

T in Cheek: Buccal Testosterone as a New Treatment for Androgen Deficiency in Men

a report by

Bradley D Anawalt, MD, FACP

Associate Professor of Medicine, University of Washington and Associate Chief of Medicine, VA Puget Sound

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Bradley D Anawalt, MD, FACP, is an Associate Professor of Medicine at the University of Washington and Associate Chief of Medicine at the VA Puget Sound. He serves on the editorial board of the *Journal of Clinical Endocrinology and Metabolism* and regularly serves as an ad hoc reviewer for many scientific publications. He is an invited presenter at national medical and scientific conferences, and his work has appeared in *Journal of Clinical Endocrinology*, *Lancet*, *Fertility and Sterility*, and *Journal of Andrology*. He completed his endocrinology and metabolism training at the University of Washington in Seattle.

Male androgen deficiency has become a burgeoning area of public and commercial interest. Male androgen deficiency (commonly called male hypogonadism) is a common and important endocrinological syndrome defined by signs and symptoms of androgen deficiency plus low serum testosterone levels. Klinefelter syndrome, the most common congenital form of male hypogonadism, occurs in one in 500 men.¹ In addition, the prevalence of men with low testosterone increases dramatically with age. For example, the Baltimore Longitudinal Study showed that the prevalence of low serum total testosterone levels rises from 12% of men under age 50 to 50% of men over age 80; the prevalence is even higher based on serum free testosterone levels.² Based on these data, there appears to be an epidemic of male hypogonadism. However, a more accurate estimation of the prevalence of male hypogonadism is derived from the Male Massachusetts Aging Study that looked at least three symptoms suggestive of hypogonadism plus low serum testosterone levels in a cohort of over 1,000 men followed for an average of nearly nine years. In this study, 4.1% of men aged 40–49 years and 9.4% of men aged 60–70 years were hypogonadal. The Baltimore Longitudinal Study and Male Massachusetts studies highlight both the high prevalence of male hypogonadism and the importance of defining this syndrome based on symptoms, signs and labs that are consistent with androgen deficiency.

The recent recognition has led to many innovations in the diagnosis and treatment of male hypogonadism. In this article, I will briefly review the diagnosis and treatment of male hypogonadism. I will discuss the potential use of buccal testosterone, one of the most recent approved androgen formulations, as an example of the promise and pitfalls of new therapies for male hypogonadism that are under development.

Diagnosis of Male Hypogonadism

The diagnosis of male hypogonadism depends on symptoms and signs suggestive of androgen deficiency; the symptoms and signs vary based on whether hypogonadism occurs pre- or post-pubertally (see *Table 1*). The symptoms and most of the signs of male

hypogonadism are very non-specific. When a man presents with symptoms or signs of hypogonadism, the clinician should determine the serum testosterone level with an accurate and reliable assay. The initial testosterone measurement ideally should be done on a blood sample drawn in the morning. It is crucial to confirm any borderline low testosterone level with a second measurement from a blood sample drawn early in the morning because up to 30% of men may have a normal testosterone level on repeat measurement.^{3,4}

There is some controversy about the best method for measuring circulating testosterone levels. However, an Endocrine Society expert panel recently recommended that total serum testosterone level should be the initial diagnostic test.⁵ Automated assays for total testosterone are widely available and are generally accurate and reliable for the diagnosis of male hypogonadism.⁶ Most circulating testosterone is avidly bound to sex hormone-binding globulin (~40%) or weakly bound to albumin (~58%); only about ~2% is unbound or free. Bioactive testosterone (the amount of testosterone in the serum that is available to produce end-organ and tissue effects) is thought to be the sum of the free testosterone and weakly bound testosterone. Generally, total testosterone and bioactive testosterone levels parallel, but, in many clinical settings, sex hormone binding globulin levels may be significantly altered (e.g. older men, obese men, men with diabetes mellitus or who are treated with anti-epileptics or corticosteroids).⁷

Accurate assays for free and weakly bound testosterone levels are not available at many local laboratories. There are accurate assays that directly measure serum free and weakly bound testosterone levels by equilibrium dialysis and ammonium precipitation respectively. It is less expensive and more convenient to use a validated formula to calculate free and weakly bound testosterone levels (using total testosterone, sex hormone-binding globulin and albumin levels plus known affinity constants).⁸ These calculated measurements correspond well to values obtained by the accurate direct assays, and national commercial laboratories offer these calculated free and weakly bound testosterone measurements. It may be useful in some cases to measure free and weakly

bound testosterone levels when total testosterone levels are equivocal or in patients with suspected abnormalities in sex hormone binding globulin or albumin levels. Assays that measure free testosterone by an automated analog method are widely available, inexpensive and notoriously inaccurate; these assays for free testosterone should not be used.⁸

When serum testosterone levels are found to be low, reversible causes should be identified and corrected if possible. For example, suppressed testosterone levels commonly occur with acute or chronic illness, medications such as corticosteroids or opiates, and many recreational drugs. Testosterone levels should be re-measured at least one month after resolution or in the quiescent phase of systemic illnesses and at least one month after cessation of opiates, corticosteroids and other drugs that affect the gonadal axis.

When the diagnosis of male hypogonadism has been confirmed and reversible causes have been corrected, then the clinician should measure serum gonadotropin (FSH and LH) levels to distinguish between primary (testicular) and secondary (pituitary-hypothalamic) hypogonadism. Serum LH level is a better marker for low testosterone secretion, but LH levels fluctuate significantly throughout the day. Reproducibly elevated LH levels confirm primary hypogonadism even when serum testosterone levels are low-normal, and elevated FSH levels are useful to verify primary hypogonadism.

For patients with primary hypogonadism, further evaluation is unnecessary. Karyotyping for Klinefelter's syndrome, the most common form of primary hypogonadism is occasionally helpful, but serum karyotyping is costly. Most patients with Klinefelter's syndrome can be easily recognized based on physical exam findings (very small, firm testes) plus elevated serum gonadotropin levels. Patients with secondary hypogonadism (low or inappropriately normal gonadotropins levels) need a directed evaluation to exclude common causes such as a large pituitary tumor, hyperprolactinemia, hemochromatosis, Cushing's syndrome, and sleep apnea.

The most difficult diagnostic dilemma is the evaluation of an older man with slightly low testosterone levels and normal or slightly elevated gonadotropins levels. This clinical scenario is very common and has been dubbed andropause. Andropause has excited much interest in the lay press as a potential reversible cause of frailty associated with aging. The limited data currently available do not support widespread use of androgen supplementation to older men with slightly low testosterone levels.

Effects of Androgen Replacement

Table 1: Symptoms and Signs of Pre- and Post-puberty Onset of Hypogonadism

Pre-pubertal hypogonadism	Post-pubertal hypogonadism
<i>Eunuchoidal stature</i>	<i>Normal stature</i>
<i>Small testes (usually < 6cm³)</i>	<i>Testes volume normal to slightly low (> 10cm³); soft</i>
<i>Small penis (< 5cm)</i>	<i>Penis normal size</i>
<i>Lack of normal scrotal rugae and pigmentation</i>	<i>Normal scrotal rugae and pigmentation</i>
<i>Small prostate</i>	<i>Normal prostate</i>
<i>Scant facial, axillary and pubic hair</i>	<i>Thinning of facial, axillary and pubic hair</i> <i>Lack of male pattern baldness</i>
<i>High-pitched voice</i>	<i>Normal voice</i>
<i>Gynecomastia</i>	<i>Gynecomastia</i>
<i>Infertility</i>	<i>Infertility</i>
<i>Lack of libido</i>	<i>Loss of libido</i>
<i>Low bone mineral density</i>	<i>Low bone mineral density</i>
<i>Low muscle mass, high % body fat</i>	<i>Low muscle mass, high % body fat</i>
<i>Mild anemia</i>	<i>Mild anemia</i> <i>Hot flushes</i> <i>Decreased sense of well-being</i>

Therapy

When the diagnosis of hypogonadism has been established, the clinician and patient must then determine if the benefits of androgen therapy warrant the potential risks and cost. For patients with unequivocal hypogonadism and no contraindications to androgen replacement therapy (e.g. untreated prostate or breast cancer, severe bladder outlet obstruction, untreated sleep apnea, or polycythemia), the benefits outweigh the risks of androgen replacement therapy. In some men with some manifestations of hypogonadism and borderline low testosterone levels, a trial of androgen therapy may be reasonable. Before beginning a trial of androgen therapy in instances where the diagnosis is equivocal, it is particularly important that the clinician document that he discussed the controversy and risks and benefits of androgen supplementation therapy with the patient.

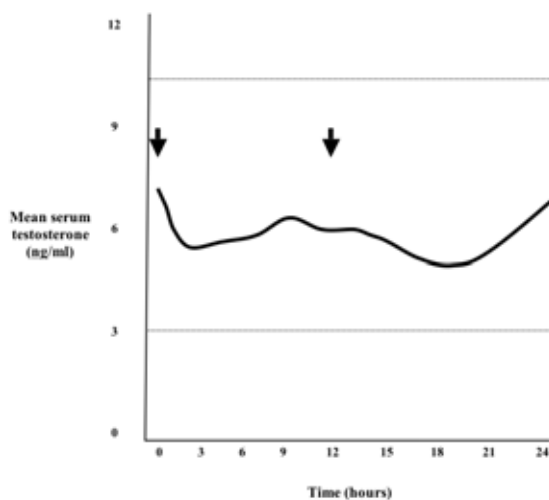
Androgens affect a broad range of tissues, organs and physiological functions including sexual function, brain, muscle, bone, prostate, and the cardiovascular system. I will review briefly some of the important effects of androgens. There are many excellent recent reviews for readers interested in further details.^{7,9-12}

Benefits of Androgen Replacement Therapy

Sexual Function

Studies using a wide variety of formulations have shown an improvement of sexual desire, sexual

Figure 1: Mean serum total testosterone levels after buccal testosterone (Striant®) 30mg was administered every 12 hours (arrows)



Data are from pharmacokinetic data from two studies (n=111 total) with blood samples drawn every hour. Dashed lines represent upper and lower limits of normal range.

Graph modified from http://www.fda.gov/cder/foi/label/2003/21543_striant_lb

satisfaction and sexual performance.^{5,7} It is generally thought that younger men may have normal sexual function with subnormal testosterone levels, but older men may have a dose-dependent effect of testosterone on sexual function.^{13,14}

Lean Body Mass, Strength and Fat Mass

Most studies have shown moderate increases (1–5kg) of lean body mass when androgen replacement therapy, but a few trials have shown no effect.^{5,7} Several small studies have shown increased strength in at least one muscle group and two studies have shown improvement in functional tests of leg strength and balance.^{5,15,16} A recent large cohort study reported that hypogonadal older men have decreased balance and increased risk of falls, but it remains unclear if androgen therapy would reduce this risk of falls.¹⁷

Bone Density and Fractures

Most trials show that testosterone replacement therapy increases bone mineral density in men with low baseline testosterone levels.^{5,7} It is likely that the duration and degree of testosterone deficiency, the mode of testosterone delivery and the average testosterone levels achieved during therapy affect the degree of bone mineral density increase. For example, studies using sublingual testosterone in younger hypogonadal men or a transdermal testosterone patch

system in older hypogonadal men did not significantly increase bone mineral density in hypogonadal men whereas a study of intramuscular testosterone therapy given to older hypogonadal men resulted in very significant increases in spine and hip bone mineral density.^{18–21} It is likely that the lower pre-treatment and higher average treatment levels achieved in the intramuscular testosterone study explain the increased bone mineral density compared to the sublingual and transdermal testosterone trials. Although epidemiological trials suggest that male hypogonadism is an important risk factor for osteoporotic fracture, there has not yet been an adequately powered, long-term clinical trial of the effects of androgen replacement on osteoporotic fracture in hypogonadal men.

Mood and Sense of Well-being

The majority of clinical trials have demonstrated an improvement of mood and sense of well-being in hypogonadal men treated with a variety of androgen replacement formulations.⁷ Mood, like sexual function, tends to improve early in the course of therapy and then plateau.

Risks of Androgen Replacement Therapy

Prostatic Disease

Most studies of androgen replacement therapy have shown that androgen replacement therapy increases prostatic size within the normal range for age. Androgen replacement therapy does not appear to alter micturition or increase the incidence of bladder outlet obstruction symptoms, but virtually all clinical trials exclude men with pre-treatment symptoms or the diagnosis of bladder outlet obstruction.¹¹ The effects of testosterone androgen replacement therapy on the risks of prostate cancer are controversial.^{5,7,11,22} Testosterone therapy probably does not cause *de novo* prostate cancer, but it can promote the growth of pre-existing prostate cancer. In general, androgen replacement therapy to older men stimulates a small increase in serum prostate specific antigen (0.3–0.6 ng/mL) that stabilizes after three to six months of therapy.¹¹ If the serum prostate specific antigen increases more than 1.4ng/ml during a year of androgen therapy, then a urological evaluation is indicated.⁵

Cardiovascular Disease

Although male gender is an established risk factor for coronary artery disease, androgens do not appear to increase the risk of ischemic heart disease. Epidemiological studies show that the risk of coronary artery disease tends to occur more frequently in men with lower serum testosterone levels, and hypogonadal men with

established coronary artery disease who are treated with androgen replacement therapy have fewer signs of ischemia during exercise than placebo-treated hypogonadal men with established coronary artery disease. In addition, androgen replacement therapy tends to have favorable effects overall on risk factors for coronary artery disease. Although androgen replacement therapy causes small, but significant decreases in high-density lipoprotein cholesterol levels, it causes larger decreases in atherogenic low-density lipoprotein cholesterol levels and causes favorable changes in body composition.^{7,23}

Erythropoiesis

Testosterone therapy stimulates erythropoiesis and may cause erythrocytosis, particularly in older men.²² Men who are treated with androgen replacement therapy should be periodically monitored with complete blood counts.

Treatment Options

There are now a myriad of androgen replacement treatment options: oral, buccal, transcutaneous (patches and gels), and short and long-acting injectable formulations that are being used in the US and around the world. It is beyond the scope of this brief review to discuss each of the formulations in depth, but each formulation has its advantages and disadvantages.⁷ I shall compare the most recently approved new formulation, buccal testosterone, with other approved formulations and will use it as a model for the promise and pitfalls of potential formulations of androgen replacement therapy that are being developed.

Buccal Testosterone

Steroid hormones are readily absorbed across the buccal mucosa into the systemic circulation and bypass first-pass hepatic metabolism.²⁴ A small pilot study of a proprietary buccal testosterone tablet showed that peak testosterone levels were achieved within 30 minutes of application but testosterone levels returned to baseline within four to six hours.²⁵ A newer proprietary buccal testosterone formulation, Striant[®], was developed that is rapidly absorbed and maintains serum testosterone levels within the normal range for 12 hours (see *Figure 1*). Initial clinical trials have shown that Striant (30mg every 12 hours) maintains serum testosterone levels in the normal range for a 24-hour period for 85–93% of hypogonadal men.^{26,27} The pharmacokinetic profile compares favorably with transcutaneous testosterone patch and gel systems that are administered once daily on the torso.^{7,27} In a three-month safety trial, about 10% of patients withdrew because of application problems or intolerance with a few weeks of initiating Striant, therapy.²⁶ About 16% of the men who

completed the three-month trial had either gum irritation or inflammation, and 3% withdrew because of oral adverse events.

The primary advantage of Striant is its mode of administration: most patients prefer an oral route for medications. There are other formulations of oral androgen replacement therapy: alkylated androgens and oral testosterone undecanoate. However, alkylated androgens cause hepatotoxicity, and Striant appears to have a longer-half and offer more stable testosterone levels than oral testosterone undecanoate. Although there have been no head-to-head comparison trials of Striant vs oral testosterone undecanoate, testosterone levels may vary significantly with oral testosterone undecanoate administration, and some men may have to take oral testosterone undecanoate three times daily.⁷ Many patients may prefer Striant over intramuscular injections of testosterone enanthate or cypionate every seven to 14 days because the discomfort of injections and to avoid the supraphysiological peaks of testosterone that occur two to three days after injection of these testosterone esters.

The disadvantages of Striant include frequency of administration, local irritation at the site of administration, and the relative dearth of information showing long-term end-organ benefits. Many men appear to prefer testosterone gel formulations that may be administered once daily (compared with twice-daily application of Striant) to the upper arm or torso while maintaining serum testosterone levels in the normal range for the majority of men.⁷ Indeed, some men find weekly or biweekly intramuscular injections of testosterone ester more convenient than either daily testosterone. On the other hand, the majority of men who participated in the clinical trials of Striant rated the formulation an acceptable method of androgen therapy and slightly less than half of the men stated that they preferred over their previous method of androgen therapy (intramuscular or transdermal therapy).

In 2003, the US Food and Drug Administration (FDA) approved Striant for androgen replacement therapy in men with primary or secondary hypogonadism. This approval was based on the pharmacokinetics of testosterone delivery with Striant, not long-term studies of end-organ effects. Because Striant provides normal daily testosterone levels to most men, it should (and appears to) be as effective in relieving symptoms of hypogonadism. Striant should also be as effective in improving function in end-organs such as muscle and bone as other formulations such as transdermal testosterone and intramuscular testosterone esters, but there are no long-term data, and it is possible that long-term use of Striant will be associated with changes in

testosterone levels due to either changes in the buccal mucosa (just above the incisor) where Striant is applied or due to decreased long-term compliance with twice daily administration.

Striant may cause side effects that have not yet been observed due the limited long-term use of Striant. Striant, like any other formulation of testosterone therapy that crosses an epithelial (skin, buccal or gut), increases serum dihydrotestosterone (DHT) levels disproportionately because of epithelial 5 α -reductase activity. DHT levels increase by >25% with Striant administration, and higher serum DHT levels theoretically could increase the risk of prostatic disease.²⁶ In addition, it is theoretically possible that excessive testosterone could be vicariously transferred to intimate contacts of Striant users.

Conclusions

In the last decade, scientists in academia and the pharmaceutical industry have made important and exciting discoveries and innovations about the diagnosis and management of male hypogonadism. The buccal formulation of testosterone therapy, Striant, represents one of the latest therapeutic innovations. Before prescribing any form of androgen therapy including

Striant, the clinician must carefully confirm the diagnosis of male hypogonadism based on symptoms and signs of the syndrome plus reproducibly low serum testosterone levels that have been measured by a reliable and accurate assay. In addition, an appropriate work-up for primary and secondary hypogonadism must be done and the risks and benefits of androgen therapy must be discussed (and documented) with the patient. Patients receiving long-term Striant or any other form of androgen therapy must be monitored for side effects with appropriate testing to detect significant erythrocytosis and prostate or breast cancer. Striant soon may represent a vestige of the past: a therapy for male hypogonadism approved purely on the basis of pharmacokinetic data showing normalization of serum testosterone levels in most hypogonadal men. Future drug formulations for androgen replacement therapy likely will need more evidence for end-organ benefit and safety. Selective androgen receptor modulators, drugs that selectively confer the benefits androgens on organs such as muscle and bone without androgenic side effects on the prostate, are already being developed. These androgen replacement therapies will require evidence that they will safely provide long-term benefit to improve muscle and bone strength and function without increasing or perhaps even decreasing androgen-related diseases such as prostate cancer. ■

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