UPMC Rehab Grand Rounds

Hypogonadism in the Aging Male Athlete

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Clinical Vignette

JT is a 66-year-old avid runner who regularly competes in local marathons. He presents to the UPMC Physical Medicine and Rehabilitation (PM&R) Clinic for evaluation of low back pain while running. Upon further investigation, while he does have low back pain, his main complaint is a decline in performance. He reports that he "does not feel like myself" ever since he hurt his back several years ago. In addition to low back pain, he also reports decreased grip strength, decreased libido, decreased muscle bulk, and general fatigue. He is particularly concerned because he feels like he requires longer recovery time between workouts, which has led to decline in both his running and weight-training routines.

JT had an extensive workup, prior to being seen in the PM&R clinic, which included CT and MRI imaging of his back that showed mild degenerative changes appropriate for his age, but otherwise negative for acute pathology. He also has tried physical therapy, which focused on core strengthening and back stretching for the last six months, over the counter supplements, and alterations to his running regimen. Unfortunately, none of these interventions helped to improve his symptoms.

At his initial PM&R clinic visit, upon examination, JT appears fatigued. Inspection is notable for an increased body mass index (BMI) and mildly diminished muscle bulk in his extremities. However, his motor strength is within normal limits. His joints have full range of motion and pain is not elicited to palpation in his trunk, back, or extremities. Pain provocation maneuvers are negative. He is very concerned because he is unable to keep up with his normal running and lifting routines and is hoping that this office visit will provide a new rehabilitation protocol that will allow him to return to an active lifestyle.

Definition of Problem

According to the 2006 Endocrine Society Clinical Practice Guidelines, hypogonadism (also known as symptomatic late-onset hypogonadism) is defined as a clinical syndrome that results from the failure of the testes to produce physiologic levels of testosterone[1]. For the purposes of this article, we are distinguishing between this syndrome and hypotestosteronism, defined as testosterone levels outside of the normative range without any clinical symptoms.

Hypogonadism negatively impacts the quality of life of males. It can present with a wide spectrum of symptoms, including decreased libido, loss of muscle strength, anhedonia, and lack of energy and motivation[2]. Hypogonadism is associated with other conditions, such as obesity, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, diabetes, end-stage renal disease, osteoporosis, and prostate disease[3].

Some studies also have associated opioid medication usage with hypogonadism[4]. Fraser demonstrated lower levels of testosterone in patients on chronic opioids, such as heroin addicts on maintenance methadone or those with chronic non-cancer pain[5]. It has been postulated that chronic opioid use suppresses testosterone levels through direct effects on the hypothalamic-pituitary axis. However, due to the lack of controls in these studies, it is unclear whether this is a causal relationship, or merely a correlative one. A possible alternative explanation is that chronic pain is a stressful event which causes lower testosterone levels, and thus chronic pain may be the underlying cause that precedes both lower testosterone and opioid usage. Chimes and Hearndon have reported on a case series of patients with chronic pain who presented with hypogonadism in the absence of opioid use[6].

Mulligan et al estimates that the prevalence of hypogonadism in males greater than 45 years of age may approach 40%. Unfortunately, large cross-sectional studies do not exist to confirm or deny this. It is quite possible that the prevalence may be even higher due to under-diagnosis.

Differential Diagnosis and Pathophysiology

Distinguishing hypogonadism from other conditions can be challenging due to the nonspecific nature of its presenting symptoms. When suspecting possible hypogonadism, the differential diagnosis also should include mood disorders, such as depression and bipolar disorder, hypothyroidism, anemia, and nutritional deficiency. During the interview, the patient should be asked questions about libido, decreased strength, depressed mood, recent stressful events, suicidal ideation, restlessness, sleep dysregulation, skin and hair changes, and weight changes (see Table 1 and Figure 1).

TABLE 1: Differential Diagnosis to Consider in Patient with Weakness When Considering Hypogonadism

▪ Depression
▪ Thyroid disease (Hypo- and Hyperthyroidism)
▪ Bipolar disorder
▪ Nutritional deficiency
▪ Anemia
▪ Malignancy
▪ Recent trauma
▪ Recent infection
▪ Chronic systemic illness

The importance of testosterone cannot be overstated, as it plays many roles in the body. It serves as a precursor for estradiol and dihydroxy-testosterone. Besides androgenic effects, testosterone has anabolic effects in maintaining muscle growth and bone mineral density. It also is involved in the stress response and pain modulation.

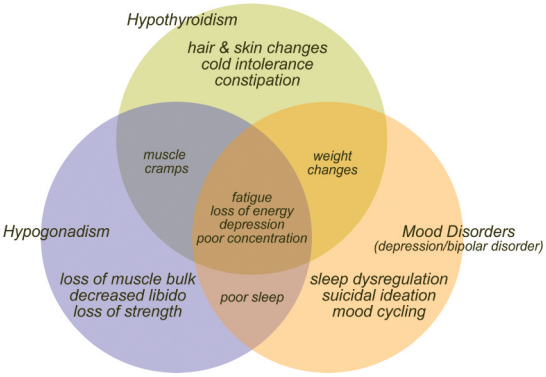

Figure 1

During stress, the normal endocrine response is to prioritize the availability of glucose in the bloodstream, thereby shifting the body from an anabolic to a catabolic state. This affects three separate hormonal pathways: an increase in cortisol, an increase in the resistance to insulin in skeletal muscle, and a drop in testosterone.

Multiple studies show the effects of stress on testosterone levels. Two studies involving young men undergoing army ranger training found that the plasma levels of testosterone were found to be significantly lower after undergoing harsh physical training[7,8]. These results have also been observed in endurance runners[9]. Psychological stress has been shown to have similar results of decreasing testosterone levels, as in the case of skydivers waiting for a jump[10].

Separate from the stress response, animal studies also have found that testosterone might be involved in pain modulation[11]. Though the exact mechanism is unclear, it is thought that low levels of testosterone lower the pain threshold. Animal studies have shown that when rodents are given estradiol, a metabolite of testosterone, their pain response in the form of paw-licking increased. A separate animal study found that testosterone administered to females eliminated differences in morphine sensitivity between males and females[12].

Examination and Laboratory Workup

Hypogonadism is a clinical syndrome. It is diagnosed both clinically and by laboratory confirmation. Screening for hypogonadism is only recommended when the patient presents with symptoms that warrant clinical suspicion (see Table 2).

Patients can present with vague complaints of subjective weakness and fatigue along with non-focal pain in their back or extremities with or without an initial injury. Patients also will frequently complain of decreased libido and strength. In JT's case, he also reported low back pain, so the musculoskeletal examination also was tailored to localize and identify the source of his pain with the use of palpation, range of motion, and pain provocation maneuvers. Because of the persistence of his back pain, JT had undergone imaging of his back, which was negative for disc disease or malignancy. The physician should carefully inspect the patient,

TABLE 2: History to Consider in the Diagnosis of Hypogonadism

Complaints more specific to hypogonadism:

- Decreased libido and sexual activity
- Decreased spontaneous erections
- Decreased muscle bulk
- Decreased explosive motor strength
- Body hair loss and gynecomastia
- Low trauma fracture

Less specific complaints:

- Decreased energy
- Depression
- Unable to concentrate
- Difficulty at workplace
- Increased body fat

taking note of muscle bulk and symmetry, body habitus, and skin and hair changes. The examiner may be able to note findings, such as decreased muscle bulk and strength, gynecomastia, and sparse body hair, depending upon the severity of the hypogonadism.

After the physician has performed the history and examination, the Endocrine Society recommends the following lab tests to diagnose hypogonadism: (1) free testosterone, which is the active, unbound form of testosterone; (2) total testosterone, which includes both bound and unbound forms; (3) follicle-stimulating hormone (FSH); and (4) luteinizing hormone (LH). Sex-hormone-binding globulin (SHBG), a glycoprotein that binds testosterone and estradiol, is ordered when the total testosterone level does not appear consistent with clinical signs. SHBG levels can be altered by different conditions. Most commonly, levels can be increased with aging, hepatic cirrhosis, and anticonvulsant use. Levels can be decreased with obesity, nephrotic syndrome, and steroid use. These labs will help distinguish between primary (testicular) and secondary (hypothalamic-pituitary) hypogonadism.

Testosterone levels should be drawn in the morning since there is a normal diurnal variation with levels dropping later in the day. Thus, labs drawn in the afternoon may be falsely low. Testosterone levels should not be drawn if the patient is acutely ill, as levels will likely be decreased due to the stress response. Liver function tests (LFTs) should also be drawn at this time to obtain a baseline, since they can be elevated from testosterone administration.

In primary hypogonadism, testosterone will be decreased, while FSH and LH will be elevated. Once primary hypogonadism has been diagnosed, a digital rectal exam (DRE) to screen for prostate disease and baseline labs, including prostate-specific antigen (PSA) level, hematocrit (Hct), and LFTs should be checked if they have not already been done, before initiation of testosterone replacement therapy. PSA level should be drawn prior to the rectal exam because the DRE may cause a temporary slight increase in levels.

In secondary hypogonadism, testosterone will be decreased, but FSH and LH will either be normal or decreased. Secondary hypogonadism warrants further workup to identify the underlying etiology, and consultation with endocrinology should be considered. This workup can include additional labs, such as prolactin level or other pituitary hormones, and possibly brain magnetic resonance imaging (MRI) to exclude malignancy of the pituitary and/or hypothalamus.

Other labs, such as thyroid-stimulating hormone (TSH), complete blood count (CBC), iron panel, folate and vitamin B-12 levels, and pre-albumin, should be considered, since conditions such as hypothyroidism, hematochromatosis, anemia, and various nutritional deficiencies can mimic hypogonadism.

Treatment Options

After the patient has presented with symptoms suggestive of clinical hypogonadism, and once the diagnosis has been confirmed by laboratory testing, physiatric management could include testosterone replacement therapy.

Testosterone may be administered through multiple routes, including intramuscular (IM), transdermal patches, transdermal gels, or buccal tablet system1. Potential benefits of therapy can include improved libido and sexual performance, increased bone mineral density (BMD), improved mood and energy, and increased lean body mass and strength[13].

Currently, absolute contraindications to testosterone replacement include prostate cancer and breast cancer. Relative contraindications include severe benign prostatic hypertrophy (BPH), prostate nodules or indurations, unexplained PSA elevation, erythrocytosis with Hct greater than 50%, unstable congestive heart failure (class III or IV), and severe untreated sleep apnea[2, 13].

IM forms include testosterone enanthate and cypionate. The recommended starting dosage is 150-200 mg every two weeks. These medications should be avoided in patients with bleeding disorders. Transdermal gel, 5-10 gm, can be applied over a covered, nongenital area of skin, with patients washing their hands after application. Transdermal patches, each 5 mg, can be applied on the back or extremities at night. Buccal tablet system, each 30 mg, can be applied to the gums every twelve hours.

In addition to medication, the patient should be advised to maintain a healthy diet along with regular moderate-intensity exercise about three to four times a week.

The Endocrine Society guidelines suggest starting with a three-month follow-up visit and then annually afterwards. Patients should be asked about changes in symptoms, such as mood, libido, energy, and physical activity, and possible medication side-effects (see section below). For IM testosterone, levels should be checked midway between injections. The target serum testosterone level is between 500 and 700 ng/dL. If the level is greater than 700 ng/dL or less than 350 ng/dL, either the dosing or frequency of the injections will need to be adjusted at the discretion of the treating physician. For transdermal testosterone, check levels three to 12 hours after application of patch. For transdermal gel, check levels one to two weeks after start of treatment. For the buccal tablet, check levels before administration of next system. The time during which to check testosterone levels changes with the routes of administration, due to their different absorption profiles.

Hct should be checked at the three-month follow-up and then annually afterwards. If Hct is greater than 50%, stop the therapy until it returns to normal values, as this abnormality appears to be more common in older men.

Prostate exam by DRE and PSA level measurement should be performed at the three-month follow-up visit and then per standard cancer guidelines afterwards. If the examination is abnormal, or if the PSA is > 4.0 ng/mL, stop therapy and refer the patient to urology for further evaluation. Because hypogonadal men often have decreased bone density, BMD of the lumbar spine and/or femoral neck density should be measured after one to two years of treatment, and then per standard of care.

Safety Profile

Currently, the main factor limiting testosterone replacement is the side-effect profile. Review of the literature, however, demonstrates that testosterone has a reasonable side-effect profile (see Table 3).

TABLE 3: Potential Side Effects of Testosterone Replacement

Absolute contraindications to testosterone replacement:

- Prostate cancer
- Breast cancer

General:

- Skin disease (acne with supraphysiologic levels)
- Benign prostatic hyperplasia exacerbation
- Gynecomastia
- Dyslipidemia
- Erythrocytosis
- Testicular atrophy
- Obstructive sleep apnea exacerbation
- Liver toxicity

Route-specific:

Intramuscular injection

- Pain at the injection site
- Mood or libido fluctuation

Transdermal patch

- Skin disease (erythema and pruritis)

Transdermal gel

- Skin disease (erythema and pruritis)
- Potential contact transfer onto others (i.e. women and children) with resulting virilization

Buccal tablet

- Localized gum irritation
- Taste alteration

General, but uncommon, potential side effects of treatment include worsening of benign prostatic hyperplasia (BPH), dyslipidemia, liver toxicity, liver tumors with the oral forms of testosterone except for testosterone undecanoate, erythrocytosis, testicular atrophy, infertility, skin problems such as erythema or pruritis, and sleep apnea[2, 13].

There are other side effects that are specific to the route of administration. Pain at the injection site is possible with intramuscular injection, along with possible mood and libido fluctuations due to the initial higher levels of testosterone in the recipient, followed by a leveling off. Skin irritation is possible with the transdermal forms of testosterone. For transdermal gels specifically, patients should take extra care to cover the application site well to prevent contact transfer onto others, such as women and children. With buccal tablets, gum irritation and alteration of taste is possible[1].

There is public concern that androgen replacement will increase prostate cancer incidence, although the evidence linking physiologic testosterone replacement to prostate cancer is unclear. In 2007, the Institute of Medicine called for more studies to examine the long-term effects of testosterone replacement[14]. Chimes has recently reviewed the amount of research devoted to testosterone and found it was disproportionately less studied given the scientific interest in the topic, especially when compared to other research topics such as estrogens and breast cancer[15]. However, the amount of research devoted to testosterone is steadily increasing.

Recent studies examining the relationship of testosterone to prostate cancer have demonstrated mixed results. Some have reported an association between higher testosterone levels and increase prostate cancer incidence[16] while others have reported no such relationship and even found an association between low testosterone levels and increased prostate cancer incidence[17,18]. Based on these conflicting results, one can conclude that the relationship between androgens and prostate cancer is poorly defined. To date, long-term controlled studies to clarify the effect of testosterone replacement on prostate cancer do not exist[13, 19].

Low testosterone levels are associated with other conditions, such as Alzheimer's disease, metabolic syndrome, and osteopenia[20, 21, 22]. In light of these findings, some preliminary studies have been performed examining androgen replacement in men with hypogonadism who had been previously treated for prostate cancer. So far, results appear promising, demonstrating stable PSA levels[23, 24].

Clinical Vignette Outcome

JT's physical examination was significant for an increased BMI and slightly diminished muscle bulk in his extremities with normal strength. Because JT had undergone extensive imaging of his back, which was essentially normal, and had complaints regarding his libido in addition to his low back pain and strength loss, there was concern for possible hypogonadism, so a screening workup was performed.

His blood work revealed total testosterone 190 ng/dL (normal 250-1100 ng/dL), SHBG 24 nmol/L (normal 17-54 nmol/L), and free testosterone 29.9 pg/mL (normal 46-224 pg/mL). His FSH and LH levels were 13.7 and 9.9 MIU/mL respectively, (normal FSH being 1.6-8 MIU/mL and LH 1.5-9.3 MIU/mL). His TSH was normal 0.97 mU/L (normal 0.4-4.5 mU/L), as was his PSA 0.9 NG/mL (range is 0.0-4.0 NG/mL). His Hct also was within normal limits.

After discussing the potential risks and benefits of testosterone replacement, JT was started on treatment with transdermal patches. Two weeks later, he called the office reporting his symptoms were greatly improved. At the three month follow-up visit, he reports that his strength and stamina returned to his baseline. He has resumed his old running routines and just recently registered for an upcoming marathon.

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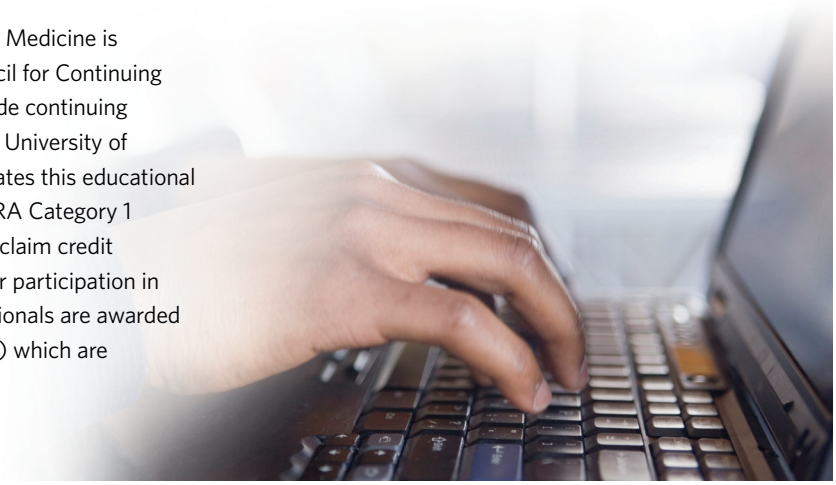

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