REVIEW ARTICLE

Testosterone therapy in children and adolescents: to whom, how, when?

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Male production of testosterone is crucial for the development of a wide range of functions. External and internal genitalia formation, secondary sexual characteristics, spermatogenesis, growth velocity, bone mass density, psychosocial maturation, and metabolic and cardiovascular profiles are closely dependent on testosterone exposure. Disorders in androgen production can present during all life-stages, including childhood and adolescence, and testosterone therapy (TT) is in many cases the only treatment that can correct the underlying deficit. TT is controversial in the pediatric population as hypoandrogenism is difficult to classify and diagnose in these age groups, and standardized protocols of treatment and monitorization are still lacking. In pediatric patients, hypogonadism can be central, primary, or a combination of both. Testosterone preparations are typically designed for adults' TT, and providers need to be aware of the advantages and disadvantages of these formulations, especially cognizant of supratherapeutic dosing. Monitoring of testosterone levels in boys on TT should be tailored to the individual patient and based on the anticipated duration of therapy. Although clinical consensus is lacking, an approximation of the current challenges and common practices in pediatric hypoandrogenism could help elucidate the broad spectrum of pathologies that lie behind this single hormone deficiency with wide-ranging implications.

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INTRODUCTION

Testosterone, the male sex hormone, can be a challenge to detect deficits within and mange replacement in children and adolescents. Testosterone is produced primarily by the Leydig cells of the testes in response to gonadotropic stimulation from the pituitary gland, with some production from the zona reticularis within the adrenal glands [1]. Testosterone acts on a litany of processes including bone maturation [2], growth [3], development of secondary sexual characteristics [4], metabolism [5, 6], hematology [7], and psychosocial status [8]. Furthermore, hypoandrogenism throughout life is linked to increased metabolic cardiovascular complications, highlighting the need for proper diagnosis and treatment [9, 10].

Prior to the adulthood, testosterone levels are relatively quiescent; however, there are three important developmental points in a child's life when the absence of physiologic testosterone levels can have a lasting impact [4, 11]. During fetal development, testosterone production leads to normal male external genital development [12, 13]. Shortly after birth, between 3 and 6 months of life, a "mini-puberty" of infancy occurs, in which gonadotropins and testosterone levels rise temporarily, leading to penile growth and, although not well understood, neurocognitive and psychosocial development [14]. After these transient elevations, testosterone remains low throughout childhood until rising during pubertal development [15]. Unfortunately, clinical signs of hypogonadism can be subtle or absent prior to pubertal development, creating a challenge for clinicians for early diagnosis and treatment, and most often it is not until delayed or incomplete pubertal development that a defect in androgen production is uncovered.

Aside from the challenges of diagnosing hypogonadism in children and adolescents, controversy exists on when and how to initiate testosterone therapy (TT) in pediatric patients. The goal of TT is to replicate normal physiology as closely as possible, including the unique functions of testosterone in child and adolescent development. In this review, we will highlight testosterone functions in children/adolescents, classify the different types of pediatric hypogonadism and specific disorders within, discuss strategies for diagnosis, treatment, and adverse effects of TT in this population.

TESTOSTERONE FUNCTION IN CHILDREN/ADOLESCENTS

Sexual development

Androgens are the key molecules of male phenotypic differentiation. Testicles begin secreting testosterone by 8 weeks of gestation [16]. From this time, antimüllerian hormone (AMH) and testosterone drive the differentiation of male internal and external genitalia, respectively [17]. During the second and third trimesters, androgens increase scrotal and penile size, and along with insulin-like peptide 3 (INSL3) are responsible for testicular descent [18].

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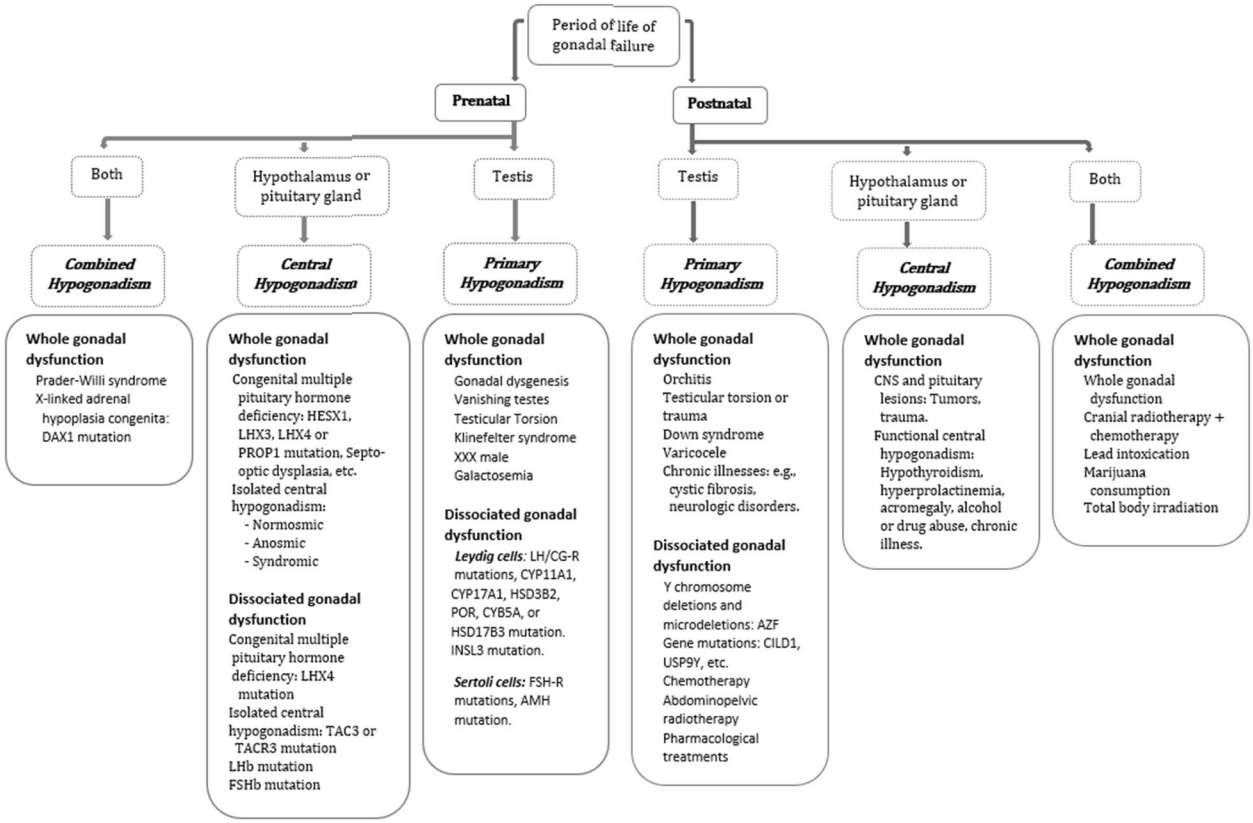

Fig. 1 Classification of male hypogonadism in the pediatric population. Hypogonadism can be acquired prenatally or postnatally. The defect can occur either in the testes (called primary hypogonadism), in the hypothalamus or pituitary gland (called central hypogonadism), or in both. Whole gonadal dysfunction takes place when the entire testes loss the capacity of producing testosterone, dissociated gonadal dysfunction occurs when only a group of cells of the testes stop synthesizing androgens. Some of the most common causes of hypoandrogenism, classified by onset of deficiency, anatomic localization of defect, and extent of testicular compromise, are outlined above.

In the first 3–6 months of life, a "mini-puberty" occurs, during which there is a rise in gonadotropins and testosterone levels, leading to an increase in testicular and penile size, although spermatogenesis does not begin due to insufficient androgen receptor activation [19, 20]. In late infancy and childhood, the hypothalamic-pituitary-testicular (HPT) axis undergoes a quiescent period, in which testosterone levels are almost undetectable, followed by a reactivation of the HPT axis in puberty resulting in the induction of secondary male sexual characteristics, stimulation of sexual function, and initiation of spermatogenesis [21].

Growth–bone mineral density

The anabolic impact of sex steroids on growth is evidenced by the rapid and profound changes of puberty [22]. Testosterone is crucial for bone health and adolescents' ability to achieve peak bone mass, as almost 35% of whole-body bone mineral content is gained during the four years surrounding peak height velocity [23]. The apex bone mass achieved is thought to impact osteoporosis risk later in life, and research indicates that delayed puberty may result in lower bone mineral density (BMD) in adulthood [24].

Patients with constitutional delay of growth and puberty (CGDP) present with short stature and delayed bone maturation [25, 26]. Although TT has been thought to accelerate epiphyseal closure, studies on testosterone's effects in this population have revealed that TT does not adversely impact final height [27]. Additionally, Uriate and colleagues investigated the impact of TT timing on final height in patients with Isolated Central Hypogonadism, finding that late initiation of androgen supplementation was associated with a higher mean stature, probably due to delayed epiphyseal fusion and a prolonged growth period [28].

The full advantages of TT on adolescent bone health are unclear. TT may increase BMD in hypogonadal adolescent males, but it is unknown if it can fully restore BMD to normal levels [29, 30]. A challenge in initiating TT is the difficulty in defining osteoporosis for children and young adults, and in recognizing biologically relevant osteoporosis when fracture rates are not increased [31].

Psychosocial and neurocognitive

Androgens exert organization and activation effects in brain development [32]. Organization effects occur during the prenatal and perinatal period, and refer to the influence of testosterone over the formation of the sexually dimorphic nuclei of the hypothalamus [33], the hippocampal pyramidal cells [34], and other cerebral structures [32]. The activation effects refer to the impact of testosterone on gendered behavior (children's gender-typical play preferences, sexual orientation, and gender identity) [35], which occurs mainly during mini-puberty as this period is characterized by a considerably high cerebral plasticity [36, 37]. Furthermore, the high levels of testosterone seen in mini-puberty have also been associated with verbal development [38].

Also, it has been demonstrated that in males, androgens maintain synaptic transmission and connectivity [39]. This CNS role may incur psychosocial consequences when deficient. For instance, long-term depression of neurons in testosterone's absence may be involved in cognitive defects and mental retardation phenotypes [40]. Late puberty has been associated with chronic psychosocial effects in men [41], including

Table 1. Primary hypogonadism: common clinical, hormonal and semen analysis findings. Adapted from Rey et al. [55] and Grinspon et al. [16].

	Physical exam	Hormonal Profile										Semen analysis
		Childhood					*Puberty and Adulthood*					
		Pituitary gland		Leydig cells	Sertoli cells		Pituitary gland		Leydig cells	Sertoli cells		
		LH	FSH	T	AMH	Inh B	LH	FSH	T	AMH	Inh B	
Whole gonadal dysfunction												
Fetal-onset												
Gonadal dysgenesis	Ambiguous genitalia	N -↑	N -↑	↓ - ND	↓ - ND	↓ - ND	↑	↑	↓ - ND	↓ - ND	↓ - ND	Azoospermia
Vanishing testes, Testicular torsion	Micropenis, empty scrotum	N -↑	N -↑	↓ - ND	↓ - ND	↓ - ND	↑	↑	↓ - ND	↓ - ND	↓ - ND	Azoospermia
Klinefelter syndrome, XX male	Micropenis, cryptorchidism, small*	N	N	N	N	N	↑	↑	N -↓	↓ - ND	↓ - ND	Azoospermia
Postnatal-onset												
Orchitis		N	N	↓ - ND	↓ - ND	↓ - ND	↑	↑	↓ - ND	↓ - ND	↓ - ND	Oligo/azoospermia
Varicocele		N	N	N	N	N	N -↑	N	N -↓	N	N	Theratozoo/ asthenozoospermia
Down syndrome		N -↑	N -↑	N -↓	N -↓	N -↓	↑	↑	↓	↓	↓	Azoospermia
Chronic illness							↑	↑	↓ - ND	↓ - ND	↓ - ND	Oligo/azoospermia
Dissociated gonadal dysfunction												
Fetal-onset												
Leydig cell dysfunction	Ambiguos genitalia	N -↑	N	↓ - ND	N -↑	N	↑	↑	↓ - ND	N -↑	↓ - ND	Azoospermia
INSL3 mutations	Criptorchidism	N	N	N	N	N	N	N -↑	N	↓	N -↓	Oligospermia
Sertoli cell dysfunction												
FSHR-mutation	Small testes	N	N	N	↓	↓	N	↑	N	↓	↓	Oligospermia
AMH mutation	PMDS	N	N	N	ND	N	N	N	N	ND	N	Normal
Postnatal-onset												
Y chromosome deletions		N	N	N	N	N	N	↑	N		↓	Oligo/azoospermia
Chemo and radiotherapy		N	N	N -↓		N -↓	N -↑	↑	N -↓		↓	Oligo/azoospermia
Pharmacological treatment		N	N	N -↓			N -↑	N -↑	↓		↓	Oligospermia

*Not always present, ↑= high, ↓ = low, N = normal, ND = undetectable, Inh B = inhibin B.

Table 2. Central Hypogonadism: common clinical, hormonal and semen analysis findings. Adapted from Rey et al. [55] and Grinspon et al. [16].

	Physical exam	Hormonal Profile										Semen analysis
		Childhood				*Puberty and Adulthood*						
		Pituitary gland		Leydig cells	Sertoli cells		Pituitary gland		Leydig cells	Sertoli cells		
		LH	FSH	T	AMH	Inh B	LH	FSH	T	AMH	Inh B	
Whole gonadal dysfunction												
Fetal-onset												
Multiple pituitary hormone deficiency	Micropenis, cryptorchidism	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	Oligo/azoospermia
		↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	Oligo/azoospermia
Isolated central hypogonadism: normosomic, anosmic and syndromic	Micropenis, cryptorchidism											
Postnatal-onset												
CNS and pituitary lesions		↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	Oligo/azoospermia
Functional central hypogonadism							N -↓	N -↓	↓		↓	Oligo/azoospermia
Dissociated gonadal dysfunction												
Fetal-onset												
Multiple pituitary hormone deficiency	Small testes	N	↓	N	↓	↓	N	↓	N		↓	
Isolated central hypogonadism	Micropenis, cryptorchidism	↓	N	↓	N	N	↓	N	↓		↓	Oligo/azoospermia
LHB mutation	Micropenis, cryptorchidism	↓	N	↓	N	N	↓	↑	↓	↑		Oligo/azoospermia
FSHB mutation	Small testes	N	↓	N		↑	↓	N				Oligo/azoospermia

↑= high, ↓ = low, N = normal, ND = undetectable, Inh B = inhibin B.

depression and substance abuse [42, 43]. After beginning TT, boys with delayed puberty have been shown to experience boosts in self-confidence and peer interaction [44].

CLASSIFICATION OF PEDIATRIC HYPOGONADISM

The normal physiology of testosterone levels during childhood and adolescence makes it challenging to establish a definition of hypogonadism in the pediatric population. For instance, the HPT axis only becomes active during the second trimester of pregnancy [45], then undergoing a functional decrease until term [46], followed by "mini-puberty" during infancy [47]. Subsequently, a quiescent period occurs in childhood, then finally undergoing an exponential surge during puberty [15].

The physiologic low levels of testosterone throughout the majority of childhood have made classifying pediatric hypogonadism challenging and contrasts the typical clinical picture and diagnosis made in adults. For example, it has been shown that patients with anorchidism can have normal to decreased levels of FSH and LH during childhood [48], and not the hypergonadotropic state due to the lack of negative feedback of testosterone on the HPT axis that would be expected in adults. As a consequence, terms such as hyper and hypogonadotropic hypogonadism, may not be related to primary and secondary testicular defects, respectively [16]. For this reason, in children and adolescents, it is more appropriate to describe the principle affected site in the HPT axis as primary if it is in the testes, central if it is in the hypothalamus or pituitary gland, or combined if it affects both components of the axis. Classification of testosterone deficiency in children/adolescence with examples of specific diseases within different types of hypogonadism are outlined in Fig. 1.

Moreover, in the pediatric population, the age of onset of testicular failure is fundamental to understand the spectrum of clinical manifestations and underlying causes. Testosterone deficiency at different developmental milestones can have different repercussions. For instance, testosterone deficiency during fetal development will result in ambiguous or female genitalia [49]. On the other hand, in the prepubertal and pubertal periods an absence of testosterone will result in delayed puberty [50]. The underlying causes can vary widely, and androgen deficiency be temporal as in CDPG or permanent as in Kallman syndrome [51, 52].

An ineludible aspect in the physiopathology of androgen deficiency in children and adolescents is the fact that the tubular and interstitial compartments can be affected individually or simultaneously depending on the underlying etiology [53, 54]. For instance, there are genetic mutations in which only the Leydig cells will be compromised (i.e., CYP11A1 and POR mutations) [55, 56]. This dissociated gonadal dysfunction would lead to insufficient androgen production due to an isolate defect in the interstitial testicular compartment [57]. On the other hand, there are pathologies, such as vanishing testes and testicular torsion, in which a whole gonadal dysfunction will be presented impairing not only testosterone production but also future spermatogenesis [58, 59].

DIAGNOSIS

Diagnosis of androgen deficiency in adults is straightforward, requiring clinical symptoms and two AM levels of testosterone below the established range [60, 61]; however, this criteria cannot be applied to the pediatric population due to physiologically low levels of testosterone and gonadotropins in the majority of infancy and childhood [14]. That is why other diagnostic tests and criteria should be implemented to assure a prompt detection of hypogonadism leading to timely initiation of TT.

Table 3. Combine hypogonadism: common clinical, hormonal and semen analysis findings. Adapted from Rey et al. [55] and Grinspon et al. [16].

	Physical exam	Hormonal Profile										Semen analysis
		Childhood				*Puberty and Adulthood*						
		Pituitary gland		Leydig cells	Sertoli cells	Pituitary gland		Leydig cells	Sertoli cells			
		LH	FSH	T	AMH	Inh B	LH	FSH	T	AMH	Inh B	
Whole gonadal dysfunction												
Fetal-onset												
Prader-Willi syndrome X-linked adrenal hypoplasia congenita	Micropenis, cryptorchidism	N -↓	N -↓	N -↓	↓	↓	N	N	↓	↓	↓	Oligo/ azoospermia
Postnatal-onset												
Cranial radio + chemotherapy		N -↓	N -↓	N -↓	↓	↓	N -↓	N -↓	↓	↓	↓	Oligo/ azoospermia
Marijuana consumption												
Lead intoxication												

↑= high, ↓ = low, N = normal, ND = undetectable, Inh B = inhibin B.

Clinical manifestations

There are several clinical manifestations that may suggest androgen insufficiency in children [62, 63]. For example, cryptorchidism and microphallus have been found to be 38% and 25% more prevalent in patients who did not undergo "mini-puberty" during infancy compared to the normal population [64]. In addition, other findings in childhood, such as anosmia or hyposmia, could guide the diagnosis to a more specific cause of hypogonadism such as Kallmann syndrome [65].

Testicular size, Tanner stage, and growth velocity are three other important clinical signs. Testicular size is closely related with Sertoli cell and germ cell volume and can correlate with the severity of GnRH deficiency [48], which could be a predictor of sperm production in adulthood [66]. Tanner stage is a useful scale to access the grade of virilization [67] and allows tracking of puberty nomograms [68]. By the age of 14 years, boys should be at least Tanner stage 2 [69]. Growth velocity is crucial in the diagnosis of testosterone deficiency, not only because androgens are necessary for the increase in height, but also because the rates of growth have shown to help differentiate between the possible causes of hypogonadism. Indeed, annual growth velocity in boys with Congenital Central Hypogonadism (CCH) or CDPG have shown to be significantly higher than in Functional Central Hypogonadism (FCH) [63].

Hormone profile

Patient age can guide which hormones should be evaluated to diagnose testosterone deficiency in children. During "mini-puberty" of infancy, pulsatile secretion of GnRH causes a rise in FSH and LH levels, which subsequently produces testosterone [70]. The transient activation of the HPT axis provides a window of opportunity for diagnosing hypogonadism [64].

In late infancy and childhood, testosterone levels fluctuate, and gonadotropins may be normal or even low in patients with primary hypogonadism [48]. Androgen levels are thus not always reliable for the diagnosis of testosterone deficiency, and other hormones may aid in establishing a diagnosis. For instance, during infancy and childhood, Sertoli cells are more active than Leydig cells, therefore inhibin B and AMH can be highly diagnostic of hypogonadism if low [71, 72]. Tables 1–3 demonstrate various hormone profiles in hypogonadism by age and underlying diagnosis.

In order to differentiate CDGP and complete forms of CCH, a HCG stimulation or GnRH secretion tests can be performed in an attempt to trigger testosterone production [73]. Unfortunately, these tests lack sensitivity/specificity [51] and have not been approved in patients younger than 10 years old [16]. Promising tests, that still need further studies to identify their potential utility, are INSL3 and kisspeptin levels. INSL3 is produced by Leydig cells and could be an excellent biomarker of their functionality [46], while kisspeptin is a potent stimulator of GnRH-induced LH secretion and its exogenous administration could lead to the diagnosis of CCH [74].

Genetic testing

Genetic testing is an important diagnostic and prognostic tool in testosterone insufficiency among the pediatric population, given that the most common causes of primary and central hypogonadism are Klinefelter and Kallmann syndromes, respectively [51]. In addition, multiple pathologies that have been associated with a long-term androgen deficiency, such as CHARGE, Dandy-Walker and Waardenburg syndromes, are also diagnosed through genetic testing [75]. Clinicians should maintain a high index of suspicion for a genetic cause of hypogonadism when other syndromic features may be present and consider testing appropriately.

TESTOSTERONE REPLACEMENT INDICATIONS

In the pediatric population, there are multiple etiologies that will require temporary or permanent TT and an individual-based

Table 4. Testosterone therapy in children and adolescents with CDGP and hypogonadism. Adapted from Raivio et al. [50], Stancampiano et al. [25], Young et al. [78], Palmert & Dunkel [69], and Mason et al. [15].

Type of testosterone	CDGP	Hypogonadism	Advantages	Disadvantages and Side Effects
Intramuscular				
Intermediate-acting T enanthate T cypionate	*Initial dose:* 50 mg monthly, for 3–6 months. ↑ 25–50 mg (not exceed 100 mg monthly).	*Initial dose:* 25–50 mg monthly. ↑ 50 mg every 6–12 months (up to 250 mg per 3–4 weeks).	Promote androgenic signs of puberty and bone maturation. Standard care: long data and clinical experience. Low cost. Good adherence.	Local side effects. Large swings in T concentrations, not physiological.
Transdermal				
Gel	Gel 2%: 10 mg daily, for 3 months.	Gel 1%: *initial dose*: 0.5 g/daily. ↑ based on T level: 1.0, 1.5, 2.5, 3.0 or to 5 g/daily as needed. Gel 2%: *initial dose:* 10 mg/daily.	Mimics normal T physiology. Noninvasive and self-administrated.	Local irritation. Risk of transmission by skin contact. Daily administration might decrease adherence.
Patch	Prepubertal: 12.5–15 years: 5 mg over 8–12 h, overnight, for 8 weeks.	Prepubertal: 14–16 years: 2.5 mg over 12 h, overnight Partially virilized: 17–19 years: 2.5 mg/daily	Mimics normal T physiology. Noninvasive and self-administrated.	Skin irritation. Daily administration might decrease adherence.
Oral				
T undecanoate	*Initial dose:* 40 mg/daily. Maximum dose: 80 mg twice daily, 20 mg/daily for 6 months; 40 mg/daily for a mean of 3.5 months; 40 mg/daily for 4 weeks; 40 mg/daily for 3 months.	Not data available in the children and adolescent's population.	Pain free	Fluctuating T levels. Multiple doses per day, might decrease adherence.
Subcutaneous				
Subdermal T pellets	Not data available in children and adolescent's population.	13.9–17.5 years: 8–10 mg/kg every 6 months, for 18 months	Good adherence. Maintain adequate T levels for long period of time.	High cost. Need constant implantations. Risk of fibrosis, infection, and extrusion in wound.

approach is preferred. Therapeutic goals of replacement therapy should be defined by the age of onset of the androgen deficiency and the presenting clinical manifestations.

During the first years of life, one indication for androgen replacement is micropenis or hypospadias, both of which can be due to decreased fetal androgens [76]. The goal of therapy is to promote penile lengthening and glans growth through short cycles of low doses of testosterone [77, 78]. Although there is no consensus on the dosage and preferred method of administration, topical testosterone application has shown an increase in penile size in patients with micropenis and hypospadias [79], and an improvement in surgical cosmesis in hypospadias repair [80]. Moreover, intramuscular testosterone presentations have also shown positive results in penile size, even increasing the length of the phallus to the adult's normal population mean [81, 82].

In prepubertal and pubertal patients, the principal indication for testosterone replacement is delayed puberty, and depending on its underlying cause, the duration of the exogenous androgen administration will be determined. For example, in CDGP, which represents 73% of the cases of delayed puberty [52, 63], the preferred management is reassurance and watchful waiting of spontaneous initiation of puberty. Nonetheless, if the patient is presenting psychosocial effects due to his appearance, testosterone should be started [50, 83]. Usually, short courses of low doses are given for 3–6 months and can be repeated depending on the patient's clinical response [44].

Permanent hypogonadism, such as in cases of testicular failure and CCH [52, 63], requires TT not only for induction but also for maintenance of puberty [15]. Induction is achieved using the same scheme as in CDGP; however, for maintenance the dose is gradually increased over 2–3 years until the adult dose is reached in an attempt of mimicking normal puberty physiology [15]. Regardless of the etiology for delayed puberty, the age of initiation of TT is debated. Some authors prefer to start TT no earlier than a bone age of 10–12 years, because TT could induce epiphyseal closure and affect adult height [15, 50, 84]. Of note, in some cases after TT, an increase in testicular size will be observed and this would indicate a spontaneous reversal of the hypogonadism [85]. If this happens, TT should be discontinued and the HGT axis should be reevaluated [85]. However, this recovery of testicular function is not always longstanding [86], so continuous monitoring is recommended. Importantly, TT does not induce gonadal maturation or fertility, and that is why gonadotropins and GnRH replacement should be considered [87, 88]. For example, pulsatile GnRH administration or subcutaneous gonadotropins injections can be used in an attempt to initiate spermatogenesis after puberty [89, 90]. HCG monotherapy is usually the preferred treatment in patients with adequate testicular volume (>4 ml) [91], and its combination with FSH is used to hasten spermatogenesis in cases of low testicular volume [87]. Clomiphene is an estrogen receptor modulator that has also been proposed as an alternative treatment to TT that preservers fertility [92, 93]. Although all the above-mentioned alternatives to TT have shown an increase in testosterone levels and a conservation of spermatogenesis [94], there is controversial data of their impact in hypogonadal symptoms [95, 96], and that is why TT remains the gold standard therapy.

TESTOSTERONE PREPARATIONS: MEDICATION, DOSE, AND FREQUENCY

There are many different formulations of TT that can be used in children and adolescents. Table 4 highlights the commonly used preparations in the age-groups with dosage, and their advantages and disadvantages. Testosterone ester injections with short/intermediate half-life, such as testosterone enanthate (TE) and testosterone cypionate (TC), are well studied in delayed puberty [97]. A randomized controlled trial in patients with CDGP showed

increases in height velocity and no adverse bone-age advancement in 8 boys receiving 200 mg IM TE every 3 weeks for a total of 12 weeks when compared to 8 boys in the control arm [44]. Similar results were shown in 148 boys with CDGP who received 100 mg IM TE monthly for 6 months. Moreover, after 1 year of testosterone therapy greater testicular size and T concentrations were observed [97]. Current recommendations for pubertal induction suggest initial doses of 25–50 mg monthly for 3–6 months with the potential to increase up to 100 mg based on response [69, 98]. Setbacks of short/intermediate half-life testosterone injections are their dynamic pharmacokinetic profile with supraphysiologic levels achieved after the injection, followed by a slow descent back to baseline [99, 100].

Long-acting injectable testosterone undecanoate (TU) has a much slower ascent and descent of serum testosterone [101]. Unfortunately, TU in pediatrics is limited as correct dosing and wash-out periods for preventing complications have not been determined in this population [102]. TU is also produced in an oral form that, because of its large size, is absorbed directly into the lymphatic system [103]. This is physiologically advantageous because it reduces the risk of causing hepatic dysfunction. Two randomized placebo-controlled clinical trials found that boys with CGDP, either taking TU 20 mg daily for 6 months or 40 mg daily for 3 months, experienced increased height velocity and testosterone levels [104, 105]. A cross-over trial using oral TU and an injectable testosterone ester mixture demonstrated comparable efficacious results between the two as well [106]. Overall, these studies demonstrate oral TU's effectiveness in helping stimulate pubertal maturation and growth in adolescents with CDGP. However, there is limited evidence of its use in general pediatric hypogonadism.

Transdermal testosterone gels have limited evidence in their use for pediatric hypogonadism. Advantages of using transdermal testosterone include ease of administration and the ability to mimic physiological testosterone levels. A prospective open-label observational study demonstrated the ability of 0.5 g of 1% testosterone gel to raise testosterone levels in boys with Klinefelter syndrome and anorchia [107]. Although there were no significant safety concerns, no clinically considerable changes were observed on physical examination. The study also highlighted a potential issue with testosterone gels as there were variable responses between subjects. A retrospective study analyzing the response of males with CDGP to 10 mg of a 2% gel for 3 months showed similar effects to 50 mg monthly of TE in terms of height velocity [108].

Similar to gels, transdermal patches deliver testosterone through the skin to help raise testosterone to physiologic levels. Like other formulations, they are produced to treat adult hypogonadism and therefore appropriate pediatric and adolescent dosing could be an issue. As such, clinicians have split the dosing period in half, only applying the patch for 12 h a day rather than 24 h. Mayo et al. showed that overnight application of a 5 mg patch in 9 adolescent boys with growth or pubertal delay demonstrated appropriate increases in testosterone levels and short-term growth [109]. There is little evidence of the effectiveness of transdermal testosterone in pediatric hypogonadism; however, the few available studies display a short-term benefit in raising testosterone levels and stimulating growth and puberty.

Subcutaneous testosterone implants (pellets) in adolescents can offer a range of advantages and disadvantages. Advantages include stable testosterone levels over long periods of time, flexible dosing scheme and greater patient compliance likely due to convenience [110, 111]. Unfortunately, pellet insertion is performed in the office and cannot be easily discontinued if treatment is no longer needed. There is still insufficient data to establish clear guidelines for use in the pediatric population. Two small uncontrolled reports on pellet use showed completion and maintenance of puberty in hypogonadal adolescents and Klinefelter syndrome [112, 113]. Although testosterone levels varied widely, subjects reported an overall improvement in mood, self-esteem, and emotional well-being. While pellet extrusion is a risk for testosterone implants, none of the patients in the above studies experienced this adverse event.

Several other forms of TT have been introduced in the past decade, none of which has been studied in the pediatric population. These include formulations, such as subcutaneous auto-injection of TE, a nasal gel and a new oral TU formulation. These formulations can be promising in pediatric hypogonadism. The TE auto-injector offers flexible dosing, relative ease of administration and less variability testosterone levels compared to other IM injections [114]. Nasal gels are easy to use and may offer benefits in maintaining spermatogenesis due to their dosing schedule mimicking physiologic testosterone secretion [115]. However, more data must be gathered before their use becomes mainstream.

ADVERSE EFFECTS

TT has potential adverse effects that are primarily associated with the dosage and mode of administration, and the underlying cause of hypogonadism. Common adverse effects across all forms of therapy include gynecomastia, erythrocytosis, risk of cardiovascular (CV) events and infertility. Adverse events commonly occur when testosterone levels are supratherapeutic over significant periods. Gynecomastia arises due to TT aromatization to estrogen and is the most common TT side effect in patients with beta-thalassemia [116], and in patients with partial androgen insensitivity syndrome (PAIS) [117]. Interestingly, in KS, gynecomastia improves with TT initiation, and breast enlargement is related to androgen supplementation cessation [118]. Erythrocytosis, which is driven by the dosage and the pharmacokinetic profile of the medication, can also develop especially at supraphysiological serum levels [119, 120]. A hematocrit over 54% is a valid reason to hold treatment until levels normalize, which can be aided by phlebotomy [119]. Erythrocytosis incidence in adolescent boys is poorly reported, likely owing to infrequent monitoring [121]. CV risk from TT is debated given that hypogonadism is also a significant risk factor for CV. Importantly, when dosed properly TT is associated with decreases in atherosclerosis and metabolic syndrome [122], and therefore diminishing the CV risk. Nonetheless, in 2015 the FDA released a statement in which testosterone should be labeled as a medication that could increase the risk of strokes and heart attacks [123]; however, this statement regards use in aging-males, therefore, further studies are needed to define CV risk in pediatric patients.

Finally, TT downregulates the HPT axis, diminishing the release of gonadotropins that normally act on the Leydig and Sertoli cells to produce testosterone and sperm respectively, leading to infertility [124]. Moreover, lowered LH levels result in decreased intratesticular testosterone and resultant impaired spermatogenesis [125]. Although the suspension of TT in adulthood has shown a recovery in spermatogenesis in some cases [126], it has not been determined if children and adolescents on long-term TT will exhibit the same phenomenon. Furthermore, in the pediatric population with androgen deficiency, TT is not the only factor that contributes to infertility; many of the etiologies that accompanied hypogonadism also present with testicular hypofunction and FSH deficiency which contribute to the long-term decline in spermatogenesis [127, 128].

Therefore, contraindications to bear in mind when considering the pros and cons of TT in adolescents include the specific etiology being treated, the aforementioned side effects, and the desire for future fertility.

MONITORING

The three main purposes of TT monitoring are to evaluate the benefits of therapy, detect side effects and evaluate for

contraindications of continuing treatment. Although guidelines for following adults on TT are highly standardized [119], there is scant guidance for adolescents and children [25, 98], and systematic monitoring is not routinely practiced [121, 129]. For instance, Nahata et al. (2015) reported that in hypogonadal boys undergoing TT, 12% and 17% did not have testosterone levels checked before and during hormone replacement, respectively. Furthermore, 63% did not have a BMD test during treatment and 31% did not have a hematocrit checked after initiation of TT.

Monitoring during TT in pediatrics should be individualized based on whether the patient requires permanent or temporary treatment. Stancampiano et al. recommend baseline serum levels of testosterone, liver function and total blood counts prior to initiation of TT in order to detect contraindications of therapy including polycythemia or transaminitis [25]. The authors further recommend evaluating Tanner stage and penile length every 3–6 months for patients requiring temporary, less than 6 months, TT. For patients requiring permanent or prolonged TT, in addition to the short-term monitoring scheme, providers should study the possible underlying cause of hypogonadism and include a metabolic profile and BMD assessment. Follow-ups should be every 3 months for one year, 6 months for the following year, and then annually if testosterone levels have stabilized with treatment or at the proper levels for pubertal age [98]. It is imperative that patients on TT are continuously monitored to ensure the goals of treatment are met without putting patients at risk of adverse effects.

FUTURE DIRECTIONS

There is a lack of literature and guidance for the initiation of testosterone therapy in adolescents and children. As mentioned earlier, little data exists on testosterone levels before and after therapy in the pediatric population. Future studies should focus on establishing standards for testing and monitoring of these patients.

CONCLUSION

The diagnosis and management of hypoandrogenism in children is challenging. While testosterone plays a large role in male development, fetal and perinatal findings can be subtle or absent, leading to diagnosis when puberty is delayed or incomplete. TT is fundamental and definitive in the management of hypoandrogenism, especially when the testicles are unable to produce adequate testosterone, despite gonadotrophic signaling. Androgen supplementation can be administrated temporarily; however, lifelong treatment may be required in some men, highlighting the need for timely diagnosis and management. Unfortunately, although well developed for TT in adults, expert consensus and pediatric guidelines about diagnostic criteria, clinical indications, appropriate monitoring, and adequate age and regimens are lacking. A concerted effort to perform future studies in children and adolescents that address these gaps in knowledge should be pursued. A comprehensive approach, tailored to the individual patient should contribute to a timely manner diagnosis and treatment, preventing the deleterious long-term effects that could be caused due to testosterone deficiency.

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M.C.S.A. conceptualized the outline, contributed to the critical review of the literature, participated in drafting primary manuscript, and created tables and figures of review. J.M.I. and E.K. contributed to the critical review of the literature and participated in drafting of the primary manuscript. L.T. discussed the content and was the secondary manuscript writer. D.E.N. revised the manuscript critically for the intellectual content, final edits, and gave final approval of the version to be submitted.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

There was no need for ethical approval as all the information used in the article was publicly available and de-identified.

ADDITIONAL INFORMATION

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