

Emerging Evidence AND Future Directions IN Treating Hypogonadism

Dear Colleagues:

Emerging Evidence and Future Directions in Treating Hypogonadism is a monograph designed for physicians who treat men with signs and symptoms of hypogonadism. Hypogonadism affects several million men in the United States, and its prevalence increases with age. However, hypogonadism is generally underdiagnosed and undertreated, due in part to the paucity of evidence from large, long-term clinical trials to clearly delineate the best course of action.

Study findings published in 2006 are part of a growing body of evidence associating hypogonadism with diabetes and glucose intolerance, suggesting a correlation between an increasing number of symptoms and decreasing total testosterone levels. Another study suggests the converse: improvements in metabolic symptoms in diabetic men treated for their hypogonadism with testosterone therapy. This monograph addresses these findings to further update physicians on the association of low testosterone and chronic endocrine conditions.

A formulation that more closely mimics endogenous testosterone secretion is continually being sought after, and development issues hinge on safe and efficacious formulations. As discussed in this paper, the advent of new products, including a unique, long-acting formulation, prompts evaluation of these agents as potential treatment options. This monograph examines issues facing physicians who manage patients with hypogonadism, offering information to help make more informed treatment decisions.

We hope that you find that this monograph contains useful information for treating male hypogonadism in your clinical practice.

Sincerely,



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Learning Objectives

Upon completion of this activity, participants should better be able to

- Recognize the association of low testosterone levels with metabolic syndrome and diabetes
- Discuss the advantages and disadvantages of current and new testosterone formulations
- Apply practice guidelines to their clinical practice

Disclosure Statement

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Introduction

Four to five million American men are affected by hypogonadism, which is defined as the failure of the testes to produce normal amounts of testosterone and sperm. The health consequences of hypogonadism are varied and affect much more than sexual function. As improvements have been made in treatments for male hypogonadism, there has been a dramatic increase in the number of men receiving testosterone, with one report estimating the cumulative increase in prescription sales of testosterone between 1993 and 2002 at 1700%.¹ However, there are several challenges concerning hypogonadism, including establishing the clinical diagnosis. In addition, long-term safety data, particularly with regard to the risk for prostate cancer and cardiovascular disease, are lacking. It is important for clinicians to have an understanding of male hypogonadism, including its diagnosis and sequelae, and know how to apply clinical guidelines in their practice to improve patient outcomes.

Hypogonadism and Its Association With Metabolic Syndrome and Diabetes: Emerging Evidence

It has long been known that sufficient production of testosterone is necessary for adult men to maintain lean body mass, bone mass, libido, sexual function, and spermatogenesis. In recent years, evidence is also emerging of an association of hypogonadism with metabolic syndrome and type 2 diabetes.

Testosterone: when to measure

The Endocrine Society recommends that men's serum testosterone levels be measured to check for hypogonadism in men under any of the following conditions²

- Sellar mass, radiation to the sella, or diseases of the sella
- Treatment with medications that affect testosterone production or metabolism (eg, opioids, glucocorticoids, ketoconazole)
- Weight loss associated with the human immunodeficiency virus
- End-stage renal disease and maintenance dialysis
- Moderate to severe chronic obstructive pulmonary disease
- Infertility
- Osteoporosis or low trauma fracture, especially in young men
- Type 2 diabetes

Testosterone levels should also be checked in older men who exhibit signs or symptoms of androgen deficiency, such as decreased libido, sexual dysfunction, fatigue, and depression, although these complaints are nonspecific.²

Testosterone levels: risk for diabetes

Ding and colleagues published a systematic review and meta-analysis of 36 cross-sectional and 7 prospective studies that evaluated the association between the risk for type 2 diabetes and plasma concentrations of testosterone, sex hormone-binding globulin (SHBG), and estradiol in nearly 6500 men. In cross-sectional studies, investigators found that men who had type 2 diabetes had significantly lower testosterone levels than age- and body mass index (BMI)-matched controls. In the prospective studies, men whose testosterone levels were in the upper dichotomy (450-605 ng/dL) had a 42% lower risk for diabetes than men whose testosterone concentrations were in the lower range (213-447 ng/dL).³

Less than 5% of testosterone circulates free in the blood; the rest is bound to either SHBG with high affinity or to albumin, from which it can readily dissociate. In the presence of insulin resistance, high insulin concentrations suppress SHBG production, and total testosterone concentrations tend to be low. It has therefore been proposed that the relationship between low testosterone concentrations and insulin-resistance states, such as obesity and type 2 diabetes, is mediated entirely by SHBG. If SHBG alone were responsible for this relationship, free testosterone levels would be normal in men who have insulin resistance. This is not the case, however.

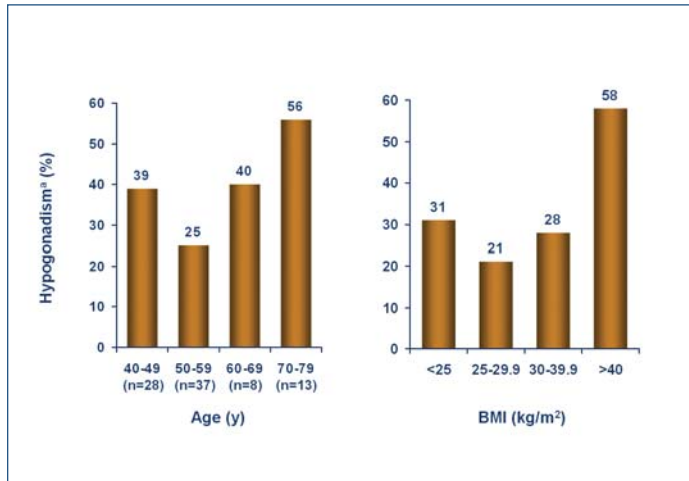
Isidori et al examined the relationship between leptin concentrations and sex hormone levels in men with BMI ranging from 21.8 to 55.7 kg/m². In these subjects, total testosterone concentrations declined with increasing BMI. However, the same inverse relationship was evident for free testosterone concentrations and BMI, suggesting that the relationship between BMI and testosterone levels is not mediated solely by SHBG.⁴

Dhindsa and colleagues were among the first to call attention to the high prevalence of hypogonadism in men who have diabetes. These investigators measured the testosterone concentrations of 103 consecutive men who visited a diabetes clinic and were

classified as hypogonadal if they had a low free testosterone level measured by equilibrium dialysis or a low calculated free testosterone level. In this study, hypogonadism was much more prevalent than expected. When the patients were stratified according to age, 56% of those between the ages of 70 and 79 years were hypogonadal. Even in younger patients (aged 40-49), 39% met the criteria for hypogonadism.⁵

Data from this study also indicate that the relationship between diabetes and testosterone levels is not explained by BMI alone. When the patients were stratified by BMI as lean, overweight, obese, or severely obese, hypogonadism was prevalent in all groups. Although the prevalence of hypogonadism was the greatest in men with BMI >40 kg/m, as illustrated in Figure 1, 31.3% of the lean patients were hypogonadal.⁵

Figure 1. High prevalence of hypogonadism in 103 men with type 2 diabetes.
^aLow free T by equilibrium dialysis or calculated free T. BMI=body mass index. T=testosterone. Reproduced with permission from Dhindsa S et al. *J Clin Endocrinol Metab.* 2004;89:5462-5468.



Testosterone levels: risk for metabolic syndrome

Low testosterone concentrations have also been shown to predict development of metabolic syndrome. Finnish investigators followed 702 middle-aged men for 11 years, measuring their testosterone levels at baseline and again at the end of the study. Men who had diabetes or metabolic syndrome at baseline were excluded from the study. In this analysis, men whose testosterone levels were in the lowest quartile had the worst outcome. For example, almost 50% of men who developed either metabolic syndrome or type 2 diabetes during follow-up had low testosterone concentrations at baseline. In contrast, only 21% of the men who developed neither condition had baseline testosterone concentrations in the lowest quartile.⁶

A study of 950 men enrolled in the Massachusetts Male Aging Study (MMAS) who did not have metabolic syndrome at baseline and who were followed for 14.4 years showed no relationship

between testosterone levels and development of metabolic syndrome in men who were overweight (BMI ≥ 25 kg/m²). However, in lean men (BMI <25 kg/m²), the risk for developing metabolic syndrome was increased 2.5-fold when testosterone levels were in the lowest 2 quartiles.⁷

Testosterone, insulin sensitivity, and diabetes: animal studies

A number of animal studies have attempted to define the causal nature of the relationship between low testosterone levels and insulin resistance. Holmång and Björntorp demonstrated that surgical castration induces acute insulin resistance in male rats. Using a euglycemic hyperinsulinemic clamp to measure glucose disposal rate, the investigators showed a reduction in insulin sensitivity in rats that were castrated that was reversed by physiologic testosterone.⁸

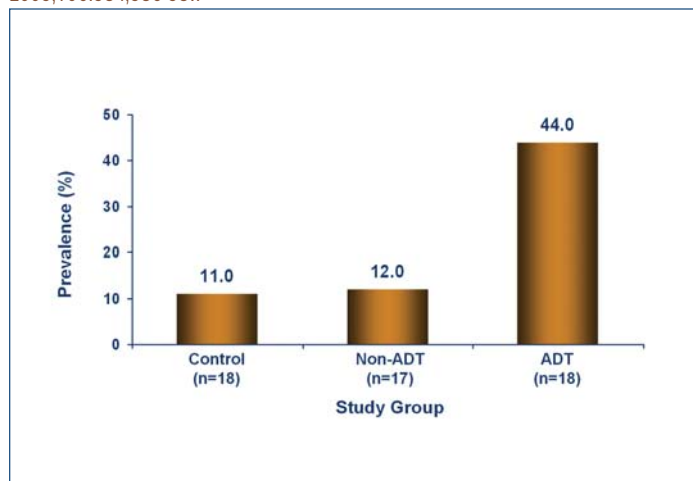
Using a different model, Lin and colleagues created androgen receptor (AR) knockout mice (mice that lack the AR and thus have inactive testosterone) to determine whether lacking the AR creates a phenotype of insulin resistance. They showed that, when challenged with a glucose load, the AR knockout mice were significantly more hyperglycemic than their wild-type counterparts. To determine whether this difference in glucose tolerance was due to a defect in insulin secretion or in insulin action, the investigators then gave insulin to both groups of mice. Insulin administration was associated with a rapid decrease in glucose in the male wild-type mice but only a very modest reduction in glucose in the knockout mice. This finding suggests that the defect underlying the hyperglycemia of the AR knockout mice is one of insulin resistance rather than insulin secretion.⁹

Testosterone, insulin sensitivity, and diabetes: human studies

Most of the available data on the relationship between testosterone and insulin sensitivity in the human comes from men who have received gonadotropin-releasing hormone (GnRH) analogs for metastatic prostate cancer. In a cross-sectional study, Basaria and colleagues compared insulin levels in 3 groups of men: men who had undergone surgery or radiation for prostate cancer but who had not received GnRH analogs, another group who were receiving androgen-deprivation therapy (ADT) for metastatic prostate cancer, and an age-matched healthy control group without prostate cancer. The men who received ADT had significantly higher insulin and glucose levels than those in the other 2 groups. In addition, the prevalence of diabetes (fasting glucose level >126 mg/dL) was 4-fold higher in the men who had received ADT than in control subjects (44% vs

11%), as illustrated in Figure 2. Thus, use of long-term ADT for metastatic prostate cancer appears to create an adverse metabolic profile and may contribute to the increased cardiovascular mortality seen in this population.¹⁰

Figure 2. Prevalence of fasting glucose >126 mg/dL in men with prostate cancer versus control subjects. Adjusted for age and BMI. ADT=androgen-deprivation therapy. BMI=body mass index. Reproduced with permission from Basaria S et al. *Cancer*. 2005;106:584,586-587.



Keating et al studied 73,196 patients with prostate cancer to determine whether those who had received ADT were at increased risk for developing diabetes and cardiovascular disease. The investigators found that use of a GnRH agonist was associated with a 44% increased risk for developing diabetes ($P<.001$). In addition, the risk for developing coronary heart disease was 16% higher ($P<.001$) for the GnRH recipients (adjusted hazard ratio, 1.16).¹¹ It is thus important for physicians to be aware of this increased risk of diabetes and cardiovascular disease when they are monitoring patients with prostate cancer who are receiving ADT so that appropriate therapy may be instituted in a timely fashion.

Despite the compelling epidemiologic data that low testosterone is associated with insulin resistance, data from interventional studies are sparse and conflicting. In a recent crossover study, Kapoor and colleagues examined the impact of testosterone therapy on insulin resistance and glycemic control in men with type 2 diabetes. In that study, 24 men who had type 2 diabetes and low testosterone concentrations were given either testosterone for 3 months followed by placebo for 3 months or placebo for 3 months followed by testosterone for 3 months. A 1-month washout period separated the 2 treatment periods in all cases. Compared to placebo, 3 months of testosterone therapy resulted in a significant reduction in insulin resistance defined by the homeostatic model assessment and an improvement in glycemic control as evidenced by a reduction in glycosylated hemoglobin.¹²

Testosterone administration has also been shown to improve insulin sensitivity in middle-aged men with central obesity and testosterone levels in the low normal range.¹³ However, findings from several other studies on the impact of testosterone on insulin sensitivity are conflicting. In one study, the administration of GnRH analog with graded doses of testosterone to 61 young, healthy men had no impact on insulin sensitivity.¹⁴ In another study, the administration of recombinant human chorionic gonadotropin (hCG) for 3 months to 13 older men caused no change in insulin sensitivity.¹⁵ In a third study, 6 months of testosterone therapy failed to alter glycemic control in a small cohort of 10 men who had type 2 diabetes.¹⁶ Thus, available data suggest that testosterone has, at best, a beneficial effect or, at worst, a neutral effect on insulin sensitivity.

The mechanism by which testosterone might influence insulin sensitivity has not been fully elucidated. Smith and colleagues showed that administration of GnRH analogs for 3 months to men with prostate cancer causes a significant increase in fasting insulin levels, which correlates with increases in fat mass observed.¹⁷ Thus, body composition plays an important role in the relationship between hypogonadism and insulin resistance.

In addition to its established effects on body composition, testosterone may impact insulin sensitivity by other mechanisms. Several different approaches have implicated mitochondrial dysfunction in the pathogenesis of insulin resistance. In a recent study, investigators examined the relationship between serum testosterone levels and both a physiologic measure of mitochondrial function (maximal aerobic capacity) and a genetic marker (expression of genes in skeletal muscle that are involved in oxidative phosphorylation). This study showed that serum testosterone levels correlate positively with both indexes of mitochondrial function.¹⁸ Further interventional studies are needed to determine the causative nature of this correlation.

Insulin resistance and the hypothalamic-pituitary-gonadal axis

Available evidence suggests that the relationship between testosterone and insulin resistance may be bidirectional, in that low testosterone levels may promote insulin resistance, and insulin resistance may have effects on the hypothalamic-pituitary-gonadal (HPG) axis.¹⁹

Studies have been conducted to determine the site of the defect in the HPG axis in men who exhibit insulin resistance. In one of these studies, in which a glucose clamp was used to calculate the glucose disposal rate, normal subjects were first given a GnRH antagonist to suppress endogenous luteinizing hormone

and testosterone secretion and then stimulated with both GnRH and hCG. The results did not show any relationship between insulin sensitivity and the response to GnRH but did show a very strong relationship ($P < .005$) between insulin sensitivity and an increase in plasma testosterone levels after administration of hCG. The more insulin resistant the subject, the smaller the increase in testosterone after hCG administration. This finding suggests that increasing insulin resistance in men is associated with a defect in Leydig cell function.¹⁹

Weight loss and testosterone levels

Given that testosterone levels have been shown to be low in obese men, it is important to know the impact of weight loss on testosterone. In a study of 58 obese men with metabolic syndrome, weight loss averaging about 35 pounds in 10 weeks caused a significant increase in serum testosterone levels. In addition, the prevalence of hypogonadism decreased from 48% at baseline, when their BMI averaged 36 kg/m², to 21% after their BMI decreased to 31.6 kg/m².²⁰ By implication, then, lifestyle modification for weight loss should be attempted initially or in concert with testosterone therapy. Similarly, if an obese man is given testosterone therapy for hypogonadism and is subsequently successful in losing weight, the need for long-term androgen therapy should be reviewed.

Metabolic syndrome, diabetes, and their association with hypogonadism: a summary

There is good evidence that low testosterone concentrations predispose men to insulin resistance and its downstream consequences of metabolic syndrome and type 2 diabetes. One of the underlying mechanisms appears to be mediated by body composition because, in the presence of low testosterone levels, there are increased activity of the enzyme lipoprotein lipase, increased triglyceride uptake in central fat depots, and decreased lipolysis, all of which tend to cause an increase in visceral fat. However, testosterone may also have effects on insulin sensitivity that are independent of body composition. Although it is as yet unproven, it is possible that low testosterone levels may adversely affect mitochondrial function, causing down-regulation of genes involved in oxidative phosphorylation.

Whether the relationship between insulin resistance and impaired Leydig cell function is due to resistance to the normally stimulatory effect of insulin on the HPG axis or to something else, such as high levels of inflammatory cytokines, tumor necrosis factor- α , interleukin-6, or leptin, is not known.

The relationship between hypogonadism and insulin resistance in men is complex. Results of a number of studies indicate that between one-third and one-half of men who have type 2 diabetes also have hypogonadism. Current Endocrine Society guidelines recommend that men with type 2 diabetes be screened for hypogonadism. However, whether testosterone therapy has a beneficial effect on metabolic parameters in men who are obese, who have metabolic syndrome, or who have type 2 diabetes is unclear and requires further study.

Clinical application of diagnosing hypogonadism

The Endocrine Society Clinical Practice Guidelines recommend that a diagnosis of testosterone deficiency be made only for men who have low serum testosterone concentrations and consistent signs and symptoms of this disorder. The Expert Panel suggests measuring testosterone levels with a reliable assay and confirming low levels by repeating the testosterone measurement.²

Implementing these guidelines requires attention to a number of complex issues. For example, many of the signs and symptoms of testosterone deficiency are nonspecific. They depend on the age of the patient at onset of symptoms, the severity and duration of the testosterone deficiency, the presence of comorbid illnesses, variations in androgen sensitivity (which depend on the length of the polyglutamine and polyglycine tracts), and whether testosterone therapy has been administered previously.²

The testosterone threshold below which symptoms appear is unknown, but new evidence indicates that the thresholds for various manifestations of testosterone deficiency vary.^{21,22} Some of the variations in testosterone levels from person to person can be explained by different SHBG concentrations. Testosterone concentrations also vary within the same person because of circadian and circannual rhythms and pulsatility in testosterone secretion.

Measuring free testosterone levels

The measurement of free testosterone concentrations is even more problematic. Unbound or free testosterone (ie, dialyzable testosterone) refers to the 0.5% to 3.0% fraction that is not bound to any plasma protein, and it can be measured by equilibrium dialysis. Data from several studies show a strong correlation between non-SHBG-bound testosterone and mean clearance rate and clinical outcomes.^{23,24}

Because of methodologic issues, measuring free hormone concentrations for diagnostic purposes is not recommended, and to make an initial diagnosis, physicians should rely primarily on measurements of total testosterone concentrations.



The Endocrine Society's prostate-specific antigen monitoring guidelines

In older men with testosterone levels between 225 and 375 ng/dL, age-related symptoms and uncertainties about long-term risks and benefits of testosterone therapy should be factored into the clinical decision-making process.

The following case introduces another important topic: the Endocrine Society's prostate-specific antigen (PSA) monitoring guidelines.

A 52-year-old man is prescribed testosterone therapy for hypogonadism. By 3 months after therapy is initiated, his PSA level has increased from 2.4 to 3.2 ng/mL. A digital rectal examination (DRE) reveals a slightly enlarged prostate gland.

What should be done in these circumstances? Follow up in 1 year? Remeasure the patient's PSA? Send him for a urologic consultation? Refer him for a prostate biopsy?

The take-home message from this case is that PSA levels are lower in hypogonadal men than in age-matched control subjects. Testosterone therapy will lead to a predictable increase in PSA level, but a crucial question in clinical practice—as in research—is, what magnitude of increase in PSA level after initiation of testosterone therapy indicates the need for prostate biopsy?

Calof and colleagues conducted a meta-analysis of randomized, controlled trials to identify adverse events associated with testosterone therapy in men 45 years of age and older.²⁵ Two key points emerged from this analysis. First, erythrocytosis (hematocrit >50%) was the most frequent testosterone-related adverse event in these trials. Second, the rates of prostate cancer, PSA >4.0 ng/mL, and prostate biopsies were numerically higher in the testosterone group than in the placebo group (21 of 643 vs 1 of 427, respectively). However, the differences between the groups were not statistically significant.²⁵

Inherent bias increases the chances that men who receive testosterone will undergo prostate biopsy, leading to more frequent detection of subclinical prostate events: Men who receive testosterone are more likely to experience increases in PSA levels that trigger prostate biopsy.²⁵

To minimize unnecessary biopsies and prostate events, physicians must apply a well-considered, standardized algorithm. To establish parameters for this PSA-monitoring algorithm, data

sets from several clinical trials were reviewed. The data indicated that the average change in serum PSA level after initiation of testosterone therapy was 0.30 ng/mL in younger men with hypogonadism and 0.43 ng/mL in older men. PSA increments larger than 1.0 ng/mL were unusual in androgen-deficient men who underwent testosterone therapy.¹

Data from the Finasteride Study Group were also reviewed. In the placebo arm, the 95% confidence interval for changes in serum PSA concentrations between samples drawn 3 and 6 months apart was 1.4 ng/mL. From that finding, it was inferred that increments greater than 1.4 ng/mL are unusual in men who do not have prostate cancer.²⁶

Similarly, data from the Baltimore Longitudinal Study of Aging suggest that, in men whose baseline PSA levels are <4.0 ng/mL, a PSA velocity of >0.2 ng/mL/year confers a greater risk for prostate cancer. However, because there is considerable test and retest variability in the measurement of PSA levels, if physicians were to use a threshold velocity of 0.2 ng/mL/year, almost every adult male patient would require prostate biopsy. Therefore, the Expert Panel of the Endocrine Society advises that a PSA velocity of >0.75 ng/mL/year be used to screen for prostate cancer when velocity is based on 3 consecutive measurements and PSA is sampled long term (over 2 years) but not short term (over 3 to 6 months).²⁷

These considerations led the Endocrine Society Expert Panel to recommend DRE and PSA measurements before testosterone therapy is started, again at 3 months, and thereafter according to the guidelines for prostate cancer screening.² This recommendation usually translates into annual PSA measurement.

It is recommended that clinicians obtain a urologic consultation in the following instances²:

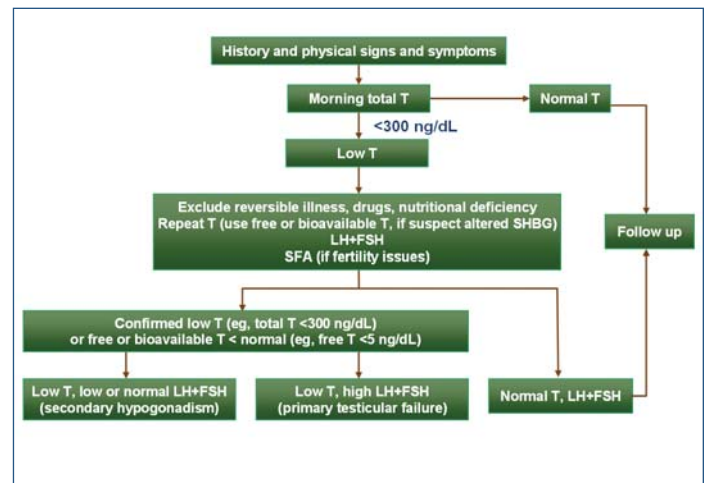
- If the patient's serum or plasma PSA level rises above 4.0 ng/mL during treatment
- If the patient's PSA level increases by >1.4 ng/mL in any 12-month period
- If the patient's PSA velocity is >0.4 ng/mL/year, using the patient's PSA level after 6 months of testosterone therapy as the reference
- If a prostate abnormality is detected by DRE
- If the patient's American Urological Association prostate symptom score is >21

Hypogonadism treatment algorithm

Clinicians should be aware of the multiple challenges in diagnosing testosterone deficiency. The algorithm in Figure 3 is recommended for evaluating men with suspected testosterone deficiency.² In general, adhering to the following 5 rules can minimize the risk of misclassifying men as testosterone deficient:

- Measure testosterone levels only in men with pertinent signs and symptoms
- Evaluate clinical features with the understanding that sexual and physical symptoms are more informative than behavioral and psychological symptoms. Avoid use of an unvalidated questionnaire
- Measure total testosterone levels with a reliable assay, such as liquid chromatography-mass spectrometry/mass spectrometry, preferably in the morning
- Use the normative ranges specific to that assay
- Confirm low testosterone levels by repeating testosterone measurements

Figure 3. Diagnostic evaluation of adult men with suspected hypogonadism. FSH=follicle-stimulating hormone. LH=luteinizing hormone. SFA=seminal fluid analysis. SHBG=sex hormone-binding globulin. T=testosterone. Reproduced with permission from Bhasin S et al. *J Clin Endocrinol Metab.* 2006;91:1995-2010.



New and Developing Formulations of Testosterone: An Update

As mentioned, the number of prescriptions for testosterone therapy has risen dramatically over the past several years. Prescribing patterns for the various testosterone products available in the United States have also undergone a dramatic change in recent years, primarily because of the steady growth in popularity of testosterone gels since they were first introduced to the market about 7 years ago. The various formulations of testosterone differ in a number of ways, including the ability to restore and maintain physiologic levels of testosterone, route of administration, and cost.²⁸ Table 1 lists the currently available testosterone formulations and the benefits and challenges with their use.

Table 1. Current Testosterone Formulations²⁸

Type	Pros	Cons
Injectables	<ul style="list-style-type: none"> Inexpensive Effective in relieving symptoms 	<ul style="list-style-type: none"> Supraphysiologic fluctuations May be painful Require office visit every 2 weeks
Transdermal patches	<ul style="list-style-type: none"> T levels mimic circadian rhythm Low incidence of polycythemia 	<ul style="list-style-type: none"> Moderate cost Visible, not discreet Difficulty in achieving adequate T concentrations Skin irritation Ineffective adhesiveness Daily administration
Transdermal gels	<ul style="list-style-type: none"> Maintain T concentration over 24-hour period High patient compliance 	<ul style="list-style-type: none"> Expensive Concerns regarding transference Drug accumulation Variable absorption Messy Daily administration
Buccal	<ul style="list-style-type: none"> T levels within physiologic range 	<ul style="list-style-type: none"> Expensive Oral irritation Twice-daily dosing

T=testosterone.

Available formulations of testosterone

Transdermal patches

Transdermal patches became available more than a decade ago. One or two patches deliver testosterone 5 mg per day. Normal testosterone levels can be achieved in most patients with the patch; however, it may prove difficult in some patients. With the patch, testosterone levels tend to mimic the human circadian rhythm. Advantages of the transdermal patch are moderate cost and a low associated incidence of polycythemia.^{28,29} The patch has several disadvantages, one of which is that 10% to 60% of patients experience contact dermatitis, which sometimes is blamed for discontinuation of treatment.³⁰ Skin irritation can be prevented or reduced by using a corticosteroid cream before applying the patch, but some patients find this unacceptable. Other disadvantages include visibility, insufficient adhesiveness, and daily application.²⁸

Testosterone gels

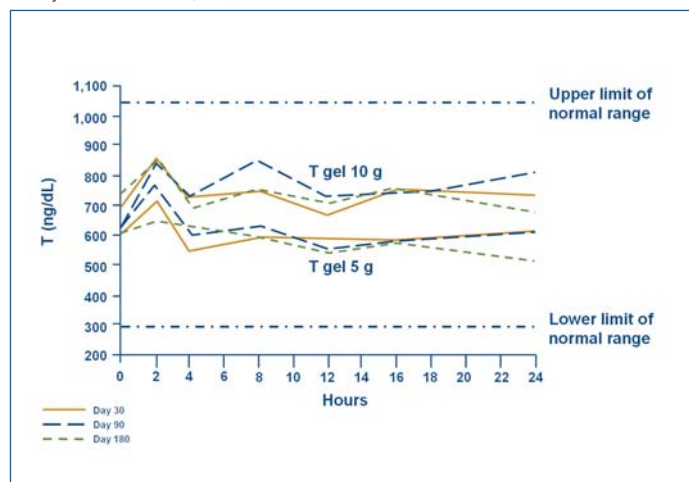
Testosterone gels were introduced about 7 years ago. They are available in packet and pump formulations and deliver testosterone 2.5 mg and 5 mg, respectively. Skin irritation is minimal with gels, and dosing is flexible because of the various methods of administration. These products generally provide steady-state serum testosterone concentrations for 24 hours, making it unnecessary to monitor patients' early-morning testosterone levels.²⁸

Skin-to-skin transfer of testosterone can occur, but this can be prevented by clothing or reduced by showering. Other disadvantages of testosterone gels include²⁸

- High cost
- Potential for drug accumulation
- Variable absorption
- Tendency to be messy
- Daily administration

Figure 4 shows the pharmacokinetic data for testosterone gel administered in 5-g and 10-g doses. Mean testosterone concentrations remain between 500 ng/dL and 700 ng/dL with these compounds.³¹

Figure 4. T concentrations in patients receiving once-daily T gel. T=testosterone. Adapted from AndroGel [package insert]. Marietta, GA: Solvay Pharmaceuticals, Inc.; 2004.



Buccal testosterone

Buccal testosterone is a new formulation that uses bioadhesive hydration technology. Testosterone is delivered with a small tablet placed above the teeth on the buccal mucosa. As the tablet is hydrated, it gradually releases testosterone, which is absorbed across the buccal mucosa. Although this product delivers testosterone within the normal physiologic range, it is expensive, can cause transient gum or mouth irritation, and requires twice-daily application (morning and evening).²⁸

Testosterone implants

Despite US Food and Drug Administration approval and favorable pharmacokinetics and pharmacodynamics, testosterone implants are seldom used because of the surgical procedure required for implantation.³² Another disadvantage is that, in rare instances, the implant is extruded.³²

Injectable testosterone

Injectable forms of testosterone therapy have been available for decades. Because these testosterone formulations are esterified, they have a relatively long half-life. Two formulations of injectable testosterone are available: testosterone enanthate and testosterone cypionate. The usual dose is 200 mg every 2 weeks or 100 mg weekly. Injectable testosterone therapy is inexpensive²⁸ and is effective in relieving symptoms.

One of the biggest disadvantages of injectable testosterone is that its pharmacokinetics are such that a rapid and often supraphysiologic increase in serum testosterone occurs for 1 to 3 days after injection.³³ However, during the dosing interval, testosterone concentrations fall, often to the lower limit of the normal range, resulting in a rollercoaster effect. Some men experience mood changes as a result of these dramatic shifts in testosterone levels.²⁸

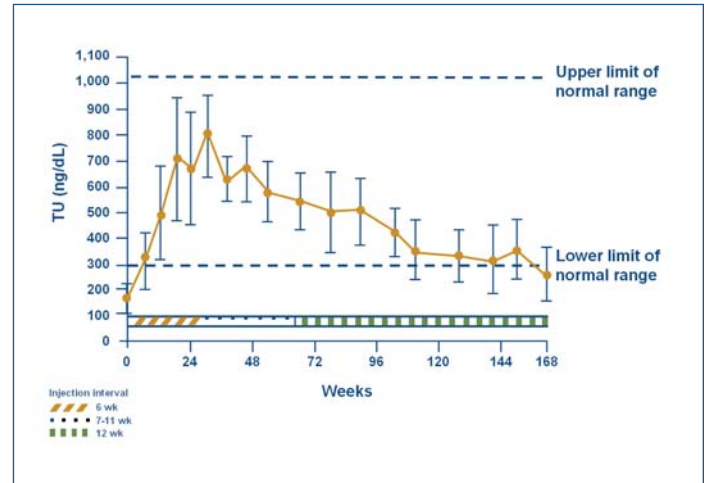
Other side effects of injectable testosterone include increases in erythrocyte production, acne, and because aromatization to estradiol occurs early on, gynecomastia. In addition, it is inconvenient for the patient to make biweekly office visits to receive injections.

Testosterone undecanoate is a novel, long-lasting injectable form of testosterone³⁴ in a concentrated formulation that achieves and maintains testosterone levels within normal range over many weeks (Figure 5).³⁵ Although not yet approved for use in the United States, it has been approved and launched in 75 countries throughout Europe and Asia. Most likely, the standard dose in the United States will be 750 mg (in 4 mL of castor oil), with a recommended dosing interval of 10 to 14 weeks following a 4-week run-in period.

The safety of testosterone undecanoate was studied in 22 men aged 30 to 65 years who were followed for 8.5 years. Serum trough levels remained within the normal range regardless of the dosing interval. Patients in this long-term study reported that testosterone undecanoate restored sexual function and caused positive changes in temperament without the mood fluctuations possible with the shorter-acting injectables. Hemoglobin and hematocrit values increased but remained within the normal range. Transrectal ultrasonography showed that testosterone undecanoate caused a small (<30 mL) increase in prostate size.

Also, PSA levels stayed within the normal range (<2.0 µg/L). Bone density improved and reductions occurred in high- and low-density lipoprotein levels.³³ The optimal dose and appropriate dosing interval will need to be established on an individual basis for each patient.

Figure 5. Pharmacokinetics of TU. N=7 men with hypogonadism given TU 1000 mg in increasing injection intervals. Values are means ± standard deviations. TU=testosterone undecanoate. Reproduced with permission from Von Eckardstein S, Nieschlag E. *J Androl.* 2002;23:419-425.



Testosterone cream

According to a preliminary analysis of Phase 2 data for a new testosterone cream, when the compound is administered to hypogonadal men as a single daily dose of 2.25 g or 4.5 g, it is effective in restoring testosterone levels to the normal range. This analysis also showed that 80% of patients who were administered the low dose (2.25 g) of the cream achieved average testosterone concentrations within the normal range by day 28.³⁶

Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) for the treatment of secondary hypogonadism are now in clinical trials. These oral agents act by competing with estradiol for the estrogen receptor at the level of the hypothalamus. The effect of SERMs is an increase in gonadotropin, which ultimately stimulates testosterone and sperm production. In a Phase 2/3 study, enclomiphene 25 mg increased testosterone concentrations by 146% over baseline ($P<.0001$). This medication may have a role in the treatment of central hypogonadism and infertility.^{37,38}

Fispemifene is another oral SERM in clinical development. Fispemifene blocks estrogen feedback to the pituitary gland, increasing luteinizing hormone and follicle-stimulating hormone secretions, which increase testosterone to within the

normal range. In a Phase 2 study in men with low testosterone levels (N=77), fispemifene 300 mg caused an average increase in testosterone concentration of 78% ($P<.001$, fispemifene vs placebo). The estrogen-related effects of this agent may have utility in treating gynecomastia, reducing the risk for prostate cancer and prostate growth, and increasing bone mass.³⁹

5 α -dihydrotestosterone

5 α -Dihydrotestosterone (DHT) is available in Europe as a 2% hydroalcoholic gel and may soon be available in the United States to treat testosterone-deficiency symptoms. The usual dosage is 5 mg or 10 mg per day. DHT acts like a SERM. Because it is not aromatized to estrogen and no intraprostatic conversion of testosterone to DHT occurs with this agent, it may have some protective effect on the prostate. DHT treatment causes an increase in serum DHT levels and a decrease in serum concentrations of testosterone, estradiol, and SHBG.⁴⁰

Selective androgen receptor modulators

Selective androgen receptor modulators (SARMs) are an exciting new development in testosterone therapy. These compounds are similar to SERMs. Since 1998, 4 different chemical classes of these nonsteroidal androgens have been identified. A potential benefit of SARMs is that they may have tissue-specific agonist or antagonist actions.⁴¹ SARMs are generally not substrates for aromatase or 5 α -reductase, so they

may have the potential to improve muscle strength and body composition and restore bone mineral density without affecting the prostate gland.

In preclinical pharmacology studies, continued use at varying concentrations of estuarine, a bioavailable oral SARM formulation, resulted in a reduction in the size of the prostate gland and seminal vesicles. Estuarine also caused an increase in muscle and bone mass as measured by the levator ani in a rat model, suggesting that estuarine may be useful in treating osteoporosis.⁴²

Testosterone formulations: a summary

The number of prescriptions for testosterone products, particularly gels, has increased dramatically in recent years. This increase is mainly a result of the testosterone formulations available today, which are easier for patients to tolerate than those obtainable in the past. Also, these testosterone therapies provide options for dose and formulation.

None of the testosterone compounds available is ideal; agents that mimic endogenous testosterone are still needed. Therefore, the various testosterone formulations in the development pipeline—testosterone undecanoate, SARMs, SERMs, and new topical treatments—promise an exciting decade ahead for the treatment of testosterone deficiency.

Conclusion

Male hypogonadism is a significant clinical condition that affects a significant number of men in the United States. Low levels of testosterone result in losses of lean body mass and bone mass, decreases in libido and sexual function, and the inability to maintain spermatogenesis. Additionally, there is evidence that hypogonadism is associated with comorbid medical conditions such as metabolic syndrome and type 2 diabetes. Challenges with diagnosis and the complexities of testosterone therapy must be addressed and overcome with physician awareness and education, specifically regarding clinical monitoring and treatment guidelines. Male hypogonadism is a condition that can be treated safely and successfully with the available testosterone preparations. Looking to the future, formulations in development more closely mimic endogenous testosterone and will provide patients with even more options for testosterone therapy.

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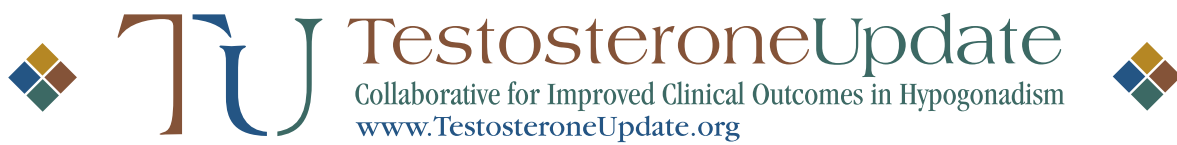
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