

THE ROLE OF ANDROGEN THERAPY IN MALE PUBERTAL DEVELOPMENT

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Abstract

Androgen treatment represents a main aspect of clinical management of boys with hypogonadism from adolescence onwards. Androgen replacement therapy is required to induce secondary sexual characteristics and adult male body composition, to optimize the accrual of bone mineral content and muscle mass and to promote physical and social wellbeing.

Testosterone is the only sex steroid hormone suitable for treatment in hypogonadal boys, as it fulfils all the physiological requirements. However, the optimal regimens for androgen replacement therapy during adolescence remain to be defined. The new testosterone formulations (patch, gel, transbuccal, and long-acting) have been designed for use in adults and the available dosages are probably too high to induce and manage puberty in adolescents properly. The aim of this paper is to provide practical indications for androgen treatment in male adolescents with hypogonadism.

Key words

Androgen replacement therapy, delayed puberty, hypogonadism, adolescence, testosterone

Introduction

Puberty is a period of rapid physical, emotional and psychological changes, leading to the development of secondary sexual characteristics, the attainment of reproductive function and the achievement of adult height, definitive body proportions and adult fat mass/muscle mass ratio [1, 2]. In addition, bone mass increases with age, height and weight throughout childhood, with a significant gain during puberty when it approximately doubles [3]. The factors driving the increase of bone mass at adolescence and the dimorphic pattern of body composition are not completely understood, but a crucial role is played by the sex steroid increase [2, 3], which is also associated with the psychosocial/psychosexual maturation [4]. Therefore, normal pubertal development should be pursued in adolescence for optimize physical and psychosocial wellbeing.

Testosterone is the main hormone involved in the pubertal changes occurring in males at puberty [1]. This androgen can act either directly or after conversion into dihydrotestosterone (DHT) and 17β -estradiol (E2) operated by 5 α -reductase and aromatase, respectively [1, 3].

Puberty may be transiently delayed or permanently impaired (hypogonadism) in several conditions (Table 1) [5-7]. Pediatric endocrinologists may be requested to prescribe androgen therapy to an adolescent boy to normalize his psychophysical development as well as to avoid short and long-term consequences of delayed puberty or hypogonadism [5, 6]. Nowadays, boys and their parents are usually more concerned for pubertal maturation than in the past [6]. The alterations of puberty represent a common cause of referral to a Pediatric Endocrinology Unit for the availability of better diagnostic tools and the higher proportion of children surviving after treatments for severe chronic disorders potentially affecting reproductive axis [5, 6].

While in adulthood androgen replacement treatment is well scheduled [8, 9], in adolescence several aspects of therapy still remain not well defined [10].

Indications for androgen replacement therapy in adolescent boys

Androgen replacement therapy should be administered to each boy in whom the diagnosis of hypogonadism has been established [6, 10, 11], taking into account the following practical recommendations:

- hormonal induction of puberty should start at the appropriate age for puberty onset [6, 11, 12] (in males: approximately 11.5 – 12.5 years) [13];
- testosterone is the only sex steroid hormone to be used because it is able to replace all the physiological requirements [7, 9];
- doses should be individualized and tailored according to age and pubertal stage [7, 11, 12];
- clinically, sex steroid treatment should permit the normal “tempo” of puberty [6, 13, 14];
- replacement therapy should provide the sex steroid concentrations consistent with the various stages of male pubertal development [15, 16], maintaining appropriate serum levels of DHT/testosterone ratio ($\sim 1/10$ in adult men) and E2/testosterone ratio ($\sim 1/200$ in adult men) [7].

The goals of sex steroid replacement therapy in adolescent males with hypogonadism are briefly summarized in table 2.

Puberty induction by androgens in hypogonadal adolescent males

In hypogonadal boys, low doses of testosterone should be used to induce pubertal development and increased progressively up to adult doses [6, 10-13]. Available formulations and therapeutic dosages in adolescence and adulthood are summarized in table 3; advantages and disadvantages of the various deliveries are reported in the same table.

No evidence based guidelines are available on the best hormone formulations, routes of administration and doses for puberty induction [6, 10-12]. A survey among US pediatric endocrinologists showed that the majority (88%) began androgen replacement therapy with low doses of testosterone esters, while only a minority used the recent transdermal patch or gel formulations [10]. Similar results have recently been found in Italy (low dose testosterone esters 89%; patch or gel formulations 11%) [17]. However, the testosterone esters (Table 3) are affected by some pharmacokinetics pitfalls: they do not mimic the natural pattern of daily testosterone secretion and result in supraphysiological levels during the first few days following injection with waning over the subsequent 2 to 3 weeks. In addition, the injections are painful and disliked by many adolescents [7, 9-12, 14]. Nonetheless, testosterone esters, such as enanthate 25-50 mg monthly given intramuscularly for 4–12 months, are commonly used to induce male pubertal development [10, 12, 17]. Thereafter, the doses are gradually

increased up to 75–100 mg/week or 150–250 mg/2–4 weeks) (Table 3) [7-9].

The following schedule may be proposed [10-12, 17]:

- first year: 25 mg every 2-4 weeks;
- second year: 50 mg every 2 weeks;
- third year: 100 mg every 2 weeks;
- fourth year onward: 200 mg every 2 weeks or switched to adult dosage.

Oral testosterone undecanoate (Andriol[®]) has been proposed to induce puberty at the starting dose of 40 mg/daily in the morning [18].

Transdermal preparations of testosterone (patch or gel) provide physiological and constant testosterone levels [7-9]. Because these formulations contain fixed doses per patch or gel formulation and are designed to provide full adult male testosterone replacement (Table 3) [7], they are difficult to handle in adolescence [8, 9]. At any rate, some encouraging experiences have been published (Table 3) [19-21]. Recently, a new gel formulation, that provides 10 mg testosterone/puff (0.5 g of gel/puff; bioavailability 12%) (Tostrex[®] or Tostran[®], ProStrakan LTD), has been commercialized. It might permit an individualized approach to androgen replacement therapy in adolescent boys. Trials with other recent formulations, such as trans-buccal testosterone (Striant[®], Columbia Laboratories, Inc.) or long-acting (3-months) injectable testosterone undecanoate (Nebid[®] or Nebido[®], Bayer Schering) (Table 3), have not yet been reported to induce puberty.

A special issue is represented by hypogonadal subjects with partial androgen insensitivity syndrome reared as males; these subjects may benefit from supraphysiological doses of testosterone from the onset of puberty [14] to improve phenotypic virilisation, but available data remain anecdotal [23, 24].

Monitoring of testosterone therapy in hypogonadal adolescents

In adolescence, regular clinical follow-up assessing growth and pubertal progression associated with bone age assessment constitute the key parameters to monitor testosterone treatment [6, 12].

Laboratory parameters that may be helpful to monitor testosterone treatment are [8, 14]:

- serum total testosterone levels (by reliable assay to investigate hormone levels in children and adolescents), taking into account the following issues:

1. therapy should restore serum testosterone levels into the mid-normal range for pubertal stage (subjects with partial androgen insensitivity may require supra-normal testosterone levels);
2. measurement of testosterone should be:
 - testosterone enanthate or cypionate: midway between injections;
 - i.m. long-acting testosterone undecanoate: before the new injection;
 - transdermal testosterone patch: 3-12 hours after application;
 - transdermal testosterone gel application: after 1-2 weeks independently from application;
 - buccal testosterone tablet: immediately before the application of new tablet;
- red blood count and haematocritus (the discontinuation of therapy is required if hematocrit is greater than 54% until it decreases to a safer level);
- lipid profile;
- bone density: at least, lumbar spine and femoral neck should be assessed; BMD data must be given as SDS for age and sex according to normative values for the DXA machine used. DXA methodology offers the opportunity to assess body composition and the appropriate development of fat mass and free fat (muscle) mass could be assessed during follow-up [8].

Since the normalization of gonadotropins is not a goal of treatment in boys with hypergonadotropic hypergonadism, the assessment of LH and FSH has poor clinical value during testosterone replacement therapy.

During pubertal induction, adverse effects of androgen treatment are uncommon [10-12]. Potential side effects of androgen supplementation are represented by fast skeletal maturation in pre-pubertal boys, ultimately leading to impaired adult height, excessive aggressiveness, excessive stimulation of libido, priapism, polycythemia, obstructive sleep apnea mainly in obese subjects [7-12].

Gynecomastia and emotional liability may be associated with the variations in serum testosterone levels related to the use of injectable ester formulations [7, 9, 11]. Skin irritation has been reported with the use of transdermal patch [7, 9], while gel formulations are usually not affected by skin side-effects [7, 9].

Conclusions

Androgen therapy in males with hypogonadism should promote linear growth and development of secondary sexual characteristics, permit the normal accrual

of muscle mass and bone mineral content, and address some of the associated psychosocial problems. Although we have now an array of androgen formulations to be used, most of them have not yet been sufficiently tested in children and adolescents. Long acting testosterone esters still represent the primary form of androgen replacement therapy used in adolescents, but timing and dosage are still empirically established. Further research should aim at providing physiology based guidelines for testosterone replacement therapy and testing efficacy and safety of the new formulations.

Disclosure

The undersigned authors declare that we have no conflict of interest with the products or services mentioned in this article.

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Table 1. Main causes of delayed puberty in males [5, 7].

Hypogonadism	Transitory delayed puberty
<p><i>Hypergonadotropic hypogonadism</i></p> <ul style="list-style-type: none"> • Klinefelter syndrome and related disorders • Congenital absence of testes (anorchia) • LH resistance • Biosynthetic defects of testosterone • Androgen insensitivity • Iatrogenic 	<p><i>Primary</i></p> <p>Constitutional delay of puberty</p>
<p><i>Hypogonadotropic hypogonadism</i></p> <ul style="list-style-type: none"> • Gonadotropin deficiency (congenital* or acquired^o; isolated or associated with anosmia or multiple pituitary deficiencies) • Isolated LH deficiency • Genetic syndromes (e.g.. Noonan syndrome, Prader-Willi syndrome) • Chronic diseases 	<p><i>Secondary to:</i></p> <ul style="list-style-type: none"> • Chronic disorders • Nutritional imbalance (including anorexia nervosa and related disorders) • Chronic endocrine diseases

*many genes may be causative; ^oneoplasia, traumatic injury, irradiation, etc

Table 2. Goals of androgen replacement treatment in adolescent males with hypogonadism [6-8, 10-12, 14].

- To induce sex-specific secondary sexual characteristics, and then maintain them in adulthood.
 - To optimize pubertal growth spurt and body proportions.
 - To reach male adequate free fat (muscle) mass and fat mass development as well as optimal bone mineral mass accrual.
 - To determine adequate penile and internal genitalia growth.
 - To reduce cardio-vascular risk (including the optimization of lipid profile and the reduction of metabolic syndrome risk).
 - To induce sex-specific psychosocial and psychosexual maturation.
 - To assure normal social/sexual life and well-being (in adolescence and adulthood) as well as fertility (in adulthood, when possible).
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Table 3. Main testosterone formulations for replacement therapy in males [7-9].

<i>Testosterone formulation</i>	<i>Drug</i>	<i>Starting dose</i>	<i>Optimal adult dose</i>	<i>Formulation specific advantages</i>	<i>Formulation specific disadvantages</i>
Injectable (i.m.)	Testosterone enanthate	25-50 mg/2-4 weeks	200-250 mg/2-3 weeks	Large clinical experience in adolescence	Peaks and troughs in circulating testosterone, gynecomastia, local pain, mood disturbances
	Testosterone cypionate	Similar to testosterone enanthate	200 mg/2 weeks		
	Testosterone undecanoate	—	1000 mg/12 weeks (range 10-14 weeks)	Stable serum testosterone levels	Local pain; lack of experience in adolescence
Oral	Testosterone undecanoate [§]	40 mg/day x 6-12 m. [16]	40-80 mg x 2-3 times/day	Oral administration	Variable clinical effects, fluctuating hormone levels
Trans-dermal	Scrotal patch	—	4-6 mg/day	Mimics circadian variations	Skin irritation, shaving of the scrotum, abnormal high DHT levels
	Non scrotal patch*	14-16 years: 2.5 mg/12 night hours [19] 17-19 years: 2.5 mg/day [19] > 20 years: 5.0 mg/day [19] 12.5-15.0 years: 5 mg/8-12 hours [20]	2.5-5.0 mg/day	Mimics circadian variations	Skin irritation; little experience in adolescence
	Gel 1%	0.5 g/day, increasing dose based on testosterone levels [21]	5-10 mg/day	Mimics circadian variations, good clinical response, no visible patch, gel dries quickly	Potential transfer to other people; little experience in adolescence
	Gel 2% (puff 0.5 mg)	—	2-4 mg/day	As 1% gel; possibility to individualized doses	Potential transfer to other people; no experience in adolescence
Trans-buccal	Biopellet 30 mg	—	1-2 cps/day	Absorption directly into systemic circulation, stable serum levels, no visible patch	Taste alteration, gum irritation, no experience in adolescence

[§]to be assumed with meals; *recently has been developed and commercialized a patch (Intrisa®; available for women) delivering 300 µg/daily of testosterone, assuring serum testosterone levels similar to those of Tanner stage II [15, 16].

