also experience further improvement in depressive symptoms after initiating TRT. Certain populations
of men tend to respond better than others to TRT for depressive symptoms. These subpopulations of men include those that have HIV/AIDS, mild depression, more severe testosterone deficiency, or use transdermal testosterone as opposed to IM testosterone, and those not responding to SSRIs.

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