Testosterone replacement therapy for the primary care physician

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Testosterone replacement therapy (TRT) can have significant beneficial effects in the appropriate hypogonadal male patient. Testosterone deficiency is common in primary care practice and recognition of the signs and symptoms of this abnormality will allow physicians to choose appropriate interventions. The symptoms of clinical hypogonadism include muscle weakness, fatigue, mood changes and a reduced libido. Signs include a reduced muscle mass, osteoporosis, anemia and increased adiposity. While routine screening for testosterone deficiency, determination of testosterone levels in high risk populations, including obesity and diabetes, will help the clinician direct TRT to the patients most likely to benefit from therapy. In this article the syndrome of male hypogonadism is discussed, together with therapeutic choices available to the primary care physician.

Key Words: testosterone replacement therapy, hypogonadism, andropause, prostate cancer, erectile dysfunction

Introduction

Significant controversy still exits among the medical community regarding the appropriate use of testosterone replacement therapy (TRT). Injectable forms of testosterone have been available since the beginning of the twentieth century and the recent introduction of safe, reliable methods of testosterone supplementation (oral agents and topical gels) have renewed physicians interest in the potential therapeutic benefits of testosterone. Andropause, a term coined in the media by Gail Sheehy in the late 1980s, widened the potential scope of therapy to men with low or low normal levels of testosterone and 'softer ' symptoms. More recently, the medical community has begun to narrow this range and identify men with the clinical signs and symptoms of androgen deficiency who are likely to receive clinically significant benefits from testosterone.[1] The end organ effects of testosterone (T) are remarkable. Improved strength, better mood, stronger muscles, increased libido, the list goes on. In the truly hypogonadal patient, one cannot argue the benefits of TRT. The possible side effects of testosterone administration include hepatotoxicity, sleep and emotional disturbances, erythrocytosis and benign prostatic hyperplasia.[2] There is little long term data on prostate cancer; short term surveillance studies have shown no increased prevalence in treated patients. A recent meta analysis of 18 papers concluded that there was no relationship to the incidence of prostate cancer and serum testosterone levels.[3]

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As a Urologist, I see patients that have been 'differentiated' by their primary care physician (PCP), the tentative diagnosis of hypogonadism made and my role is confirm the diagnosis, initiate and to reassure that as long as the PCP has addressed the possible risks of TRT that he can consider a trial of testosterone, if it is indicated. The endocrinologist's role is similar. Primary care physicians, on the other hand, must wade through large numbers of male patients with hypogonadal like symptoms before actually uncovering a patient that might benefit from therapy. This is not an easy task, while considering the risk/benefit ratios. Hypogonadism shares many of the clinical manifestations of depression, erectile dysfunction and normal aging.[4] This has lead to a sense of frustration among many practitioners. The following pages are an attempt to help physicians narrow their sites and find the hypogonadal patient who requires treatment and to discuss different treatment options.

Background

Hypogonadism has a variety of biochemical definitions, but most simply can be defined as a morning serum testosterone value 2.5 standard deviations (SD) below the normal mean level in young adults. Most investigators use 300 ng/dl (Canada 7-38.0 nmol/l) as the lower limit of normal, below which many patients exhibit the biochemical and clinical signs of testosterone deficiency. Attempts to define a better marker for T deficiency (bioavailable or Free testosterone) have added little to our diagnostic abilities.[5] The other concept that is to be considered is that of "testosterone change/velocity". If one was at the upper end of the "normal" range 5 years ago, but is now at the lower "normal" (but still within) end, is that "change" significant enough for that particular individual to create the symptoms and signs of hypogonadism? Low testosterone levels are associated with a constellation of signs and symptoms including poor libido, erectile dysfunction, reduced ability to concentrate, decreased bone density, anemia, sleep disturbances, decreased lean muscle mass and fatigue. Many of these symptoms are often ignored by patients and their physicians and attributed to the natural consequences of aging. With the amount of publicity surrounding the possible 'performance enhancement' qualities of testosterone, patients have returned to their physicians to explore TRT. Andropause was coined to describe men with symptomatic androgen deficiency. While a majority of women manifest some of the symptoms of estrogen deficiency due to the rapidity of the decline, the gradual decline of testosterone in men results in a more variable and less dramatic symptom complex, hence andropause has become a less popular descriptor, replaced with symptomatic late onset hypogonadism (SLOH).[5]

As men age, there is a gradual decline in the amount of testosterone that is available at the cellular level. This is largely due to declining testosterone production from testicular Leydig cells and an increase in sex hormone binding globulin (SHBG). The result is that there is less absolute testosterone being produced and more is bound up by the SHBG, which is then isolated from the tissues. The "free" testosterone (not bound to albumin or SHBG) together with the albumin- bound testosterone, makes up what is now called "bio-available testosterone", or that component that is available to have its impact on the body. At 60, the amount of available testosterone is roughly one half that at the age of 20, suggesting that many of the symptoms attributed to aging are in part a result of reduced testosterone production.

The impact of hypogonadism on long-term morbidity is not well known. Osteoporosis and frailty have been linked to testosterone deficiency, as has erectile dysfunction and depression. A number of investigators have documented the improvement in mood, muscle strength, body composition and sexual function in hypogonadal populations appropriated treated with testosterone replacement therapy. It is largely this data, and the absence of any significant safety concerns that has convinced clinicians that TRT may have a role in improving the quality of life men with SLOH.

Effects of testosterone

Bone

Hypogonadal men are at significant risk for osteoporosis. In men over 65 years of age, the incidence of osteoporosis was twice that of eugonadal men, (12.0% versus 6.0%). In the prostate cancer population treated with androgen deprivation therapy, patients are at significant risk of osteopenia and osteoporotic fractures. Testosterone plays a role in the maintenance of bone mineral density and testosterone replacement therapy can improve bone mineral density, although its role in fracture risk reduction is unknown. Some studies have shown that minimal trauma hip fractures in men were much more common in those men with lower free testosterone than those that were eugonadal ($p < .001$).[6] Hypogonadal men, particularly those on androgen deprivation therapy for prostate cancer, should have a baseline DEXA scan with periodic evaluations depending on their clinical course.

Metabolic syndrome

There is a significant increase today in the diagnosis of metabolic syndrome.

Why be concerned about metabolic syndrome?

1) Increased risk of cardiovascular events - 2-fold

2) Increased risk of type II diabetes - 5-fold[7]

It has also been shown that there is a higher incidence of hypogonadism in men with metabolic syndrome. There is also increased risk of finding low testosterone levels in men with obesity, diabetes and hypertension, which are three of the criteria for metabolic syndrome.[8]

It seems reasonable to both look for hypogonadism in men with any of the signs of metabolic syndrome. As well, testosterone therapy in these men may help to improve upon the signs and prevent the sequelae of metabolic syndrome.

Prostate

The prostate requires the presence of testosterone for normal growth and development. The widespread use of 5 alpha reductase agents, (Proscar, Merck Inc., and Avodart, GlaxoSmithKline) which decrease intracellular levels of dihydrotestosterone, have demonstrated the dramatic reduction in prostate growth when deprived of testosterone. In addition, the effects of chemical castration on metastatic prostate cancer further demonstrates the dependence of prostate cells on androgens. There is little evidence to suggest that, the use of androgens to restore physiologic levels of testosterone could exacerbate voiding difficulties or unmask an indolent prostate cancer. Several randomized trials have failed to show an increase in prostate cancer detection in testosterone treated males.[9]

Hypogonadal patients treated with testosterone will often see an increase in prostate-specific antigen (PSA) and prostate volumes that only reach the levels of their eugonadalage-matched controls. Primary care physicians should be aware that this transient increase to age specific levels is to be expected during the first year of therapy. Subsequent PSA changes should be assessed according to the standard of care and evaluated within the context of the patients' risk factors. Always do a digital rectal examination.

Heart

Evidence suggests a modest increase in HDL levels in hypogonadal men treated with testosterone and a possible beneficial effect of testosterone on cardiovascular health. Men with lower levels of testosterone have been found to have a higher incidence of abnormal coronary angiograms. Certainly, at the present time, there is little scientific data to support a potential detrimental effect of testosterone supplementation on cardiac health. Polycythemia is most common adverse effect of TRT, patients receiving intramuscular preparations being at greatest risk. Because of this, periodic monitoring of CBC during testosterone therapy is recommended. Erythocytosis that develops in these patients responds well to cessation of therapy.[10]

Prevalence of hypogonadism in family practice populations

The range of symptoms exhibited by hypogonadal men makes them a diagnostic nightmare for the practicing physician. These patients share symptoms with large groups of other diagnoses such as depression, erectile dysfunction and obesity. What is the true prevalence of low testosterone in the typical family practice office and is it cost effective to consider screening more patients with testosterone levels?

The Hypogonadism in Males study[8] estimated the prevalence of men > 45 years of age with serum testosterone levels < 300 ng/dl visiting primary care practices in the United States. While this is a highly selected population (men seeing their physicians!), the study does give primary care physicians a rough idea of the scope of hypogonadism in their older male population. The prevalence of men with low testosterone was 38.7%. More significant though, were the comorbid conditions where low T was likely to be present. The odds ratios for men having low T levels were significantly higher in men with hypertension (1.8), hyperlipidemia (1.5), diabetes (2.0), obesity (2.4) and prostate disease (1.2). This suggests a good starting point for primary care practitioners when considering the diagnosis. When one sees a patient with any of these comorbidities it is appropriate to obtain an early morning testosterone level to use as a baseline. If significantly low and the patient seems to be refractory to treatment for their primary condition, such as diabetes, then one should consider testosterone therapy to possibly enhance the response. To date there is little evidence that low testosterone levels without the clinical manifestations of androgen deficiency poses a significant health risk. Routine screening is to be discouraged until the consequences of asymptomatic androgen deficiency are better defined.

Most men with low testosterone levels are asymptomatic and may not require treatment. The Boston Area Community Health (BACH) survey illustrated the importance of considering testosterone deficiency in the context of clinical symptoms. As

part of a general healthcare screening program, men underwent a panel of laboratory exams and answered detailed health questionnaires. Twenty-four percent of the patients studied had serum testosterone levels < 300 ng/dl, approximately 47% of men at least 50 years old with low T were asymptomatic.[8] This must be considered in context though, as a detailed history and physical exam by a trained physician might uncover significant signs and symptoms missed by patient surveys.

These data support a conservative approach to the diagnosis and treatment of androgen deficiency. An index of suspicion in the groups at high risk is likely to identify patients who might benefit from testosterone supplementation.

Diagnosis

The diagnosis of hypogonadism requires a high index of suspicion based on symptoms, exclusion of other causes and consideration of the patients' risk profile and comorbidities. In the absence of the sequelae of low T levels, patients with morning serum testosterone levels < 300 ng/dl may not require treatment.

When hypogonadism is suspected, a morning total testosterone level should be obtained. Because of the significant variablility of T levels, it is suggested that all abnormal levels be repeated before considering therapy. If the results are borderline, the test should be repeated along with LH, FSH, Prolactin and free T levels.[11]

Elevated Prolactin levels need clarification usually with an MRI of the sella turica and an endocrinology opinion. Clinical signs and symptoms are often the determining factor with respect to TRT. The threshold for initiating therapy may be lower in the anemic or osteoporotic patient, particularly if levels are in the low normal range.

A variety of questionnaires are available to assist the clinician in the diagnosis of testosterone deficiency. They are appropriate only as screening instruments due to their poor specificity. The instruments most widely used are the St. Louis University ADAM and the Aging Male Survey (AMS). Unfortunately, there are no validated instruments that can assist physicians in measuring treatment effects.[12]

Before starting testosterone, a digital rectal exam and PSA should be documented. The changing landscape of PSA's use for prostate cancer screening mandates a discussion of the risks of prostate cancer in those men who are at high risk due to their family history. While TRT has not been shown to cause prostate cancer, patients with siblings already diagnosed with prostate cancer should probably be referred to a urologist for education and a prostate biopsy if TRT is in order. In addition, patients with an elevated age specific PSA or abnormal digital rectal exam require a urologic evaluation prior to TRT administration.[13] Despite its safety, historically, testosterone remains tied to prostate cancer due to the dramatic effects of castration on the management of the disease.

A more complete discussion of the specific effects of testosterone on bone, cognitive function, body composition, sexual function and prostate can be found in a recent article published in The Canadian Journal of Urology Supplement in Dec 2007.[13]

Who should be screened for low testosterone levels?

Because almost 20% of men aged 60-69 and 30% of men aged 70-79 have low testosterone levels, screening is to be discouraged. Narrowing our sites to the high risk groups is more likely to uncover clinically significant androgen deficiency and provide physicians with a patient group with improved outcomes due to testosterone supplementation. With the introduction of safe testosterone preparations, physicians have begun to widen their scope and consider androgen deficiency when evaluating men with mild depression, frailty, decreased lean muscle mass, increased central obesity, decreased energy levels and sexual difficulties.

Metabolic syndrome

As mentioned earlier, men with obesity, diabetes and hypertension have an increased likelihood of androgen deficiency. This group of patients should have their testosterone levels assessed even if they exhibit no signs of hypogonadism. The effect of testosterone on body composition includes a decrease in fat mass and an increase in lean muscle mass, along with a decrease in insulin resistance. Testosterone also has been shown to effect the redistribution of adiposity to the viscera and the subcutaneous tissues typical of eugonadal men.[13]

The effect of testosterone supplementation on lipid levels is yet to be fully elucidated, but preliminary evidence suggests a minimal decrease in HDL levels. Population studies have demonstrated an inverse relationship between bioavailable testosterone levels and aortic atherosclerosis.[14] Previously, especially with the older (no longer available) methylated testosterones, there was a potential for significant lipid imbalance that lead to premature atherosclerosis and heart attacks. With the present esterified testosterones that are metabolized through the lymphatics, TRT can actually be cardio-protective.

Erectile dysfunction

In the absence of poor libido, the cost effectiveness of routine T determination in men with erectile dysfunction is questionable. On the other hand, patients who have failed a course of phosphodiesterase 5 inhibitors (PDE5i)) should have their testosterone levels drawn. Approximately 30% of men who fail PDE5i who are found to have low serum T will be improved by testosterone supplementation.[15] It is very safe to use the PDE5i at the same time that the patient is on TRT.

When to refer to an endocrinologist or urologist

Certainly, the majority of men with the signs and symptoms of androgen deficiency can be managed by the primary care physician. In a few instances, a team approach with input from a urologist or endocrinologist is appropriate. Secondary causes of hypogonadism such as hyperprolactinemia require endocrinologic input. Men with a strong family history of prostate cancer, an elevated PSA or abnormal digital exam should be evaluated by a urologist. In addition, significant changes in PSA levels that do not normalize with cessation or alteration of therapy should be investigated.

It has been shown that testosterone therapy does not cause prostate cancer. In men that have had a radical prostatectomy for the curative approach to prostate cancer, there is about a 20% chance for the development of symptomatic hypogonadism. If the patient is miserable with the condition and requests TRT, then he should be referred to the urologist. If the patient is a few years out and has a PSA of zero, after a significant informed consent, some physicians may consider testosterone. Very lengthy and rigid follow-up and monitoring is mandatory.

Treatment

Once the clinical and biochemical diagnosis of androgen deficiency is made, the clinician has a variety of therapeutic options to consider. The route of testosterone administration should be discussed with each patient as there are cost and compliance issues that may determine treatment success. All available preparations can normalize testosterone levels. Present options include injectables, oral preparations and topical gels. The advantages and disadvantages of each route are summarized in Table 1.

Once testosterone supplementation is instituted, patients require regular monitoring for response and safety. Certainly, during the first year of therapy, more frequent assessments of PSA and hemoglobin (q 3 months) might be in order. One should also do baseline and 6 monthly liver function tests, and DREs although the newer preparations are very safe. Patients should be informed that a 3 to 6 month trial of therapy may be necessary before discontinuation for lack of efficacy. Some patients will absorb one preparation better than others, so if one fails at maximum dosage, then switching to another preparation, could salvage some patients.

Compliance is always an issue, particularly in our male patients. In addition to supplementation, the physician can use this diagnosis as an opportunity to discuss the benefits of weight loss and exercise.

TABLE 1. **Advantages and disadvantages of testosterone administration**

Route of administration	Dose	Advantages	Disadvantages
Injectable (delatestryl)	200-400 mg q 3 weeks	Low cost Good compliance	Requires supervised administration May have higher risk of hemoconcentration
(Testosterone Undecoanate-Nebido)	1000 mg q3 months	Increased compliance and steadier blood levels	Costly Not easily reversible because long lasting
Oral (Andriol) (Canada only)	80-120 mg bid	Easy to titrate dose Familiar route for	Must be taken with food Variable absorption most patients
Topical gel (Androgel, Testim)	5-10 gms daily	Once a day dose Reliable absorption	Can be messy Low risk of transference
Patch (Androderm)	1 patch daily	Easy to apply, reliable absorption	Skin irritation in over 30% of patients

Testosterone's effects on body composition (adipose redistribution) and chest to waist ratio will only be augmented by combining your prescription with an exercise program and dietary counseling, if necessary.

Monitoring

Baseline hemoglobin, liver function tests and PSA should be repeated after 3 months of therapy. If within normal range, there is some controversy on the frequency on monitoring necessary, but there is no evidence to suggest that more than twice a year is necessary.

Many patients will have a transient rise in their PSA's, usually to age specific levels. Continued elevations should be investigated and a urologic referral considered.

The occasional patient will develop significant increases in Hgb (> 180). This is usually corrected by reducing the dose of testosterone.[16]

Risks of testosterone supplementation

In general, TRT has minimal risks in the appropriate patient. The biggest concern most patients and physicians have is that of prostate health. A recent publication by the Endogenous Hormones and Prostate Cancer Collaborative Group reviewed 18 studies which included over 3000 men with prostate cancer and 6438 controls. No association with serum concentrations of sex hormones and prostate cancer risk was found. Prudent use of TRT in high risk populations (family history of prostate cancer, previous high grade PIN on prostate biopsy, previous surgery to remove localized prostate cancer) is suggested until better safety data is available.[17]

Another concern is that of testosterone abuse. We have all encountered patients in our practice that are seeking testosterone for performance enhancement. Many confuse what they see in the media (steroids in sports, for example) with the type of preparations used by physicians for TRT. Testosterone has minimal anabolic effects and there is little scientific data to support any athletic performance effect at higher than therapeutic doses. In Canada, testosterone remains a controlled substance and it is extremely difficult for patients to over treat themselves. In my experience, those seeking testosterone for nonmedical purposes obtain it via internet pharmacies without the consent of their physicians.

It is this inherent safety of the newer testosterone preparations, that allows for a trial of therapy. In those patients where one is equivocating over treatment, a 3-month trial of one of the TRTs can be both diagnostic and therapeutic. The issue is the treatment in those patients that are in the "normal" range. What one does not know is what is "normal enough" for that particular individual.

Summary

Androgen deficiency can have a significant impact on the quality of life of our male patients. These effects can be reversed by the administration of testosterone with acceptable risks. The diagnosis of hypogonadism requires appropriate biochemical testing and clinical judgment. There are a number of high risk groups where the prevalence of androgen deficiency warrants consideration of the diagnosis and where treatment may produce significant positive patient outcomes.

The primary care physician should consider directed testosterone determination in these populations (diabetes, obesity, hypertension, sexual dysfunction, frailty syndrome). There are a number of safe treatment options available that will allow the physician to restore normal testosterone levels in a safe and effective manner. Only a small percentage of these patients require specialist consultation.

Disclosure

Dr. Casey has received financial support from Bayer, Eli Lilly and Pfizer. Dr. Barkin has been a clinical investigator for Solvay and Organon and sits on the medical advisory committees for both companies. He has spoken about all drugs for hypogonadism and all testosterone producing pharma-companies for the last 25 years. □

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DISCUSSION

Question (Dr. Rosenberg):
In males that undergo treatment for prostate cancer is there ever a point when one should consider initiating testosterone therapy?

Answer (Dr. Casey):
Symptomatic hypogonadal men who have received curative therapy for their localized prostate cancer can be treated with testosterone replacement therapy. While the amount of clinical data examining the risks in this prostate cancer population is sparse, there is no reason to suggest that restoring patients to eugonadal status increases their cancer morbidity. Men who are being treated with androgen deprivation therapy for locally advanced or metastatic prostate cancer should not be considered for supplementation until there is data supporting its safety. It is my opinion that TRT in this population should be managed by the same physician who is responsible for managing the patient's prostate cancer.

Question (Dr. Laroche):
Please comment about the utilization of testosterone in women to increase libido.

Answer (Dr. Casey):
Decreased libido in our female patients represents a particularly difficult diagnostic and therapeutic dilemma. In the post menopausal woman, with extremely low free testosterone levels, a trial of testosterone therapy might be warranted in addition to estrogen replacement therapy. There seems to be a positive correlation between female sexual functioning index (FSI) and testosterone levels in both pre and postmenopausal estrogen replaced females. However there is little clinical trial data to support its widespread application in the hypoactive sexual desire disorder population. Anectdotal reports of its potential benefits in selective populations has kept the concept of testosterone supplementation alive for HSDD patients.

Question (Dr. Miner):
At which point, if at all, should a patient with history of depression, decreased libido and frailty be considered a candidate for TRT?

Answer (Dr. Casey):
There is some evidence that depressed hypogonadal men might receive significant relief from their illness with TRT despite a poor correlation between depression and testosterone levels. In the eugonadal population there is unlikely a role for TRT as a treatment for depressive illness.

Frailty syndrome is a complex syndrome and requires a multidisciplinary approach to treatment. Certainly, motivated hypogonadal patients can receive significant benefit from TRT and weight bearing exercises. Appropriate attention to prostate health in this elderly population is necessary to insure that an undiagnosed prostate cancer is not present.

Question (Dr. Greenberg):
How clinically useful is getting a baseline Testosterone level on all patients by the time they are 40.

Answer (Dr. Casey):
Until there is more data to support the cost effectiveness of screening for hypogonadism, routine testosterone determinations in the absence of at least some supporting clinical evidence, is to be discouraged.