Subcutaneous Pellet Testosterone Replacement Therapy: The "First Steps" in Treating Men With Spinal Cord Injuries

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The authors describe the case of a 36-year-old man who presented with hormone level concerns 6 months after a rock climbing accident that resulted in paraplegia. Hypogonadism was diagnosed, and the patient received subcutaneous pellet testosterone replacement therapy. Within 6 months, the patient had substantial improvement in muscle function and was able to take several steps with the assistance of crutches or a walker. This case highlights the potential improvement in quality of life and overall prognosis resulting from the subcutaneous pellet form of testosterone when used as part of the overall treatment plan in such patients. Considering the overwhelming preponderance of hypogonadism in men with spinal cord injuries, the standard of care for such patients should include screening, laboratory hormone evaluation, and prompt treatment for testosterone deficiency.

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The incidence of spinal cord injuries in the United States is approximately 12,000 per year, with more than a quarter of a million people in the United States living with spinal cord injuries.[1] More than 80% of spinal cord injuries occur in males, with the primary causes being motor vehicle accidents, falls, acts of violence (primarily gunshot wounds), and recreational sporting activities.[1] The estimated lifetime cost varies depending on the severity of the injury, but it is estimated to be around $292,740 for the first year of injury and an additional $29,789 per year thereafter in patients with paraplegia (amounts in 2008 dollars).[1] Spinal cord injuries can have a substantial impact on a patient's quality of life, including decreased functionality, lack of independence, impaired activities of daily living, and loss of occupation. Secondary medical complications are diverse and impact nearly every aspect of health, particularly cardiovascular, respiratory, endocrine, bone, bladder, bowel, and sexual health.[2] The prevalence of insufficient testosterone levels in men with spinal cord injuries is anywhere from 47% to 60%[3,4]; however, the prevalence may actually be higher because of the low reference ranges used in the studies providing these data and because of a lack of stratification of appropriate lower limits of normal serum testosterone levels by age. A retrospective study[5] reported a positive relationship between testosterone replacement therapy and strength gains in men after spinal cord injury.

In the present report, we describe the case of a patient with paraplegia who believed that his hormone levels needed to be checked. Hypogonadism was diagnosed, and the patient's symptoms and overall quality of life improved with subcutaneous pellet testosterone replacement therapy.

Report of Case

In June 2012, a 36-year-old man with paraplegia presented to the internal medicine office with the chief complaint of "I think I need my hormones checked." He reported that he had sustained a spinal cord injury at spinal levels T10 through L2 approximately 6 months earlier after a rock climbing accident and that he had noticed several physical and mental changes since that time. He stated that he was currently attending physical therapy for rehabilitation 5 times per week but that "no matter how hard I hit it, I don't feel like I'm getting anywhere. Some days I feel like I'm going backwards." Past medical history was notable for spinal cord injury in December 2011, which required spinal stabilization and spinal fusion of the T10-L2 vertebrae (*Figure*) and subsequent hospitalization. He denied any other surgical or medical history. His medications included oral hydrocodone bitartrate/acetaminophen (5 mg/325 mg), 2 tablets twice daily for pain. He denied any drug or environmental allergies. The patient expressed a feeling of loss of self, which he reported was separate from the losses engendered by his injury. Review of systems revealed fatigue, lack of motivation, poor concentration, depressed mood, unexplainable crying episodes, gynecomastia, weight loss, muscle atrophy in the legs, and absent libido. He denied hot flashes, changes in vision, or headache.

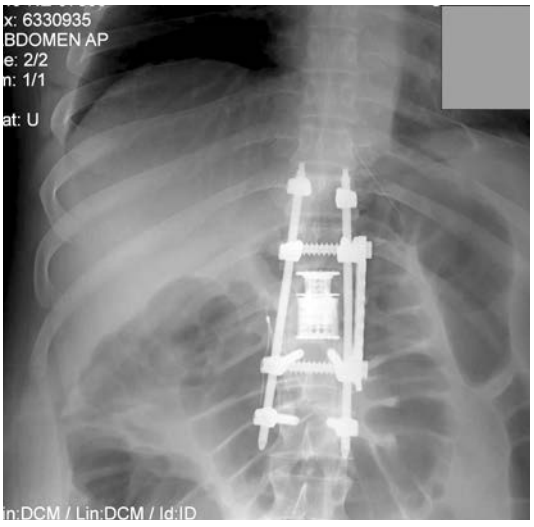

Figure.
Radiologic image of spinal stabilization and fusion in a 36-year-old man with paraplegia and hypogonadism. Hardware was placed from spinal levels T10 through L2. Gonadal innervation classically occurs at spinal levels T10 through T11.[25]

On physical examination, the patient was pleasant, appeared his age, was in a wheelchair with appropriate affect, and was obese (body mass index, 31.9). Vital signs at the time of examination revealed a normotensive blood pressure (136/36 mm Hg), normal temperature (97.3°F), regular pulse rate (98 beats per minute), and nonlabored breathing (16 respirations per minute). His skin revealed scars in the lower thoracic region from prior surgery, but he had no rashes, pressure sores, or tattoos, and his body hair was sparse. Breast examination revealed grade III gynecomastia. Musculoskeletal examination revealed muscle atrophy in the thigh and calf muscles: muscle strength was 5/5 in the upper extremities, 3/5 in the quadriceps bilaterally, and 0/5 below the knees. The patient was able to stand and balance against the examination table with the assistance of full-length leg-locking braces but was unable to ambulate. Cranial nerves II through XII were intact; mild sensation was reported above the knee and no sensation below the knee. Osteopathic structural examination showed tissue texture changes with hypertonicity at the T3-L2 spinal levels and the L3-L5 vertebrae to be extended, rotated, and sidebent right. All other findings were unremarkable.

Laboratory test results revealed low levels of creatinine (0.51 mg/dL), 25-hydroxyvitamin D (21.4 ng/mL), serum testosterone (175 ng/dL), and free testosterone (5.0 pg/mL). The patient's blood urea nitrogen/creatinine ratio (25) and C-reactive protein level (6.07 mg/L) were high. All other laboratory results were within normal limits.

On the basis of the patient's medical history, physical examination, and laboratory results, the diagnosis of hypogonadism was made. The patient also exhibited a vitamin D deficiency, which increased his risk of developing osteoporosis and related fractures, a condition common among patients with spinal cord injuries. After discussion of the risks, benefits, alternatives, and various preparations of testosterone replacement therapy, 1800 mg testosterone pellets were placed subcutaneously. The patient underwent repeat laboratory analysis at 4 weeks, which revealed slightly subtherapeutic levels, and an

additional 1000 mg was placed. Despite his subtherapeutic levels he still reported improvements in symptoms of mood and energy. Most importantly, he increased the duration of his physical therapy and was able to stand and walk a few steps with the aid of leg braces and a walker. At his 3-month checkup, the patient was very excited by his progress. He reported that he advanced from 50% to 85% weight bearing on the antigravity treadmill used in his physical therapy. At 6 months, the patient reported that he was able to walk 10 steps with the assistance of crutches and his leg braces. Pellets were replaced at a dose of 1800 mg.

Approximately 1 year after presentation, the patient was able to walk up to a quarter mile on a regular treadmill with the use of lower leg braces only and reported being able to stand on his own with the lower leg braces for extended periods of time. He attributed the accelerated pace of his progress to the testosterone replacement therapy. He had an elevated hematocrit level, which resolved after he donated blood. All symptoms at presentation improved. Although the patient reported that his increased libido was somewhat "distracting," he did not feel it bothersome enough to warrant reducing his dosage.

Currently, the patient is able to perform activities of daily living without the use of a wheelchair or walker and is able to walk both faster and for extended times with the use of a single cane before requiring rest. A video of his progression in walking is available at http://www.jaoa.org/content/113/12/921/suppl/DC1.

Comment

The pathophysiologic process of low testosterone levels in patients with spinal cord injuries is uncertain, but some evidence points to altered neural or hormonal pathways between the hypothalamus and the pituitary gland.[6] Other evidence suggests that the decrease in physical activity causes metabolic changes that decrease serum testosterone levels or conversely may be caused by low testosterone levels.[7,8] Evaluation of a patient suspected of having hypogonadism involves confirmation of decreased sperm in the semen or low serum concentration of testosterone. To distinguish between primary hypogonadism, which is a result of testicular dysfunction, vs secondary hypogonadism, which is caused by pituitary or hypothalamic dysfunction, luteinizing hormone (LH) and follicle stimulating hormone (FSH) are also measured. If the LH and FSH concentrations are elevated, the cause of the hypogonadism is testicular damage or primary hypogonadism, and if the LH and FSH are not elevated, the cause is pituitary or hypothalamic disease.[9,10]

The differential diagnosis for hypogonadism with an onset after pubertal development and with previously normal growth includes pituitary macroadenoma, prolactinoma, hyperprolactinemia, and depression. It is also important to rule out underlying external (eg, statin therapy, antipsychotic or antidepressant medications) and lifestyle (eg, excessive alcohol intake) factors that may mimic or cause decreased testosterone levels.[2,11]

It is accepted practice to measure the serum total testosterone concentration, which includes free and protein-bound testosterone. In cases in which sex-hormone binding globulin is suspected as the abnormality, free testosterone measurements may be of additional benefit. Most laboratories consider a normal total testosterone range to be about 300 to 1200 ng/dL. However, some data indicate that the upper range of normal could be significantly higher.[12,13] Testosterone in males is secreted in a diurnal fashion with maximum serum concentrations at approximately 8 AM for most males, which is when it is advisable to have blood drawn. It may also be beneficial to evaluate LH, FSH, prolactin, and hematocrit levels to rule out disease processes that are part of the differential diagnosis and to obtain a baseline level to monitor for erythrocytosis.[14]

Testosterone replacement therapy is appropriate in hypogonadal men irrespective of whether the cause is primary or secondary.[2] The goal in therapy is to restore normal serum testosterone levels; it is not known if mimicking the diurnal pattern of testosterone when undergoing hormone replacement is necessary or beneficial.[15,16] There are multiple preparations of testosterone replacement therapy. Oral alkylated androgens such as methyltestosterone are considered highly dangerous because of the side effect profile and are generally not recommended.[17] Testosterone esters such as testosterone enanthate and testosterone cypionate can be administered intramuscularly in doses starting at

100 mg once per week, 200 mg every 2 weeks, or 300 mg every 3 weeks and are biologically effective.[18,19] The disadvantage of intramuscular injection—besides the frequency required to maintain therapeutic levels—is fluctuations in energy, mood, and libido.[20] For persons with limited mobility such as the patient described in the present report, it is a logistical challenge to have such frequent office visits. Transdermal methods include creams, gels, and patches in various dosages. Although these preparations are effective and have less severe fluctuations compared with intramuscular testosterone replacement, disadvantages include transfer to women, children, and pets; odor (depending on preparation); and, infrequently, reduced absorption.[21]

The subcutaneous testosterone pellet is less common than other testosterone replacement therapies. The appropriate dose is inserted in a sterile fashion just under the skin in the subcutaneous space. Although it is considered a surgical procedure, the incision site is less than 5 mm long and requires reinsertion only 2 to 3 times per year, which made this option more suitable for our patient. Compared with the serum levels of hormone from the other therapy options, the serum levels of hormone from the pellet form tend to be released more evenly, and patients in the clinic where this service is provided report fewer complaints of fluctuations in energy, mood, and libido and increased satisfaction on the overall effect and ease of hormone replacement preparation.[22]

Regardless of the method of testosterone replacement therapy, follow-up laboratory tests within 6 to 8 weeks are recommended after initial dosing and after any change in dosage strength to ensure that the patient is receiving therapeutic levels. Adverse effects of testosterone replacement therapy mimic potential adverse effects of endogenous testosterone and can include an increase in prostate volumes and serum prostate specific antigen, possible worsening of sleep apnea, erythrocytosis, skin irritation, and secondary exposures, as previously mentioned.[2]

The present case highlights several of the tenets of osteopathic medicine, in particular that of structure and function being reciprocally interrelated.[23] By appreciating the interrelationship between the viscerosomatic responses and the connectedness between structure and function, it is not surprising that men with lower thoracic spinal cord injuries have an increased susceptibility to hypogonadism.[24] A spinal cord injury at the T10-T11 levels, which are most classically associated with the gonads, should make osteopathic physicians suspicious of dysfunction of the organ system involved.[25] By replacing the natural, bioidentical hormone testosterone, the body—with its natural healing power—was able to respond at an exponential pace.

The holism that osteopathic medicine embraces extends beyond respecting the interconnectedness of the body to appreciating the social, emotional, spiritual, and financial challenges that patients face. Although his feeling of loss of self could have been interpreted as a depression-like symptom, it fit better under the true underlying pathologic process that the patient was experiencing; for this patient, antidepressant medication would have been inappropriate. By acknowledging the loss of libido that often accompanies hypogonadism, the osteopathic physician can provide reassurance that the symptom is correctable, which was a comfort to our patient and his wife. Compared with men who have not been injured, men who have spinal cord injuries and who are single at the time of injury are less likely to marry, and those who were married at the time of injury tend to have higher divorce rates.[1] Thus, sexual health is important to the healing process and maintaining a sense of normalcy.

In addition, appreciating patients' logistical challenges, such as frequency of doses, can have a positive impact on patient compliance with medications and treatment. Our patient's insurance company initially considered testosterone replacement to be "experimental therapy." Knowing the insurance company's view allowed the provider's office to advocate on behalf of the patient to ensure that he received necessary treatment.

Manual therapy will be an important component of this patient's continued therapy. Although osteopathic manipulative treatment was not used on this patient, it could be beneficial for patients with similar presentations. Muscle energy of the spine and lower extremities may improve hypertonicity associated with stressing the muscles during physical therapy, treatment of tender points may help decrease the need for future narcotics, and lymphatic techniques such as pedal pump can

improve the exchange of waste products for nutrients and enhance circulation in a person with limited lower extremity mobility.[24]

Conclusion

Because of the overwhelming prevalence of hypogonadism in men with spinal cord injuries—and in light of the social, emotional, and physical benefits of hormone replacement therapy—the standard of care for treatment of such patients should include screening of symptoms, laboratory hormone evaluation of serum testosterone levels, and, if appropriate, prompt treatment. In any case of spinal cord injury, osteopathic physicians should provide additional attention to the organ system that may be impacted by an injury at that spinal level. The present case highlights the need for further clinical research comparing the progress of men with spinal cord injuries and hypogonadism to similar counterparts undergoing testosterone replacement therapy.

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