Prevalence Diagnosis and Treatment of Hypogonadism in Primary Care Practice

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Hypogonadism is defined as deficient or absent male gonadal function that results in insufficient testosterone secretion. Hypogonadism may be primary due to testicular failure, or secondary due to hypothalamic-pituitary axis dysfunction, resulting in the production or release of insufficient testosterone to maintain testosterone-dependent functions and systems. Hypogonadism can also result from a combination of testicular failure and hypothalamic-pituitary axis dysfunction.

Hypogonadism affects an estimated 4 to 5 million men in the United States, and although it may occur in men at any age, low testosterone levels are especially common in older males. More than 60% of men over age 65 have free testosterone levels below the normal values of men aged 30 to 35. Studies suggest that hypogonadism in adult men is often underdiagnosed and under treated. This may be because the symptoms are easily attributed to aging or other medical causes, or ignored by patients and physicians. In fact, only about 5% of hypogonadal men receive testosterone replacement. Some experts also believe that we need to reevaluate normal testosterone the levels and lower the diagnostic cutoff for hypogonadism. By doing so, many patients who we now consider to be "low- normal" would probably be considered candidates for androgen replacement.

Signs and Symptoms of Hypogonadism

Low testosterone, or male hypogonadism, is associated with a number of signs and symptoms, most notably loss of libido and erectile dysfunction (ED). Other signs of low testosterone include depressive symptoms, a decrease in cognitive abilities, irritability and lethargy or loss of energy. Deficient endogenous testosterone also has negative effects on bone mass and is a significant risk factor for osteoporosis in men. Progressive decrease in muscle mass and muscle strength and testicular dysfunction, often resulting in impaired sperm production, are also associated with low testosterone levels.

A younger patient may have pure hypogonadism as a primary event, whereas an older man may have an age-related decline in testosterone production that is a part of his ED profile. However, because both ED and loss of libido are hallmarks of hypogonadism, any patient who presents with ED should have a basic hormone profile to determine if he has low testosterone. Treatments to normalize testosterone can not only improve libido, energy level and the potential to have normal erections, but can also improve the response to sildenafil, if that is deemed appropriate treatment.

Screening for Hypogonadism

An inexpensive and reliable screening test for hypogonadism is a morning serum total

testosterone level, which measures free testosterone plus protein-bound testosterone. A morning sample is recommended, because testosterone levels demonstrate a diurnal pattern in which the highest level is reached in the early morning hours. Morning testosterone values <300 ng/dL (10.4 nmol/L) suggest hypogonadism and should be confirmed by a second assay.

If a repeat assay confirms low testosterone, luteinizing hormone (LH) should be measured to determine whether the cause is primary or secondary. LH levels <2 ng/mL suggest a hypothalamic lesion (pituitary adenoma, trauma, etc), whereas LH levels >10 ng/mL indicate primary testicular failure. Levels within the normal range suggest an age-related, decreased hypothalamic response to declining testosterone levels. In addition, serum prolactin should also be measured to rule out the presence of a pituitary tumor.

At our institution we are also currently measuring dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) levels. Some investigators believe that replacing DHEA in patients with low libidos and normal or borderline testosterone is an important component of treatment to restore sexual desire and performance. Although controlled clinical studies are needed to confirm this approach, there is growing evidence that DHEA may play an important role in the treatment of male sexual dysfunction.

ADAM Questionnaire

In addition to laboratory tests and a careful physical examination, a brief screening instrument has also been developed to aid in the diagnosis of hypogonadism. Researchers at St. Louis University created the Androgen Deficiency in the Aging Male (ADAM) questionnaire, which has been shown to be a highly sensitive (88%) instrument but with low specificity (66%), largely due to questions that identify patients with depression. However, because many men with hypogonadism don't seek medical attention, instruments such as the ADAM questionnaire can be a useful way to screen for clinical symptoms of androgen deficiency. Once testosterone deficiency is confirmed, we then consider testosterone replacement therapy.

Goals of Treatment

The goal of testosterone replacement therapy is to provide and maintain a normal level of testosterone, thereby restoring libido and improving erectile function; improving mood and providing a sense of well-being; decreasing fatigue; and improving lean body mass, strength and stamina. Also, because hypogonadism is the most common cause of osteoporosis in men, testosterone replacement may improve bone density to help prevent this disease and related complications.

Contraindications

Testosterone treatment may stimulate tumor growth in androgen-dependent cancers

and is therefore contraindicated in men with breast or prostate cancer. Some experts believe, however, that it may be used judiciously in men who are cured of prostate cancer when the benefits clearly outweigh the risks.

It is important to stress that hormone therapy doesn't cause prostate cancer. However, if a patient already has prostate cancer cells, it can increase the growth rate of that cancer. Thus, we need to monitor patients closely for prostate cancer. Accordingly, a thorough examination of the breast and prostate should be performed on the initial visit and at follow-up visits in patients on testosterone therapy. A digital rectal examination and baseline and follow-up measurements of PSA levels are recommended for older men at increased risk for prostate cancer.

In addition to the absolute contraindications, relative contraindications for testosterone replacement are sleep apnea and benign prostatic hypertrophy (BPH). Some experts believe that high cholesterol levels and hematologic abnormalities should also be considered relative contraindications to hormone therapy.

Treatment Options

Several treatment options exist for testosterone replacement, including oral preparations of testosterone derivatives; intramuscular injections of long-acting testosterone esters; transdermal patches applied to the scrotum or other areas of the body (eg, upper arms, legs, abdomen, or back); and a recently approved 1% testosterone gel. Each method possesses a unique profile as described below.

The classic form of androgen replacement is injection therapy using one of the long-acting testosterone preparations such as testosterone enanthate or testosterone cypionate. Both of these agents have been widely used for many years and are the most cost-effective method of male hormone replacement. However, both preparations must be administered every 2 to 4 weeks, and although they are effective, they are not physiologic. Testosterone levels surge to supranormal levels approximately 72 hours after injection and then decrease for 14 to 21 days. By day 14 post injection, serum testosterone levels are again below normal. These highs and lows in serum testosterone may produce significant mood swings with noticeable fluctuations in libido and sexual functioning.

Oral Testosterone

The oral testosterone preparations (methyl testosterones) available in the United States result in unacceptable levels of hepatotoxicity and should not be used for testosterone replacement therapy. In addition, these oral agents have erratic androgenic effects, since they increase serum levels of testosterone metabolites rather than produce true elevations in testosterone.

Patches and Gel

Transdermal testosterone patches and gel formulations provide relative convenience, as well as controlled release of testosterone that maintains serum levels within the normal range. This controlled release mimics the normal circadian patterns of testosterone secretion and provides a more physiologic approach to testosterone replacement by producing high morning levels of the hormone.

The first available testosterone patch was applied to the scrotum at bedtime. Although it effectively produced physiologic levels of testosterone, it had the disadvantage of excessively increasing dihydrotestosterone levels, raising concerns about its potential effects on the prostate. In addition, the scrotal patch required weekly scrotal shaving and was difficult for some patients to apply and maintain in place for 24 hours.

Other transdermal testosterone patches are now available. These patches are applied at night to skin on the arms, back, abdomen, upper buttocks or thighs. They effectively produce peak physiologic levels of testosterone in the morning, as measured by objective laboratory methods. However, the downside of the nonscrotal testosterone patches is that many patients experience dermatologic reactions at the patch site. Even after pretreatment with topical steroids, some patients may develop severe, unacceptable dermatitis, requiring discontinuation of treatment.

Testosterone Gel 1%

The newest method of transdermal androgen replacement is testosterone gel 1%, which is available in 2.5 and 5 g packets. Patients are instructed to apply testosterone gel 1%, preferably every morning, to clean, dry, intact skin on the shoulders, upper arms, and/or abdomen. The rise in serum testosterone produced by the gel can be closely monitored, allowing you to accurately restore the patient's testosterone into the normal range. Whereas testosterone patches are applied at night to accommodate their slow absorption, testosterone gel is applied each morning after a shower, as it is rapidly absorbed in only 2 hours.

Monitoring and Follow-up

Once a patient begins hormone replacement, it is critically important to have regular follow up visits to monitor dosage and side effects, the most significant of which relates to concerns about prostate cancer. As noted earlier, although testosterone replacement does not cause prostate cancer, it can increase the growth rate of existing cancer cells. Even with careful screening, some patients may have occult cancer cells that escape detection. As a result, we have patients come back 4 to 8 weeks after they start testosterone replacement therapy and do a PSA to see if they've had a change from baseline. We also measure testosterone levels to confirm that their dose is appropriate. We then follow them every 6 months with a rectal exam, a PSA and a testosterone assay. Liver function, hemoglobin and cholesterol levels are monitored every 6 months as well. If the PSA increases, we discontinue therapy and perform a biopsy. In the unlikely event that cancer is found, it is treated – and probably earlier than it would have been had the patient not been undergoing treatment and careful

monitoring. However, it really is quite rare that a patient will have prostate cancer issues with any of these replacements.

Conclusions

Testosterone replacement therapy can return hormone levels to normal ranges and help alleviate the symptoms associated with hypogonadism. Once testosterone levels are normalized, we may need to add sildenafil or other treatments to the regimen of men who experience ED. However, normalizing testosterone first greatly improves the likelihood that sildenafil or other ED treatments will be successful.

Suggested Readings

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