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Expert Opinion

Treating hypogonadism in younger males

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Importance of the field: Hypogonadism in the young and middle-aged male is a well-established clinical entity. The majority of the patients have primary gonadal insufficiency with Klinefelter syndrome a common cause. Secondary hypogonadism in these age groups can be congenital, secondary to medications, or associated with a hypothalamic–pituitary mass or inflammatory lesions. Signs and symptoms in males with hypogonadism can include impaired sexuality, decreased muscle strength, increased body fat, decreased bone mass, impaired mood and mild anemia; in young patients puberty can be delayed. Several new treatment modalities have become available in recent years and a number of future compounds are in development.

Areas covered in this review/What the reader will gain: This review explores the treatment options for children, young adult and middle-aged males with hypogonadism related to various etiologies, including currently available and future testosterone formulations and other non-testosterone compounds. The long-term treatment effects, particularly on prostate health, remain unclear and may be particularly relevant for the younger patient initiated on chronic therapy; treatment monitoring and recommended clinical follow-up based on current guidelines are also reviewed.

Take home message: Hypogonadism in younger males can be the result of a diversity of etiologies. Treatment options for hypogonadism and induction of puberty have expanded and can be individualized based on patient preference, side effect profile, and a number of other parameters.

Keywords: androgen deficiency, delayed puberty, dihydrotestosterone, disorder of sexual development, human chorionic gonadotropin, hypogonadism, induction of puberty, Kallmann's syndrome, Klinefelter syndrome, testosterone

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1. Introduction

Hypogonadism is defined as failure of testes to produce adequate testosterone and/or to conduct normal spermatogenesis. Testosterone deficiency and infertility may occur together or independently in hypogonadal men. Infertility will not be dealt with in this commentary as the focus will be on low-testosterone syndromes. Hypogonadism can be due to a number of processes that are generally classified as either primary, secondary, or mixed etiologies. Whereas primary and secondary causes can be due to either congenital or acquired etiologies, mixed causes are usually acquired.

Primary hypogonadism is characterized by failure of the testes to respond to luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Low testosterone levels are insufficient to inhibit LH and FSH secretion and, as a consequence, LH and FSH levels are elevated. The most identifiable cause of primary hypogonadism is Klinefelter syndrome, which involves seminiferous tubule dysgenesis and a 47, XXY karyotype. Other etiologies include testicular failure due to cryptorchidism, bilateral torsion, orchitis, orchidectomy, and testicular trauma (i.e., resulting from

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Article highlights.

- Serum testosterone < 300 ng/dl generally indicates hypogonadism, but not all symptoms and signs occur at the same testosterone level.
- It is important to distinguish constitutional growth delay and temporal delay in puberty from secondary hypogonadism because the latter requires life-long treatment.
- Currently available T formulations include transdermal gels (easily titrated but have a risk of interpersonal transfer), injections (widely used but relatively less convenient and may be less acceptable to younger patients), patches (convenient, but may cause skin irritation and are not appropriate for younger males), oral T undecanoate (easily administrated, convenient but requires multiple daily dosing) and subcutaneous implants (safe and effective but require surgical incision).
- The effect on final adult height when testosterone is used to induce puberty appears to be minimal.
- More data are needed to assess the long-term effects of testosterone on prostate health.

This box summarizes key points contained in the article.

surgery, radiation, or chemotherapy). There is also some evidence suggesting an association between male subfertility and testicular cancer [1,2]. In most cases of primary hypogonadism the cause is unknown.

Secondary (hypogonadotropic) hypogonadism is due to either hypothalamic or pituitary defects. Hypothalamic abnormalities result in inadequate secretion or action of gonadotropin-releasing hormone (GnRH). Causes include Kallmann's syndrome, radiation, excessive stress, inflammatory disorders, neurotropic and pain medications, and anorexia nervosa [3]. Pituitary defects result in inadequate LH and FSH production. Consequently, LH and FSH levels are low or inappropriately normal. Etiologies include tumors (i.e., adenomas, craniopharygiomas), hyperprolactinemia (produced in the pituitary with suppression of hypothalamic GnRH), infarction, trauma, autoimmune hypophysitis, and infiltrative diseases such as sarcoidosis [3]. Whereas disorders of defective androgen action (i.e., androgen resistance) may mimic hypogonadism, they are not associated with low serum testosterone levels (serum testosterone is often elevated or high normal).

In general, the age at the onset of hypogonadism determines the clinical presentation. Congenital causes are particularly relevant in the younger male patient. During the first trimester of fetal life, complete absence of testosterone results in the development of normal-appearing female external genitalia. Incomplete early fetal testosterone deficiency results in a range of abnormalities, including hypospadias or ambiguous genitalia. Onset during the second or third trimester of fetal life can result in undescended testes or micropenis. Isolated LH deficiency can result in eunuchoid body proportions (long arms and legs), low testosterone levels and oligospermia [4]. As FSH is necessary for normal spermatogenesis, isolated FSH deficiency results in oligospermia or azoospermia in normally androgenized males [5].

In the adolescent male, hypogonadism may result in delayed puberty and lack of secondary sexual characteristics, underdeveloped muscle mass, low bone mineralization, shorter adult height, and central adiposity [6]. Experimental models in young men have demonstrated a reduction in several anabolic parameters with testosterone deficiency. In healthy young men (mean ± SEM age 23 ± 0.5 years) serving as their own controls who underwent gonadal suppression with the GnRH analog Lupron for 10 weeks, a significant decrease in lean body mass was observed [7]. Decreased rates of lipid oxidation, protein synthesis, resting energy expenditure, and muscle strength [7] were also seen.

The decline in serum testosterone levels with aging has been well established. In normal, healthy men who are not on medication, levels begin to decline in the mid- to late-thirties. The decline continues in a linear fashion into the nineties at a rate of 0.4 – 2% per year [8,9]. Testosterone therapy in the older male (i.e., those with late-onset hypogonadism) has been discussed elsewhere in this review series and will not be covered here.

This article briefly reviews the diagnosis of low-testosterone syndromes in younger males. The clinical uses of testosterone therapy with respect to these conditions will be covered in more detail, in addition to current and future testosterone formulations and other non-testosterone compounds for these various applications.

2. Diagnosis

2.1 Diagnosis of hypogonadism

In general, the diagnosis of male hypogonadism is made in patients with signs and symptoms consistent with a low serum testosterone (**Box 1**) together with unequivocally low serum testosterone levels. Due to diurnal variations in testosterone levels and the observation that levels are generally higher in the morning, it is recommended that the initial diagnostic test be a morning testosterone level measured by a reliable assay [10]. Testosterone levels < 300 ng/dl are generally considered to be indicative of hypogonadism, although symptoms may occur at differing testosterone levels [10]. Confirmation should be made by repeating measurement of morning total testosterone; in some patients it may also be helpful also to measure free or bioavailable testosterone using accurate assays [10].

2.2 Disorders of sex development

Most causes of disorders of sex development (DSD) are recognized in the neonatal period. First-line testing in newborns includes: karyotyping with X- and Y-specific probe detection (even when prenatal karyotype is available), abdominopelvic ultrasound, measurement of 17-hydroxyprogesterone, testosterone, gonadotropins, anti-Müllerian hormone, serum

Box 1. Symptoms and signs of androgen deficiency in men.

Symptoms and signs suggestive of androgen deficiency in men:
Incomplete or delayed sexual development, eunuchoidism
Reduced sexual desire (libido) and activity
Decreased spontaneous erections
Breast discomfort, gynecomastia
Loss of body (axillary and pubic) hair, reduced shaving
Very small (< 5 ml) or shrinking testes
Inability to father children, low or zero sperm count
Height loss, low trauma fracture, low bone mineral density
Hot flushes, sweats
Other symptoms and signs associated with androgen deficiency that are less specific than those above: [10]
Decreased energy, motivation, initiative, and self-confidence
Feeling sad or blue, depressed mood, dysthymia
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild anemia (normochromic, normocytic, in the female range)
Reduced muscle bulk and strength
Increased body fat and body mass index
Diminished physical or work performance

electrolytes and urinanalysis [11]. DSD often requires a specialist to correctly characterize the causal mechanism.

2.3 Delayed puberty

The timing of puberty is highly variable and is dependent on many factors, including familial and environmental factors. Delayed puberty is generally defined by the lack of testicular enlargement to at least 3 ml (using an orchidometer) by 14 years of age, which may reflect lower than normal gonadotropic effects on the testes [12]. An important but often difficult distinction to make is that between permanent (secondary) hypogonadism, which involves dysfunction of the hypothalamic-pituitary axis and necessitates life-long androgen replacement, from constitutional growth delay and temporal delay of puberty. In the latter case, treatment may only be required to induce puberty until the hypothalamic–pituitary–gonadal axis starts to function at adult levels.

Evaluation of the patient with delayed puberty should include an evaluation of the sense of smell, as anosmia or hyosmia can be associated with Kallmann's syndrome. As delay in puberty may be familial, a careful family history is often helpful. Measurement of LH and FSH will assist in distinguishing primary hypogonadism from hypogonadotropic hypogonadism. Measurement of gonadotrophs will not, however, distinguish permanent hypogonadotropic hypogonadism from constitutional growth delay as gonadotrophs may be low in both cases. Prolactin measurement is recommended to rule out prolactinoma. Insulin-like growth factor-I (IGF-I) should be measured to rule out growth hormone deficiency, as mistakenly treating such a patient with androgens may result in a reduced adult height [12]. Linear growth should be plotted, and the heights of parents should be measured when possible. Bone age is also helpful, as boys with delayed puberty may have bone ages delayed by two or more standard deviations [12]. Magnetic resonance imaging (MRI) of the sella region is necessary when there is suspicion of pituitary/CNS tumor. Karyotyping should be undertaken when there is suspicion of an underlying genetic disorder (i.e., Klinefelter's syndrome). Most patients with the XXY karyotype have elevated serum LH/FSH, behavioral abnormalities, and learning disabilities that are manifest by reduced school performance and dyslexia.

2.4 Androgen deficiency in young and middle-aged adults

Men whose serum testosterone levels have fallen in subnormal levels after puberty present clinically with decreased libido, decreased muscle mass and strength, decreased bone mass, increased body fat (especially visceral), decreased facial and body hair, decreased mood, and mildly decreased red blood cell mass, and may have a predilection to metabolic syndrome, diabetes mellitus and cardiovascular disease [10]. The symptom profile will differ in individuals and may be dependent on the degree of deficiency.

3. Goals of therapy and rationale

The primary clinical uses for testosterone therapy are: i) the induction of puberty; and ii) correction of adult androgen deficiency signs and symptoms. The goals of testosterone therapy in the adolescent male are to promote: i) linear growth; ii) secondary sexual characteristics; iii) acquisition of normal muscle mass; and iv) accrual of adequate bone mineral content [6]. (Testosterone treatment will stimulate long bone growth but also accelerates epiphyseal fusion. Thus treatment must be carefully undertaken to avoid increased height at the expense of ultimate short stature.) Although not all patients with constitutional growth delay and puberty require hormone treatment, therapy has been recommended in all patients with 46, XY DSD and hypogonadism (**Box 2**) [13].

Hormonal induction of puberty should begin at the average age of puberty onset for males, which is between 12 and 13 years [11], although waiting for at least 1 – 2 years has been a common practice if further linear growth is desired [14]. Delay of puberty may lead to social and psychological issues secondary to short stature, and to delay of secondary sex characteristics [15]. The goals of therapy are thus to achieve the normal tempo of puberty including a growth spurt, as well as maturation of secondary sexual characteristics, development of reproductive function, accumulation of bone mineral mass, and achievement of adult height, body proportions, and fat mass/muscle ratio [13]. If induction of puberty is contemplated after the patient has reached the average age of puberty onset, then it may be desirable to attempt to accelerate the tempo of pubertal development.

Box 2. Main indications for sex steroid substitutive treatment in persons with hypogonadal disorders of sex development [13].

Induction of:
Sex-specific secondary sexual characteristics and then maintenance in adulthood
Normal pubertal growth spurt and body proportions
Adequate free-fat (muscle) mass and fat mass development according to assigned sex
Optimal bone mineral mass accumulation
Adequate penile growth and internal genitalia (if present)
Sex-specific psychosocial and psychosocial maturation
Normal social/sexual function and well-being (in adolescence and adulthood)

The aim of therapy with any of the approved formulations is to achieve serum testosterone levels in the mid-normal range [10]. Suggested monitoring schemes for males with 46, XY DSD have proposed the goal of restoring serum testosterone levels to the mid-normal range based on Tanner stage (**Table 1**).

Testosterone therapy in younger males has been shown to enhance linear growth, secondary sexual development and promote achievement of predicted adult height [16]. In hypogonadism with onset after puberty (young and middle-aged adults), testosterone replacement has been shown to improve a number of clinical parameters, including muscle function and strength, sexual function, sense of well being, quality of life, and bone mineral density [17-25]. Improvements in lipid profile (lower total cholesterol, low-density lipoprotein, and triglycerides) have also been demonstrated [26,27] in some but not all studies. Reduction in high-density lipoprotein cholesterol may occur when super-physiological doses of testosterone are administered or when some oral testosterone formulations are used.

4. Approved compounds

The choice of therapy can depend on a number of factors, including pharmacokinetics, convenience, cost, and overall patient preference. Various testosterone preparations are available (**Table 2**). In addition, human chorionic gonadotropin (hCG) may also be used for puberty induction and is required in hypogonadotropic hypogonadism for sufficient spermatogenesis to allow normal fertility potential. Gonadotropin therapy can be delayed until pregnancy is desired as testosterone treatment does not prevent later gonadotropin treatment success.

4.1 Testosterone

4.1.1 Topical testosterone preparations: patches and gels

T Patches were among the earliest transdermal testosterone formulations; scrotal patches became available in 1994. Testoderm® is a patch worn on a hair-free area of the scrotum; it is no longer available in the US. Testosterone levels peak at 2 – 4 h and are held in the normal range for 24 h of patch use [28]. Androderm® (available in the US) and Andropatch® (available outside the US) are used in 2.5- or 5-mg preparations. These non-scrotal patches are applied nightly and achieve the normal circadian variations of testosterone and dihydrotestosterone (DHT) as well as normal plasma concentrations of testosterone, DHT, and DHT/testosterone in healthy young men [29]. The use of testosterone patches in younger males is somewhat limited because they are too large for use in prepubertal and early pubertal boys and the doses of testosterone delivered through patches are too high for inducing puberty [6]. Skin erythema and blistering limit acceptability in many patients.

Testosterone gels first appeared in 2000 and remain an effective androgen substitution therapy with several advantages over other products. They are available in various doses easily adjusted based on a patient's requirements. In the US, two gels currently available are Testim® and AndroGel® (the latter is marketed as TestoGel® in Europe) [30]. Testim [31] is available in 1% strength. AndroGel is available in 1% strength and topical administration of 5, 7.5, or 10 g contains 50, 75, or 100 mg testosterone, respectively [32]. Tostran® is a 2% strength formulation available in Europe, which delivers 60 – 80 mg of testosterone in 3 – 4 g of gel applied daily, with the higher-strength formulation indicated for men over 18 years. The gels are applied in the morning to the shoulders, abdomen, or upper arm. Although gels generally dry within several minutes, it is recommended patients remain dry for 2 – 6 h after application, depending on the gel used. Mean serum testosterone and DHT levels double approximately 30 min after first application and reach steady-state levels in the normal adult range with daily administration [33]. A study of 163 hypogonadal men (mean age 51.4 ± 0.91 years) treated with AndroGel at various doses for up to 42 months demonstrated improvement and maintenance of sexual function, increased lean body mass, decreased fat mass and increased serum bone markers and bone density in the hip and spine [21]. Currently, there is no approved formulation for use in prepubertal boys [6]. TestoGel has been used for induction of puberty with a recommended starting dose of one-third of a 5 g sachet daily for the first year, titrated by one-third of a sachet daily each year to a final dose of 5 g daily in the third year [34]. Duplication of blood levels could be attained using a gel-dispensing pump bottle.

One concern associated with the use of testosterone gel is unintentional transfer to children or women by skin contact with the application site. Case reports of hyperandrogenism likely related to intrapersonal transfer have been published [35], suggesting that the risk of transfer is both possible and clinically relevant. Label warnings of this risk exist and manufacturers recommend wearing covering clothes over the application areas during times of close contact with other persons, especially women and children.

Table 1. Mean (range) testosterone levels (ng/ml) according to Tanner Stage [15].

Stage	Testosterone, ng/ml expressed as mean (range)
I	0.1 (0.03 – 0.11)
II	0.2 (0.02 – 3.0)
III	0.5 (0.3 – 3.9)
IV	1.7 (0.9 – 8.4)
V	3.5 (2.8 – 10.0)

4.1.2 *Injectable preparations*

Intramuscular (IM) depot injections of testosterone esters are the most widely used in pediatric practice [14] and are adaptable for the increasing amounts of androgen necessary for the various stages of pubertal development [6]. In patients with constitutional growth delay and puberty, as well as those with primary or secondary permanent hypogonadism (including DSD) with normal sensitivity to androgens, proposed regimens have initiated therapy with either testosterone enanthate or cypionate at 50 – 75 mg every 4 – 6 weeks for 6 – 12 months, then gradually increasing the dose over several months before changing to adult weekly (75 – 100 mg) or twice monthly dosing (150 – 200 mg) [6,13].

Patients with delayed puberty may require treatment for 6 – 18 months before the hypothalamic–pituitary–gonadal axis functions at the late adolescent/adult level [6]. Various regimens have proven to be safe while promoting several favorable characteristics, including increased linear growth velocity, increased muscle mass, appearance of secondary sexual characteristics and increased testicular volume [36]. While testosterone given in supraphysiologic amounts will predictably suppress LH and FSH and thus impair spermatogenesis, the aforementioned regimens allowed (but did not cause) increases in testicular volume [36].

In adult patients, 75 – 100 mg of testosterone enanthate or cypionate IM weekly, or 150 – 200 mg administered every 2 weeks is usually adequate for replacement therapy. Peak values are achieved at 2 – 3 days and a return to baseline at about 10 days after injection. The higher the dose, the greater the peak and the longer the action; patients may complain of 'highs and lows'.

Injectable testosterone undecanoate (TU) has become the most common replacement therapy in Europe, where the drug is administered as 1000 mg at the onset, repeated at 6 weeks and then every 10 – 14 weeks thereafter. Blood levels after several months are reasonably stable. The primary advantage of this formulation is less frequent injections. A different dosage schedule has been published in clinical trials in the US but the drug is not presently approved by the Food and Drug Administration (FDA). Cough has been reported immediately after injection in a very small number of treated men. This has been attributed to oil embolization to the lungs.

4.1.3 *Oral preparations*

Oral testosterone is well absorbed after administration but ordinarily undergoes rapid degradation by the liver. Methyl testosterone is still available but not recommended by most experts because of risk of hepatic dysfunction.

In Europe, Asia, and Canada (but not the US) an oral formulation of testosterone undecoanoate (Andriol®) has been available for four decades. There are currently no FDA-approved, oral, non-17 alkylated testosterone preparations in the US. The primary limitations of oral testosterone undecanoate are unreliable bioavailability, fluctuating serum levels, and a short half-life [6]. Oral TU must be taken with food, as absorption is markedly reduced in the fasting state. Typical doses are 120 – 240 mg daily given in three divided doses which are necessary to attain normal 24-h area under the curve (AUC) blood levels. Peak levels are measured 2 – 6 h post-administration. The hepatic metabolism of oral TU is reduced as a portion of it is absorbed into the lymphatics and travels directly to the systemic bloodstream, avoiding the first-pass hepatic effect [28].

A transbuccal T bucinate tablet (Striant®) is available for twice a day use. When applied on the upper gum by the incisor, blood levels remain in the normal range in most patients. Some patients complain of awareness of a gel-like tablet at the site of application, gum irritation, or headache [37,38].

4.1.4 *Implants*

Implantable preparations are a safe, effective, convenient option when life-long treatment is needed. Blood levels are dependent on the number of pellets implanted. The levels achieved with current formulations could be high for the induction of puberty [6] unless careful dose titration is accomplished. In adolescents with either primary or secondary hypogonadism who have already entered puberty, long-acting subcutaneous testosterone pellets promote appropriate growth velocity for bone age, progression of puberty, and virilization, and may be a convenient mode of testosterone delivery in adults as it reduces the compliance problems of frequent injections or daily gel administration. Pellets are used more often in Europe, where 100- and 200-mg pellets are available; 75-mg pellets are marketed in the US.

The number of pellets needs to be individualized. Insertion requires surgical incision. Extrusion rates of 0.3 – 12% have been reported [39-41]. Extrusion appears to be somewhat more problematic with the larger pellets. Pellets do not require patients to remain dry after application, which may be an important benefit to young men and children who wish to participate in aquatic activities. As pellets do not require frequent administration or have the aroma that can be associated with some gels, patients are not reminded daily of their androgen deficiency.

5. Non-FDA approved compounds (in the US)

5.1 Transdermal Axiron®

The Australian firm Acrux Ltd (Melbourne, Australia) reported results from an international Phase III study of a

Table 2. Some approved testosterone formulations.

Formulation	Typical regimen	Pharmacokinetic profile	Advantages	Disadvantages
Oral				
Testosterone undecanoate (Andriol)	40 – 80 mg orally 2 or 3 times daily	When administered in oleic acid, TU is absorbed through the lymphatics, bypassing the portal system; considerable variability in same individual on different days and among individuals; peak levels 2 – 6 h after administration	Oral administration	Frequent dosing needed; variable serum T levels and clinical responses achieved; high DHT:T ratio; relatively expensive
Transbuccal				
Transbuccal (Striant)	30 mg controlled-release tablet twice daily	Peak T levels at 10 – 12 h; steady state achieved after second dose; following removal of tablet levels drop below normal after 2 – 4 h; not affected by first-pass hepatic metabolism; absorption does not appear to be affected by drinking or eating [59]	Corrects symptoms of androgen deficiency in healthy, hypogonadal men	Concern for transfer to intimate contacts with saliva; gum-related adverse events in 16% of treated men; relatively expensive
Injectable				
Testosterone cypionate or enanthate	75 – 100 mg IM weekly or 150 – 200 mg IM every 2 weeks	Supraphysiologic levels achieved soon after injection then gradual decline to hypogonadal range at end of dosing interval; half-life of eight days [60]	Corrects symptoms of androgen deficiency; easy dose adjustment; relatively inexpensive if self-administered; most widely used in pediatric practice	Requires IM injection. Peaks and valleys in serum T levels
Testosterone undecanoate (long-acting formulation in oil)	1000 mg IM followed by 1000 mg at week 6, then 1000 mg every 12 weeks	Serum T levels maintained in normal range in majority of treated men; C_{max} values achieved 7 days after first dose; half life of 90 ± 40 days [61]	Corrects symptoms of androgen deficiency; relatively inexpensive; less frequent administration required	Requires IM injection of a large volume (4 ml); concern for possible effects on prostate health
Transdermal				
Nonscrotal patch (Androderm, Andropatch)	1 or 2 patches (each 2.5 or 5 mg) over 24 h on non-pressure areas	Physiologic range T, DHT and E2	Corrects symptoms of androgen deficiency; ease of application; recreates normal circadian rhythm of T and DHT	Serum T in some men may be in low normal range and may require two patches daily; generally too large for use in prepubertal boys or patients in early puberty; relatively expensive; potential for skin irritation
Gel (AndroGel, TestoGel, Testim, Tostran)	5 – 10 g containing 50 – 100 mg applied in morning to shoulders, abdomen, or upper arm	10% per dose absorbed within 24 h; 2 – 3 × increase in serum T levels in 2 h and 4 – 5 × increase at 24 h; T and DHT reach steady state within 48 – 72 h	Corrects symptoms of androgen deficiency; can be used for induction of puberty; flexible dose adjustment; ease of application; good skin tolerability	Possible transfer to female partner or child by direct skin-to-skin contact; moderately high DHT levels

Adapted from [10].

DHT: Dihydrotestosterone; E2: Estradiol; IM: Intramuscular; T: Testosterone; TU: Testosterone undecanoate.

Table 2. Some approved testosterone formulations (continued).

Formulation	Typical regimen	Pharmacokinetic profile	Advantages	Disadvantages
Subcutaneous implant				
Pellet (TestoPel®)	150 – 450 mg pellet implanted SQ every 3 – 6 months [62]	Serum T peaks at 1 month then is sustained in the normal range for 4 – 6 months; mean residence time of 87 days and a half-life of 70.8 days [63]	Corrects symptoms of androgen deficiency in adolescents; implants promote appropriate growth velocity for bone age, progression of puberty, and virilization; non-daily administration may enhance compliance	Requires surgical incision for insertions; spontaneous extrusion possible

Adapted from [10].
DHT: Dihydrotestosterone; E2: Estradiol; IM: Intramuscular; T: Testosterone; TU: Testosterone undecanoate.

new topical 2% testosterone formulation called Axiron®. Eighty-four per cent of subjects using Axiron® achieved average blood testosterone levels within the normal range; 76% of treated subjects achieved normal blood levels of testosterone after 2 weeks of treatment [42]. The optimum dose for 75% of patients was 60 mg testosterone per day, equivalent to a single application of Axiron® to each armpit. While outcome data are somewhat limited, there was 'significant improvement…in all psychosexual parameters' [43,44].

5.2 Gel preparations available outside the US

Fortigel® (ProStraken, Galashiels, UK) is available as Tostran® in Europe (see Section 4.1.1) and is a 2% transdermal gel. It can provide serum AUC levels within FDA guidelines. Skin irritation occurs in more than 10% of patients [45].

5.3 Human chorionic gonadotropin

Human chorionic gonadotropin is not a testosterone preparation but can be used to stimulate testosterone secretion in patients with testicular Leydig cell reserve. In children and adolescents, hCG can be used to promote descent of cryptorchid testes [6]. hCG has also been shown to induce puberty in patients with idiopathic hypogonadotropic hypogonadism [46]. Several studies have shown beneficial effects on spermatogenesis, testicular growth, and testosterone levels in hypogonadotropic hypogonadal males treated with hCG. In azoospermic males with idiopathic or acquired hypogonadotropic hypogonadism, pretreatment with hCG (1000 IU three times weekly or 1500 – 2000 IU twice weekly adjusted to individual response) for 3 – 6 months will normalize testosterone levels in 81% [47]. Most adult patients with prepubertal onset hypogonadotropic hypogonadism will need additional combination treatment with hCG and recombinant human FSH (75 – 150 IU three times weekly) to increase sperm counts to levels sufficient to allow fertility. In a long term study of 17 patients (mean age 21.8 ± 1.4 years, range 18 – 37 years) with isolated hypogonadotropic hypogonadism, hCG improved testosterone levels and spermatogenesis regardless of initial testicular volume or age [48].

A variety of different regimens have been used. Forty-four of 46 patients with chronological ages 12.5 – 17.5 years treated with hCG 1500 – 2000 IU twice weekly for 6 months achieved genital stage 3 or 4 at the end of therapy, and patients initially growing less than 7 cm/year had the greatest increases in height velocity [49]. In prepubertal males with panhypopituitarism or idiopathic hypogonadotropic hypogonadism, hCG 1000 – 1500 IU given with FSH 75 – 100 IU on alternating days until puberty was achieved, resulted in normal sexual maturation, normal or nearly normal adult male levels of testosterone, and significant increases in testicular size in all patients [46].

5.4 Aromatase inhibitors

Aromatase inhibitors act on the enzyme aromatase (also known as estrogen synthase) and decrease estrogen production. Lower estrogen levels result in reduced negative feedback on pituitary LH production. The higher LH levels that result in turn stimulate the production of endogenous testosterone in men with residual hypothalamic–pituitary function. Letrozole and anastrozole are third-generation aromatase inhibitors; they are potent and do not inhibit related enzymes. Third-generation aromatase inhibitors will decrease in men the mean plasma estradiol/testosterone ratio by as much as 77% [50]. Testolactone, an anti-estrogen, increased sperm count and motility in men with severe male-actor infertility or hypergonadotropic hypogonadism [51]. Neither of these classes of drugs is approved by the FDA for treatment of male hypogonadism. They have been used off-label in men with partial androgen deficiency, as well as older men with late-onset hypogonadism. They may be used to reduce recent onset gynecomastia and those men with excess aromatase activity.

5.5 Dihydrotestosterone

In prepubertal male pseudohermaphrodites marked by predominantly female external genitalia, minute phallus, bifid scrotum, urogenital sinus, and palpable gonads with 5α-reductase type II deficiency, topical administration of DHT was successful in promoting phallic growth and facilitating corrective surgery [52]. In patients with micropenis related to other etiologies, phallic growth ranging from

0.5 to 2.0 cm was achieved after 3 – 4 months of DHT treatment and achievement of DHT levels in the adult range [53]. DHT 1% gel is approved for treatment of hypogonadism in several European countries. Several reports of experimental DHT use in the US indicate some degree of efficacy in hypogonadism [54].

5.6 Selective androgen receptor modulators

Selective androgen receptor modulators (SARMs) are in development but have not yet been approved and will not be discussed in this review. They have the postulated advantage of relative selectivity (i.e., action on bone with limited effects on the prostate).

6. Contraindications to therapy

Most guidelines [10] recommend against starting therapy in adult patients with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen (PSA) level > 4 ng/ml or > 3 ng/ml in men at high risk for prostate cancer (including African–Americans, men with first-degree relatives with prostate cancer without further urologic evaluation), erythrocytosis (defined as a hematocrit > 50%), hyperviscosity syndrome, untreated severe obstructive sleep apnea, or severe lower urinary tract symptoms.

7. Monitoring

The Endocrine Society Task Force on Hypogonadism recommends measuring testosterone at 3 – 6 months after starting therapy, and then annually to assess for improvement in symptoms and development of adverse effects [10]. When either testosterone cypionate or enanthate are used, measurement of serum testosterone midway between injection periods (usually 7 days after the injection) is recommended. For patients using transdermal patches, testosterone levels should be measured 3 – 12 h after application. When buccal tablets are used, the testosterone level should be assessed immediately prior to the next application. For transdermal gel users, serum testosterone levels should be assessed at any time of the day after patient has been on treatment for 1 – 2 weeks. When injectable testosterone undecenoate is used, serum testosterone levels should be measured prior to next injection. Testosterone levels should be checked before reimplanting pellets.

Additional laboratory evaluation in male hypogonadal adults should include hematocrit at baseline, 3 and 6 months, then annually. In men with concurrent osteoporosis, bone mineral density should be reassessed after 1 – 2 years of testosterone therapy. The Endocrine Society Task Force also recommends obtaining PSA and performing digital rectal examinations at baseline, 3 and 6 months, and then according to evidence-based age and racial prostate cancer screening guidelines. PSA levels > 4 ng/ml and perhaps > 2.5 ng/ml in African–American and patients with a strong family history should be used as a risk factor for prostate cancer. Patients with PSA levels > 4 ng/ml should have the test repeated and careful prostate examination and possible biopsy performed.

No specific guidelines exist for monitoring younger patients, although a minimal tentative monitoring scheme has been proposed using the Endocrine Society Task Force guidelines [10] as a foundation. Full clinical evaluation with Tanner staging, serum testosterone measurement and hematocrit levels are recommended at baseline, 3-, 6-, 12-, 18-, 24-months, and then annually [13]. Erythrocytosis is the most common adverse event seen with testosterone treatment. If hematocrit is > 54% then therapy should be stopped, the dose lowered or phlebotomy performed until the hematocrit decreases to a safe level [10]. In prepubertal boys, bone age should be determined at baseline, 6-, 12-, and 24-months, then yearly until adult height is attained and epiphyseal closure occurs [13]. LH and FSH should be measured at baseline and checked at 3-, 12- and 24-months, then yearly.

8. Long-term effects of therapy

The potential long-term effects of therapy are particularly relevant when treating younger hypogonadal males. The effects of testosterone therapy on prostate growth or on the development of prostate cancer in adolescents and men with 46, XY DSD are unclear. Several guideline committees have stated that, despite the lack of definitive data there is no evidence that testosterone treatment will either cause prostate cancer or convert preclinical prostate cancer to a more aggressive form [55]. In a retrospective study of 81 hypogonadal men with a mean age of 56.8 years, 5% developed prostate cancer at a mean 32.5 months after initiation of testosterone replacement therapy, although there were no significant changes in PSA for up to 5 years in men who remained cancer free [26]. In another retrospective study, there were no significant differences in PSA after 1 year of testosterone replacement by either injection or transdermal routes, nor were there differences in change in PSA based on patient age, baseline PSA, total or free testosterone levels [55]. More data with respect to the long-term effects of testosterone therapy on the occurrence rates of prostate cancer and benign prostate hyperplasia are needed; such studies will require very large study groups and longer treatment durations to determine if increased risk exists.

Testosterone, when used in selected doses to induce puberty, appears to have minimal effect on final (adult) height [56-58].

9. Expert opinion

Hypogonadism in the young and middle-aged adult is well established as a clinical entity, with the majority of the patients having primary gonadal insufficiency. The causes of primary gonadal insufficiency are often cryptic. Klinefelter syndrome is common and often missed unless careful

consideration of children and adults with learning disabilities/performance deficiencies are considered. A karyotype in patients with secondary hypogonadism will make the diagnosis. The symptoms and signs of delayed sexual maturation are usually obvious. Secondary hypogonadism in these age groups can be either congenital (idiopathic hypogonadotropic hypogonadism), secondary to medications (i.e., opioids), or associated with hypothalamic-pituitary mass or inflammatory lesions. MRI of the sella and prolactin measurement are important aspects of the evaluation of men with secondary hypogonadism (low testosterone, LH, and FSH).

Delayed puberty and hypogonadotropic hypogonadism may be difficult to distinguish based on hormonal and clinical assessment. Signs and symptoms in men with hypogonadism are no longer limited to impaired sexuality as decreased muscle strength, increased body fat, decreased bone mass, impaired mood, and mild anemia are now well established manifestations. There is increasing interest in hypogonadism as either a risk factor or marker for metabolic syndrome, type 2 diabetes, and cardiovascular disease. The decision to treat males with hypogonadism is usually based on identification of a low-serum testosterone on a morning blood sample. Unfortunately, the assays in clinical laboratories have not been harmonized and each laboratory has different reference ranges which may be quite disparate. Low serum testosterone levels should be validated by a second morning blood sample. The guidelines for treatment have argued for clinical symptoms or signs to accompany the low testosterone before instituting treatment. This is rational but individual components of the clinical syndrome may be manifest at different serum testosterone concentrations. While decreased libido is usually present in hypogonadism, erectile dysfunction is less common and most patients with erectile dysfunction have another causal mechanism.

Treatment options for hypogonadism have expanded and can be individualized. We have limited understanding of the ideal time to begin treatment of hypogonadism in the prepubertal period, and treatment is usually instituted at the normal time of puberty. Contraindications for treating with testosterone include prostate cancer and erythrocytosis. Monitoring patients under treatment for benefit, hormone levels, adverse effects (including complete blood count and PSA) is prudent and expected. Much less data are available for benefit of treatment of older men with low serum levels of testosterone but large-scale efficacy studies are ongoing. The long-term adverse effects of testosterone, particularly on prostate health, remain to be elucidated in studies following patients for longer periods of time.

Declaration of interest

R Swerdloff serves as a grantee and consultant for Clarus Pharmaceuticals and serves on the Advisory Committee for Endo Pharmaceuticals.

Bibliography

1. Peng X, Zeng X, Peng S, et al. The association risk of male subfertility and testicular cancer: a systematic review. PLoS One 2009;4:e5591
2. Raman JD, Nobert CF, Goldstein M. Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis. J Urol 2005;174:1819-22
3. Kronenberg HM, Larsen PR, editor, Williams textbook of endocrinology. 11th edition. Saunders; 7 A.D
4. McCullagh DR. Dual endocrine activity of the testes. Science 1932;76:19-20
5. Zirkin BR, Awoniyi C, Griswold MD, et al. Is FSH required for adult spermatogenesis? J Androl 1994;15:273-6
6. Rogol AD. New facets of androgen replacement therapy during childhood and adolescence. Expert Opin Pharmacother 2005;6:1319-36
7. Mauras N, Hayes V, Welch S, et al. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. J Clin Endocrinol Metab 1998;83:1886-92
8. Bhasin S, Bagatell CJ, Bremner WJ, et al. Issues in testosterone replacement in older men. J Clin Endocrinol Metab 1998;83:3435-48
9. Morley JE, Kaiser FE, Perry HM III, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metabolism 1997;46:410-3
10. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006;91:1995-2010
11. Hughes IA, Houk C, Ahmed SF, Lee PA. Consensus statement on management of intersex disorders. J Pediatr Urol 2006;2:148-62
12. Ambler GR. Androgen therapy for delayed male puberty. Curr Opin Endocrinol Diabetes Obes 2009;16:232-9
13. Bertelloni S, Dati E, Baroncelli GI. Disorders of sex development: hormonal management in adolescence. Gynecol Endocrinol 2008;24:339-46
14. Walvoord E. Sex steroid replacement for induction of puberty in multiple pituitary hormone deficiency. Pediatr Endocrinol Rev 2009;6(Suppl 2):298-305
15. Pozo J, Argente J. Ascertainment and treatment of delayed puberty. Horm Res 2003;60(Suppl 3):35-48
16. Mauras N, Haymond MW, Darmaun D, et al. Calcium and protein kinetics in prepubertal boys. Positive effects of testosterone. J Clin Invest 1994;93:1014-9
17. Skakkebaek NE, Bancroft J, Davidson DW, Warner P. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. Clin Endocrinol (Oxf) 1981;14:49-61
18. Nieschlag E, Buchter D, von ES, et al. Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men. Clin Endocrinol (Oxf) 1999;51:757-63
19. Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. J Urol 2000;164:371-5
20. Steidle C, Schwartz S, Jacoby K, et al. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab 2003;88:2673-81
21. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab 2004;89:2085-98
22. Pope HG Jr, Cohane GH, Kanayama G, et al. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. Am J Psychiatry 2003;160:105-11
23. McNicholas TA, Dean JD, Mulder H, et al. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. BJU Int 2003;91:69-74
24. Wang C, Swerdloff RS, Iranmanesh A, et al. Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. Clin Endocrinol (Oxf) 2001;54:739-50
25. Snyder PJ. Effects of age on testicular function and consequences of testosterone treatment. J Clin Endocrinol Metab 2001;86:2369-72
26. Coward RM, Simhan J, Carson CC III. Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy. BJU Int 2009;103:1179-83
27. Schleich F, Legros JJ. Effects of androgen substitution on lipid profile in the adult and aging hypogonadal male. Eur J Endocrinol 2004;151:415-24
28. Pfeil E, Dobs AS. Current and future testosterone delivery systems for treatment of the hypogonadal male. Expert Opin Drug Deliv 2008;5:471-81
29. Meikle AW, Mazer NA, Moellmer JF, et al. Enhanced transdermal delivery of testosterone across nonscrotal skin produces physiological concentrations of testosterone and its metabolites in hypogonadal men. J Clin Endocrinol Metab 1992;74:623-8
30. ANDROGEL. Solvay Pharmaceuticals, 2009. Available from: http://www.solvaypharmaceuticals.com/Products/group/product/0,,30643-2-0,00.htm. [Last accessed 9 November 2009]
31. Bentley Granted European Patent for Its Testosterone Gel. Business Wire, 2007. Available from: http://www.allbusiness.com/legal/intellectual-property-law/5249773-1.html. [Last accessed 9 November 2009]
32. Androgel (Testosterone Gel for Topical Use) Drug Information. RxList, 2009. Available from: http://www.rxlist.com/androgel-drug.htm. [Last accessed 22 November 2009]
33. Wang C, Berman N, Longstreth JA, et al. Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a General Clinical Research Center

Study. J Clin Endocrinol Metab 2000;85:964-9

34. Han TS, Bouloux PM. What is the optimal therapy for young males with hypogonadotrophic hypogonadism? Clin Endocrinol (Oxf) 2009. [Epub ahead of print]
35. de Ronde W. Hyperandrogenism after transfer of topical testosterone gel: case report and review of published and unpublished studies. Hum Reprod 2009;24:425-8
36. Richman RA, Kirsch LR. Testosterone treatment in adolescent boys with constitutional delay in growth and development. N Engl J Med 1988;319:1563-7
37. Wang C, Swerdloff R, Kipnes M, et al. New testosterone buccal system (Striant) delivers physiological testosterone levels: pharmacokinetics study in hypogonadal men. J Clin Endocrinol Metab 2004;89:3821-9
38. STRIANT – Professional – STRIANT Patient Booklet. STRIANT Patient Booklet, 2010. Available from: http://www.striant.com/Professional/patient_booklet/patient_booklet.asp#FAQs. [Last accessed 6 January 2010]
39. Kelleher S, Conway AJ, Handelsman DJ. A randomised controlled clinical trial of antibiotic impregnation of testosterone pellet implants to reduce extrusion rate. Eur J Endocrinol 2002;146:513-8
40. Kinniburgh D, Zhu H, Cheng L, et al. Oral desogestrel with testosterone pellets induces consistent suppression of spermatogenesis to azoospermia in both Caucasian and Chinese men. Hum Reprod 2002;17:1490-501
41. Cavender RK, Fairall M. Subcutaneous testosterone pellet implant (Testopel) therapy for men with testosterone deficiency syndrome: a single-site retrospective safety analysis. J Sex Med 2009;6:3177-92
42. Acrux Announces Axiron Phase III Results. Wireless News Newspaper, 2010. Available from: http://findarticles.com/p/news-articles/wireless-news/mi_hb5558/is_20091003/acrux-announces-axiron-phase-iii/ai_n39986194. [Last accessed 30 December 2010]
43. News: Acrux' Testosterone Treatment Triumphs in Phase III Study. Genetic Engineering & Biotechnology News, 2010. Available from: http://www.genengnews.com/news/bnitem.aspx?name=64091122. [Last accessed 26 November 2009]
44. Axiron Fact Sheet 2009. www acrux com au, 2010. Available from: http://www.acrux.com.au/IRM/Company/ShowPage.aspx?CPID=1417. [Last accessed 14 January 2010]
45. Available from: http://xpil.medicines.org.uk/ViewPil.aspx?DocID=19703. medicines org uk, 2010. [Last accessed 14 January 2010]
46. Barrio R, de LD, Alonso M, et al. Induction of puberty with human chorionic gonadotropin and follicle-stimulating hormone in adolescent males with hypogonadotropic hypogonadism. Fertil Steril 1999;71:244-8
47. Warne DW, Decosterd G, Okada H, et al. A combined analysis of data to identify predictive factors for spermatogenesis in men with hypogonadotropic hypogonadism treated with recombinant human follicle-stimulating hormone and human chorionic gonadotropin. Fertil Steril 2009;92:594-604
48. Vicari E, Mongioi A, Calogero AE, et al. Therapy with human chorionic gonadotrophin alone induces spermatogenesis in men with isolated hypogonadotrophic hypogonadism–long-term follow-up. Int J Androl 1992;15:320-9
49. Gordon D, Lauder JC, Cohen HN, et al. An evaluation of human chorionic gonadotrophin (HCG) therapy in boys with delayed puberty. Q J Med 1990;74:247-56
50. de Ronde W. Therapeutic uses of aromatase inhibitors in men. Curr Opin Endocrinol Diabetes Obes 2007;14:235-40
51. Pavlovich CP, King P, Goldstein M, Schlegel PN. Evidence of a treatable endocrinopathy in infertile men. J Urol 2001;165:837-41
52. Odame I, Donaldson MD, Wallace AM, et al. Early diagnosis and management of 5 alpha-reductase deficiency. Arch Dis Child 1992;67:720-3
53. Charmandari E, Dattani MT, Perry LA, et al. Kinetics and effect of percutaneous administration of dihydrotestosterone in children. Horm Res 2001;56:177-81
54. Wang C, Iranmanesh A, Berman N, et al. Comparative pharmacokinetics of three doses of percutaneous dihydrotestosterone gel in healthy elderly men–a clinical research center study. J Clin Endocrinol Metab 1998;83:2749-57
55. Rhoden EL, Morgentaler A. Influence of demographic factors and biochemical characteristics on the prostate-specific antigen (PSA) response to testosterone replacement therapy. Int J Impot Res 2006;18:201-5
56. Arrigo T, Cisternino M, Luca DF, et al. Final height outcome in both untreated and testosterone-treated boys with constitutional delay of growth and puberty. J Pediatr Endocrinol Metab 1996;9:511-7
57. Buyukgebiz A. Treatment of constitutional delayed puberty with a combination of testosterone esters. Horm Res 1995;44(Suppl 3):32-4
58. Caruso-Nicoletti M, De Sanctis V, Raiola G, et al. No difference in pubertal growth and final height between treated hypogonadal and non-hypogonadal thalassemic patients. Horm Res 2004;62:17-22
59. Professional - STRIANT Prescribing Information. STRIANT, 2010. Available from: http://www.striant.com/Professional/prescribing_info/prescribing_info.asp. [Last accessed 14 January 2010]
60. Depo®-Testosterone, testosterone cypionate injection, USP. Pfizer, 2010. Available from: http://www.pfizer.com/files/products/uspi_depo_testosterone.pdf. [Last accessed 14 January 2010]
61. Nebido: Summary of Product Characteristics (SPC). emc medicines org uk,2010. Available from: http://emc.medicines.org.uk/medicine/15661/SPC/Nebido+1000mg+4ml,+solution+for+injection#PHARMACOKINETIC_PROPS. [Last accessed 14 January 2010]
62. Testopel: Prescription Drug Information, Side Effects. PDRHealth,

2010. Available from:
http://www.pdrhealth.com/drugs/rx/rx-mono.aspx?contentFileName=tes1595.html&contentName=Testopel&contentId=754.
[Last accessed 14 January 2010]

63. Jockenhovel F, Vogel E, Kreutzer M, et al. Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal men. Clin Endocrinol (Oxf) 1996;45:61-71

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