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Testosterone Therapy in Adolescent Boys: The Need for a Structured Approach

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Abstract
Background: In adolescents, testosterone may have several effects including promotion of secondary sexual characteristics and pubertal growth, attainment of optimal muscle mass and peak bone mass, optimization of the metabolic profile, and psychosocial maturation and well-being. ***Summary:*** Testosterone therapy is a cornerstone of the management of hypogonadism in boys. Since the initial report of the chemical synthesis of testosterone, several formulations have continued to develop, and although many of these have been used in boys, none of them have been studied in detail in this age group. Given the wide ranging effects of testosterone, the level of evidence for their effects in boys and the heterogeneity of conditions that lead to early-onset hypogonadism, a standardized protocol for monitoring testosterone replacement in this age group is needed. ***Key Messages:*** In this review, we focus on the perceived benefits of androgen replacement in boys affected by pubertal delay and highlight the need to improve the health monitoring of boys who receive androgen replacement therapy, proposing different approaches based on the underlying pathophysiology.

Introduction

Puberty represents a complex physiological process that culminates in the attainment of sexual maturity and reproductive capability. It is regulated by several factors, including genetic and environmental cues [1, 2]. Historically, the mean onset of puberty in boys is around 11.6 years, with 95% of boys entering puberty between 9.5 and 14 years of age [3]. In boys, delayed puberty is traditionally defined as the absence of testicular enlargement at over the age of 14 years, and it is estimated that delayed puberty affects approximately 2% of adolescent population [4]. Several conditions may determine the delay in pubertal maturation in boys, and a thorough knowledge of these factors is essential to develop a plan for its management [5, 6]. Sex steroid therapy with testosterone (T) is considered one of the cornerstones of the management of adolescents with delayed puberty; in a routine tertiary

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hospital setting in the United Kingdom, approximately 10–15% of boys reviewed for suspected hypogonadism may proceed to testosterone therapy [7].

The induction and maintenance of secondary sexual characteristics have a crucial impact on the physical and psychosocial well-being, both in adolescents and young adults. Hypogonadism can cause short- and long-term consequences such as increase the risk of metabolic syndrome [8, 9], and secondary osteoporosis [10] and boys affected by pubertal delay can also feel distressed by their condition. This may have an important impact on quality of life, even many years later, in adult age [11, 12]. However, testosterone therapy, may also be associated with behavior disturbance [13, 14], acne [15], and if inappropriately administered, with bone age advancement, resulting in a shorter adult height than initially predicted.

The Aetiology of Delayed Puberty

The most frequent cause of delayed puberty in boys is physiological constitutional delay of growth and puberty (CDGP), which is transient and self-limiting, followed by functional hypogonadism secondary to another chronic illness, and finally, organic or genetic conditions associated with hypogonadotropic hypogonadism or hypergonadotropic hypogonadism [7, 16, 17]. However, this only includes those boys who are referred for a paediatric endocrine evaluation and given that the clinical extent of hypogonadism may be variable, it is possible, therefore, that the real prevalence of self-limited as well as prolonged hypogonadism may be higher. For certain conditions, the incidence of male hypogonadism may change over time in response to temporal shifts in therapy and clinical management. For instance, endocrine disorders are among the most frequent long-term sequelae reported in childhood cancer survivors [18, 19] and a quarter of long-term cancer survivors may suffer from hypogonadism [20] but this may change depending on advances in cancer therapy. Similarly, hypogonadism is increasingly recognized in boys with Duchenne Muscular Dystrophy who are surviving for longer with the help of high dose glucocorticoid therapy [21]. Another stark example of this changing prevalence is the finding that an increasing number of undervirilized XY infants with a disorder of sex development are now raised as male rather than female [22], thus raising the possibility of a larger number of young hypogonadal men in the future. Lastly, an increasing number of transgender adolescents may start on testosterone as part of cross-sex hormone therapy [23].

Testosterone Action

Although small amounts of testosterone are secreted by the zona reticularis of the adrenal glands, the majority is produced by the testes and secreted by Leydig cells. In the adult male, testosterone production rate ranges from 3.0 to 7 mg/day [24, 25]. About 7% of testosterone is converted, via 5α-reductase, to a more potent metabolite named dihydrotestosterone, with an estimated production rate of 200–300 μg/day; approximately 0.5% of testosterone is metabolized to estrogen via aromatization [26–29]. The principal actions of testosterone are mediated via the androgen receptor (AR) encoded by the AR, which is a single copy gene located on the X chromosome [30]. In the cytoplasm, AR associates with heat shock proteins, which modulate the receptor's conformation for efficient ligand binding [31, 32]. Androgens cross the plasma membrane, enter the cytoplasm, and bind to the AR, leading to dissociation of chaperone proteins and translocation to the nucleus. At the nucleus, this complex undergoes dimerization and binds to androgen response elements [33], resulting in recruitment of histone acetyltransferase enzymes [31] and other essential coregulators that leads to gene transcription and, thereafter, protein synthesis [29]. The AR, like other nuclear receptors, is structurally comprised of three different functional domains: the N-terminal domain, the DNA-binding domain, and the C-terminal ligand-binding domain, connected to the DNA-binding domain by a hinge region [34]. The N-terminal domain is encoded by exon 1 of *AR* and contains a polyglutamine (CAG) sequence whose length is highly variable in humans [35]. The normal size of the CAG sequence is estimated to be between 11 and 31 triplets and a lower as well as a higher number of CAG repeats are associated with an impaired AR function [36]. This may have an important impact on well-being, considering that *AR* is expressed not only in male reproductive organs [37, 38], but also widely in several other human tissues (Fig. 1), including the cardiovascular system, gastrointestinal tract and smooth muscle [39]. Studies on Global AR Knockout male mice have investigated the pathological effects of AR dysfunction on bone [40, 41], brain [42], muscle [43], cardiovascular system [44], glucose and lipid metabolism [45], immune and hemopoietic system [46, 47], underlying the key role of androgens on several discrete tissues. Testosterone can also exert its effects via nongenomic pathways, as demonstrated by many cells that do not express the nuclear AR. This rapid androgen response is not inhibited by classical AR

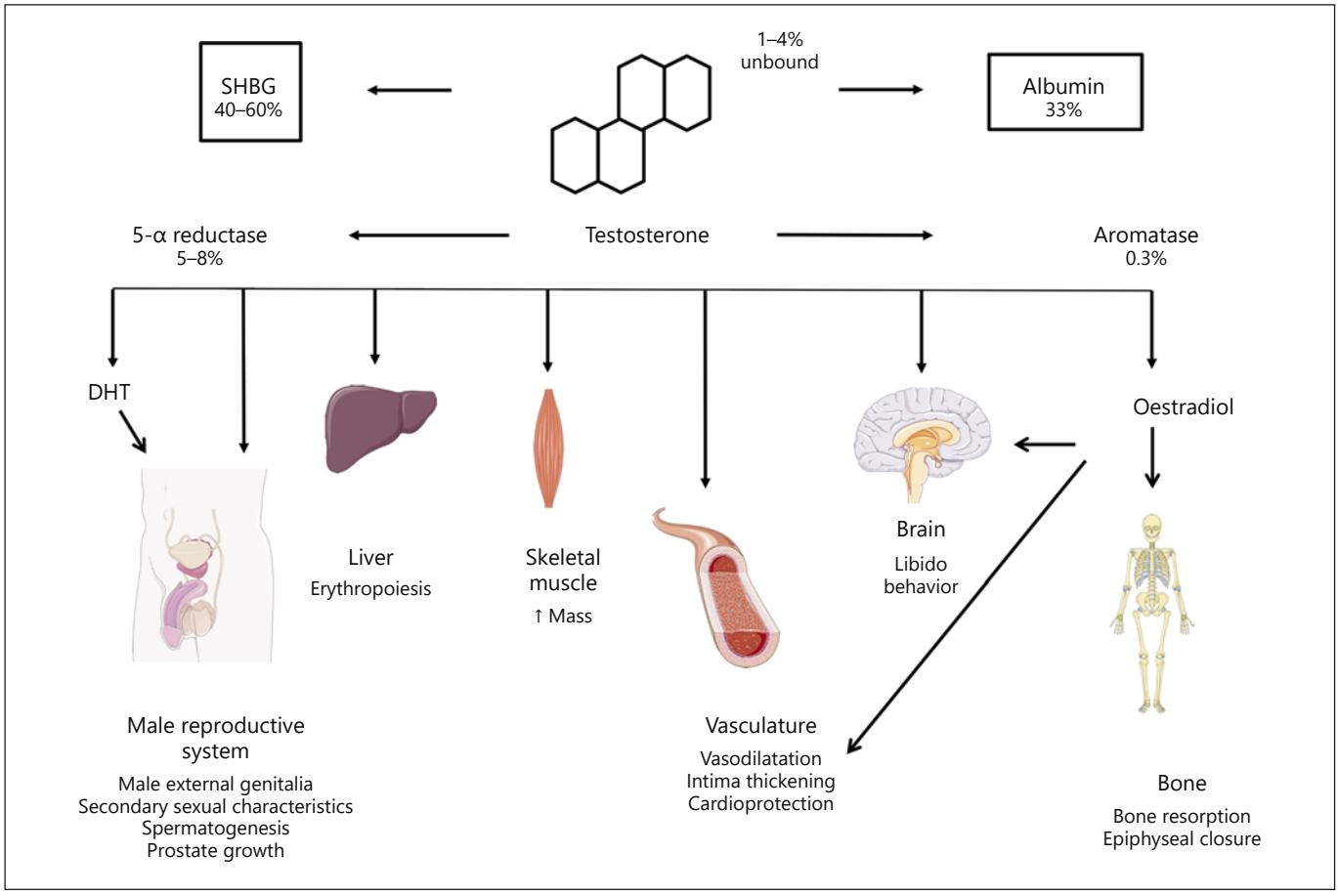

Fig. 1. Testosterone action on different organ systems. SHBG, sex hormone binding globulin; DHT, dihydrotestosterone.

antagonists [48]. The nature of these signals depends on the type of target cell and can include rapid Ca^{2+} release and consequently activation of the RAS/MEK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase)/MAPK (mitogen-activated protein kinase) pathway [48]; direct modification of ion channels including TRPM8 [49–51]; activation of the G-protein-coupled receptor GPRC6A [52]; or activation of the zinc transporter ZIP9 [53].

The Effects of Testosterone

Testosterone has several effects on many different tissues and systems, and in an ideal setting, sex steroid therapy should mimic this physiology. The effects of testosterone on the major systems are discussed below.

Bone

In children, bone mass tracks from childhood into late adolescence, and the onset of puberty is accompanied by increased bone accrual velocity [54], and the bone mass in pubertal children is higher than that of prepubertal children of the same age [55]. In healthy boys, almost 35% of whole-body bone mineral content is achieved during the 4 years surrounding peak height velocity [56]. The peak bone mass that is attained following puberty is also considered a critical factor that determines the osteoporosis risk later in life [57]. There are several reports suggesting that delayed puberty is associated with lower BMD in adulthood [58–62]. However, other reports have not confirmed these observations and, furthermore, did not find any difference in BMD when comparing testosterone-treated and -untreated men affected by CDGP [63, 64]. Although there is strong experimental evidence to suggest that androgens have both anabolic effects on

bone, via AR, and indirect effects via conversion to estrogen by aromatase [65, 66], the effects of testosterone on bone health in humans and, particularly adolescents, are less clear [67, 68]. In hypogonadal men, testosterone therapy may increase BMD [69–72], but whether it can restore BMD to the normal reference range, especially in those with early-onset hypogonadism, is not clear. Testosterone therapy has been reported to increase trabecular BMD in a subgroup of adolescents with open epiphyses, but this period of bone mineral accretion would have also coincided with an increase in height [73]. In addition, despite this increase, BMD still tends to remain below the normal reference range [73, 74]. Given the added complexities of defining osteoporosis in children and young adults [75, 76] and in the absence of any reports of increased skeletal fragility (e.g., fracture rates), the challenge of identifying biologically relevant osteoporosis is much greater in those with early-onset hypogonadism. Two different studies of young adult hypogonadal males receiving testosterone treatment reported a BMD reduction in 10% of the study population [77, 78]. Varimo et al. [78] reported a prevalence of osteoporosis in 3 out of 30 male patients affected by congenital hypogonadotropic hypogonadism. At the time of the survey, the mean age of the population was 38.1 years (range 16–61 years), and the mean age at starting testosterone treatment was 18.3 years (range 11–34 years). Tam et al. [77], in a cross-sectional study, analyzed 21 young males diagnosed with hypogonadism under the age of 18 years, due to several underlying diseases and who were receiving testosterone therapy. The mean age of the population was 27.1 ± 6.3 years, 33% had osteopenia and 10% had osteoporosis as defined according to WHO criteria [79]. Recently, Antonio et al. [80], in a single-center retrospective observational study, evaluated 25 young men, diagnosed with congenital hypogonadotropic hypogonadism. Among these, only 6 had a DXA evaluation before starting treatment and all (100%) had a T score <–1 at lumbar spine and 5 (83%) had a femoral T-score <–1. The median age of this treatment-naïve group was 22.5 years (18–35). The remaining 19 patients started T treatment at a median age of 19 years (12–57). Analyzing the totality of patients who were continuously treated with testosterone (n = 23), 61 and 48% of patients remained in the osteopenic/osteoporotic range for lumbar and femoral T-score, respectively (median follow-up time between first and last DXA 11 years, range 2–28 years). The authors speculated that a possible explanation for the persistent low BMD, even after a long-term treatment, could be the late age of starting testosterone therapy, supporting the hypothesis of an "adolescent window" of opportunity for peak bone mass attainment [81, 82].

In summary, there is good evidence that BMD is affected in young men with hypogonadism, and it is possible that it may increase following testosterone therapy. It is also possible that routine knowledge of BMD status in the adolescent who is on long-term testosterone therapy allows the clinician to make more informed decisions on the pace of dose escalation. However, the level of evidence on the value of regular assessment of BMD during adolescence in those who are on testosterone therapy is limited and may only improve if clear guidelines were introduced for monitoring and interpretation of BMD.

Growth

Sex steroids have a crucial role on several aspects of growth regulation, with the period of pubertal growth as an excellent example of this association [83, 84]. They are able to control the pubertal growth rate acting at 2 different levels [84]: testosterone stimulates GH-IGF1 secretion via its conversion to oestrogen, that interacts with the estrogen receptors (estrogen receptor-α and estrogen receptor-β) expressed in the hypothalamus and the anterior pituitary gland [85, 86]; at another level, both testosterone and estrogen directly interact with the AR and ERs localized in the growth plate cartilage [87].

Boys with CDGP usually present with relative short stature combined with delayed bone maturation. Observational studies on adolescents with such self-limited delayed puberty report a near adult height that is similar to the predicted adult height or mid-parental height [88–91]. However, other studies suggest that these boys may not achieve their genetic height potential [92–94]. Several studies have examined the effects of testosterone therapy and reported no significant differences in adult height between treated and untreated boys, underlining that testosterone therapy does not adversely affect adult height [95–98]. In a recent review, Zhu et al. [99] compared and contrasted the studies published so far, analyzing the effect of pubertal delay and the eventual treatment on adult height. Boys with hypogonadotropic hypogonadism who are treated at a later age tend to be taller than average [100] and have abnormal body proportions, with relatively longer lower segment and increased arm span [101]. Thus, the aim of optimal therapy would be to increase linear growth during adolescence while ensuring adult height is within the mid-parental height range and that it is associated with normal body proportions [100, 102].

Secondary Sexual Characteristics

One of the main goals of testosterone therapy in boys is to induce the adequate development of secondary sexual characteristics, including a satisfactory development of genital appearance. Some studies have demonstrated that, in boys, an abnormal appearance of the genitalia can directly affect the self-esteem and quality of life [103, 104]. During treatment, a periodic clinical assessment is recommended [105], and it should include the evaluation of pubertal progression, according to Marshall and Tanner [3], as well as the measurement of the stretched penile length. Normal reference values for penile size related to age and Tanner stage and different ethnic groups do exist [106–109], but such parameters are not used routinely to judge response to sex steroid therapy. While a change in penile length may be an objective and measurable clinical outcome in response to testosterone therapy, there is a greater need for standardization of the technique as well as an understanding of the precision of the technique. During testosterone therapy, adverse events such as testicular pain or priapism are not frequent. However, it is possible that some boys such as those with sickle cell disease, for example, may have a higher risk of priapism compared with unaffected boys [110]. It is speculated that priapism may be related to a higher dose of testosterone [111], but this effect has also been reported when using lower doses [112]. Gynecomastia is common in adolescent boys and, particularly, in those with conditions such as Klinefelter Syndrome and partial androgen insensitivity syndrome (PAIS) [113]. In PAIS, it is possible that the introduction of testosterone therapy itself may lead to a worsening of gynecomastia through aromatization to estrogens. On the other hand, it is possible that testosterone therapy may lead to a regression of gynecomastia in Klinefelter Syndrome [114], but this needs further studies.

In boys with hypogonadotropic hypogonadism, the aim of testosterone therapy is to primarily induce pubertal virilization rather than primarily increasing spermatogenesis. Pubertal induction with gonadotrophins has been proposed as a more appropriate means of optimizing fertility outcome compared to testosterone treatment despite its cost and inconvenience [115–118]. On the other hand, initial therapy with testosterone for pubertal induction followed by subsequent therapy with gonadotrophins has also shown satisfactory outcomes [119], but carefully designed trials are needed to investigate this conclusively.

Metabolism

Testosterone has marked anabolic effects [120, 121], and puberty is characterized by marked changes in body composition, with an increase in body size, muscle mass, and growth acceleration [122]. On the other hand, low testosterone levels are associated with metabolic impairment, increased fat mass, and reduced lean mass [123], even at a young age [124]. It is also possible that pubertal timing may have an impact on long-term metabolic and cardiovascular risk in men [99], but it is unclear whether treating adolescents with hypogonadism alters this long-term risk. Men with Klinefelter's syndrome, affected by primary gonadal failure, have a significantly increased risk of developing metabolic syndrome, compared to age-matched peers [125, 126]. Young men with untreated hypogonadotropic hypogonadism have an adverse metabolic profile, significantly lower HDL cholesterol, and a higher cardiometabolic risk, compared to healthy controls [127, 128]. There is accumulating evidence that testosterone therapy in hypogonadal men increases fat-free mass and muscle strength and reduces whole body, intraabdominal, and intramuscular fat [8, 121, 129, 130]. Observational studies have also documented an association between low testosterone level and nonalcoholic fatty liver disease (NAFLD) in adult men [131–133]. A recent retrospective case–control study reported a significantly higher prevalence of NAFLD in hypogonadal young males (34.9%), compared with healthy matched controls (4.4%) [128]. Interventional studies in hypogonadal men, receiving testosterone treatment in recommended dosages, have demonstrated a positive effect on liver fat and enzymes [134, 135]. However, the prevalence of NAFLD in the range of conditions associated with hypogonadism and the therapeutic effect of testosterone on NAFLD require further studies. On the contrary, high doses of testosterone therapy may decrease the concentrations of ApoA1 and HDL cholesterol [136], and administration of anabolic steroids in supraphysiological doses results in an increased risk of liver diseases, including hepatocellular carcinoma [137]. Liver toxicity has been reported mostly with oral 17α-alkylated androgens, and for this reason, this formulation is no longer used [129]. Currently available testosterone formulations are not associated with an increased hepatotoxicity risk, and the most recent clinical guidelines for adults receiving testosterone therapy do not recommend routine monitoring of liver function [129].

Haematology

Testosterone had been used for a long time for the treatment of chronic anemia, due to its erythrogenic effects [138]. For the same reason, it may cause erythrocytosis, clinically defined as an Hb level higher than 18.5 g/

dL; a hematocrit higher than 52% in men; or by an erythrocyte mass that exceeds 125% of that predicted for sex and body mass [138]. The risk of erythrocytosis may vary between different formulations [139]. Pharmacokinetic profile and dosage are considered the major factors linked to the risk of erythrocytosis, determining the amount and the duration of supraphysiological testosterone levels [129, 138, 140]. It is generally recommended to check hematocrit at baseline, 3–6 months after starting treatment, and then annually and a hematocrit level higher than 54% should be considered a reason to pause therapy [129]. The incidence of erythrocytosis in adolescent boys treated with testosterone is not well reported, probably due to the low frequency of monitoring complete blood counts [7, 141].

Psychosocial Status

In clinical practice, boys with delayed puberty referred to the hospital for clinical management, often seem to be less comfortable and more distressed by the delay and after starting testosterone therapy they generally report feeling more confident with themselves and their peers. Late pubertal timing has been associated with lasting psychosocial consequences in men [99]. A UK Biobank study described a significative association between later voice breaking (as a self-reported sign of puberty delay) and higher risk of anxiety, panic attacks, and depression in affected men [142]. Two separate studies have suggested that late pubertal maturation may be related to a higher risk of depression [143] and substance abuse [144]. On the other hand, a systematic study of quality of life (QoL) in hypogonadal young males compared to age-matched general population did not find any significant differences; however, younger adolescents did exhibit lower scores in some domains concerning vitality and physical functioning [77]. Among a group of young males with congenital hypogonadotropic hypogonadism, Varimo et al. [78] did report impaired QoL in dimensions associated with psychological well-being. Interestingly, the age at diagnosis is correlated negatively with the QoL score, and the authors concluded that late diagnosis and a consequent delayed start of testosterone therapy may have a lasting adverse influence in adulthood. While these studies emphasize the importance of addressing the psychosocial needs of the adolescent with delayed puberty, they also highlight the lack of structured assessment of these needs and the response to androgen replacement therapy.

Testosterone Therapy

Since the initial reports of the chemical synthesis of testosterone in the 1930s [145], [146], several testosterone formulations have become available, but none of them are licensed under current regulations for use in children. After subcutaneous testosterone pellets were first introduced in the 1940s, intramuscular injections of testosterone esters (T propionate, T enanthateand T cypionate) became available in the 1950s, oral T undecanoate was developed in the 1980s, transdermal patches were introduced in the 1990s, and the 2000s saw the introduction of topical gels, buccal patches, and a long-acting intramuscular preparation of T undecanoate [147]. In 2016, a nasal T preparation was introduced [148], and recently, in March 2019, the FDA announced the approval of a new testosterone undecanoate (TU) soft gel oral formulation as replacement therapy in men with hypogonadism [149]. Although all of these formulations may be considered to be effective, each formulation shows a different pharmacokinetic profile [150], and in adults, therapy is based on patient preference, the pharmacokinetics of the formulation, the treatment burden, and the cost, with the overall aim of ensuring adequate testosterone replacement [129]. Boys with CDGP and early-onset hypogonadism initially require a low dose of testosterone for pubertal induction followed by dose escalation in those requiring longer-term therapy [105, 151]. For this reason, formulations where a steady dose increase can be incorporated (starting from a low initial dose) are generally favored. Hormonal induction of puberty in boys with permanent hypogonadism should be started at an appropriate age for a physiological onset of puberty [105]. In practice, testosterone therapy is often started around the chronological age of 12 in these boys [7]. Postponing the timing of pubertal induction could be considered in those boys with concomitant GH deficiency or severe short stature and bone delay, to increase the near adult height [152, 153]. In boys with CDGP, testosterone therapy has usually been introduced around the age of 14 years [99].

Testosterone Preparations That Have Been Used in Male Adolescents

The vast majority of experience in the initiation and progression of pubertal development has been with the intermediate-acting esters of testosterone (T enanthate and cypionate), or with a mixture of very short and short-acting esters (Sustanon®) [105, 154, 155]. Few data have been published so far, regarding the clinical use of other testosterone formulations in adolescent populations (Ta-

Table 1. Testosterone therapy in boys with CDGP and hypogonadism

Testosterone (T) formulation	CDGP	Hypogonadism
T enanthate, cypionate or mixture of T esters, i.m. injection	Initial dose: 50 mg monthly, for 3–6 months. Possible to increase the dosage by 25–50 mg. Not recommended to exceed 100 mg monthly [5, 105]	Initial dose: 25–50 mg monthly. Increase of 50 mg every 6–12 months [5, 105] Adult dosage: 150–200 mg every 2 weeks [129]
T undecanoate, i.m. injection	No data available	Used for pubertal induction only in young men [156–158] Adult dosage: 750 mg every 10 weeks [129] 1,000 mg every 10–14 weeks [156]
T transdermal gels	Only one study available [167] Gel 2% (Tostrex®): 10 mg daily, for 3 months	Few data available [165, 166] Gel 1% (Androgel®); initial dose: 0.5 g/daily. Increase based on T level: 1.0, 1.5, 2.5, 3.0 or to 5 g/daily as needed [165] Adult dosage: 5.0–10.0 g/daily [129] Gel 2% (Fortesta®); initial dose: 10 mg/daily [166]. Adult dosage: 40–80 mg/daily [129]
T undecanoate, oral tablets	Few data available [17, 159, 160–162] Initial dose: 40 mg/daily. Maximum dose, 80 mg twice daily [17] 20 mg/daily for 6 months [159] 40 mg/daily for a mean of 3.5 months [160] 40 mg/daily for 4 weeks [161] 40 mg/daily for 3 months [162]	No data available in adolescent population Adult dosage (Andriol®): 40–80 mg, 2–3 times/day [129]; New formulation for adults, approved in USA (Jatenzo®): 158–396 mg twice/daily
T transdermal patches	Prepubertal 12.5–15 years: 5 mg over 8–12 h, overnight, for 8 weeks [164]	Prepubertal 14–16 years: 2.5 mg over 12 h, overnight Partially virilized 17–19 years: 2.5 mg/daily Virilized men >20 years: 5 mg/daily [163]
T pellets subcutaneous	No data available	13.9–17.5 years: 8–10 mg/kg every 6 months, for 18 months [168]
T nasal gel	No data available	No data available in adolescent population
T transbuccal bioadhesive tablets	No data available	No data available in adolescent population

CDGP, constitutional delay of growth and puberty.

ble 1). The long-acting TU intramuscular formulation in promoting puberty maturation has been used only in older boys with permanent hypogonadism [156–158] and is clearly not appropriate for treatment of boys with CDGP. The efficacy and safety of oral TU formulation, in boys affected by puberty delay, have been explored in few studies [159, 160]. Ahmed et al. [161], in a randomized, cross-over comparison study, concluded that the oral formulation had a similar effectiveness on linear growth compared with an intramuscular depot preparation. Lawaetz et al. [17], in an open observational study, reported that the TU oral formulation was effective in inducing secondary sexual characteristics and promoting height velocity, without accelerating bone age advancement. Gregory et al. [162] documented a significant increase of height velocity and fat-free mass in boys with CDGP treated with TU oral formulation for 3 months. In a small study including 9 patients affected by beta thalassemia, diagnosed with hypogonadotropic hypogonadism, De Sanctis et al. [163] reported that the transdermal application of testosterone (Androderm® in different regimens) was effective in promoting growth and virilization. Mayo et al. [164], in a cross-over study including 8 boys treated with a transdermal patch (Virormone® in different regimens), described a significant increase in salivary testosterone, with concomitant improvement of short-term growth and bone turnover markers. In 2014, Rogol et al. [165] reported the efficacy of testosterone gel 1% in promoting secondary sexual characteristics in a group of boys affected by Klinefelter's syndrome or anorchia. During treatment, the most common adverse events registered were cough, acne, headache, and local cutaneous dermatitis. In 2016, Contreras et al. [166] described the effective and safe use of testosterone transdermal gel 2% (Fortesta®) and 1% (Androgel®) in three late adolescent hypogonadal boys with concomitant hypertransaminasemia. Re-

cently, Chioma et al. [167] reported that in boys affected by CDGP, testosterone transdermal gel 2% was as effective as intramuscular testosterone in increasing height velocity, compared with untreated subjects. Other testosterone formulations that have been used include long-acting subcutaneous testosterone pellets [168]. In the past, boys with delayed puberty who had growth delay have been treated with oxandrolone, a nonaromatizable androgen [169–171], but its use has declined. Dihydrotestosterone (gel 2.5%) has been used in boys with 5-alfa reductase deficiency and PAIS to increase penile length [172, 173]. Recently, Varimo et al. [174] compared the use of intramuscular testosterone (1 mg/kg/4 weeks) to oral letrozole (2.5 mg/day), for promoting puberty in boys with CDGP through a randomized, open-label trial. Over the study period of 6 months, letrozole was associated with a greater rise in gonadotrophins and testicular growth, but other outcomes such as growth and bone age advance were similar. In boys with hypogonadotropic hypogonadism, pulsatile GnRH or hCG in combination with FSH or FSH in combination with testosterone has also been used [151, 175, 176]; the relative benefits of the several different regimens require further clarification.

Monitoring of Testosterone Therapy in Boys

In clinical practice, the principal parameters used to assess the effectiveness of testosterone therapy are represented by the progression of pubertal maturation, height velocity, and changes in body composition. For this purpose, regular clinical follow-up is generally performed every 3–6 months [105]. However, together with the clinical assessment, other laboratory and imaging-based examinations (like DXA for bone mineral density and hand-wrist radiograph for bone age) may be helpful for monitoring both benefits and side effects of testosterone treatment. In guidelines developed for adult men receiving testosterone therapy, monitoring is highly recommended and standardized [129], whereas in adolescents there is a scarcity of such guidance [105, 177] and clear evidence that systematic monitoring is rarely undertaken [7, 141]. In the study by Lucas-Herald et al. [7], of the 46 boys treated with testosterone at a single center, only 26% had liver function tests, 13% had a hematocrit, and 13% a BMD in the year prior to starting hormone therapy. Moreover, during testosterone therapy, liver function tests were assessed only in 13% and a hematocrit in 6% of the population [7]. Similar results were reported by Nahata et al. [141], analyzing retrospectively the management of hypogonadal boys, on testosterone therapy, at another center: 12% had no testosterone levels checked prior to starting hormone therapy, 17% did not have a testosterone level checked during treatment, 63% did not have a BMD at any point, and 31% did not have a hematocrit checked after starting testosterone therapy. It is possible that this variation in monitoring is due to the wide range of conditions that necessitate sex steroid therapy in adolescents. Bertelloni et al. [177], discussing the hormonal management in patients affected by disorders of sex development, proposed a scheme to monitor the effectiveness as well as safety of androgen therapy in males. To date, we are not aware of any other publication suggesting a targeted approach based on the underlying condition that leads to hypogonadism. With a greater appreciation of a wider range of effects of testosterone and the advent of several newer forms of testosterone replacement, the need for careful monitoring is becoming greater. This may especially be the case if there is a regulatory requirement for postmarketing surveillance of any preparations that are approved for boys.

We propose 2 different schemes of androgen replacement therapy monitoring, based on the temporary or permanent requirement for ongoing testosterone therapy (Tables 2, 3). We recommend an assessment of total blood count (including Hct and Hb levels) and liver function before starting testosterone for the determination of a "baseline," in all boys. This would identify the presence of underlying disease (such as polycythemia or hypertransaminasemia) that may contraindicate testosterone therapy or direct the physician to the diagnosis of an underlying condition, to choose the formulation with minor side effects and then start a personalized monitoring scheme. Moreover, those boys who are suspected to have CDGP, but require therapy for longer than 6 months, should not only have a thorough evaluation for the underlying cause but also follow the same monitoring protocol for hypogonadal patients, including the assessment of metabolic profile and bone mineral density (expressed as Z-score and adjusted for bone age) as it is possible that they may continue on testosterone for a longer period. In boys with permanent hypogonadism, the assessment of bone mineral density by DXA is performed on a relatively ad hoc basis [113, 141], and there is a need to perform this at regular intervals using validated methods adjusted for age, size, and sex [178]. To assess the psychosocial impact, we propose that the use of a standardized QoL tool such as the EQ-5D-Y should become routine practice [179]. In clinical practice, in boys with permanent hypogonadism, the effectiveness of testosterone treatment should be based mainly on clinical response, in terms of progression of Tanner stage (considered as enlargement of the stretched

Table 2. Proposed scheme of testosterone therapy monitoring in boys with CDGP, generally treated for 3 or 6 months with subsequent revaluation

	Baseline	3 months	6 months
Full clinical evaluation pubertal assessment*	√	√	√
Bone age	√		
Total blood count (Hb, Hct)	√		
Liver function test (AST, ALT, GGT)	√		

Those boys who require therapy for longer than 6 months for "CDGP" should have a thorough evaluation for the underlying cause and follow the care pathway in Table 3, starting from the baseline. * Tanner stage, stretched penile length. Hb, haemoglobin; Hct, haematocrit; AST, aspartate transaminase; ALT, alanine transaminase; GGT, Gamma-glutamyltransferase; CDGP, constitutional delay of growth and puberty.

Table 3. Proposed scheme of testosterone therapy monitoring in boys with hypogonadism, until complete pubertal development

	Baseline	3 months	6 months	12 months	Then every 6 months	Then annually	Then every 1–2 years
Full clinical evaluation Pubertal assessment*	√	√	√	√	√		
Bone age	√			√			√
BMD•	√			√			√
Total testosterone #	√	√	√	√	√		
LH, FSH	√						
Total blood count (Hb, Hct)	√	√	√	√		√	
Liver function test (AST, ALT, GGT)	√						
Metabolic profile (TC, LDL, HDL, TGD)	√			√			√

* Tanner stage, stretched penile length. • BMD, bone mineral density should be expressed as SDS for age and sex and may require adjustment for size or bone age. # Total testosterone during treatment should be maintained in the mid-normal reference range for pubertal stage. Timing of measurement depends by the type of T formulation used. Hb, haemoglobin; Hct, haematocrit; AST, aspartate transaminase; ALT, alanine transaminase; GGT, Gamma-glutamyltransferase; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TGD, triglycerides.

penile length) and secondary sexual characteristics (muscle mass accretion, facial and body hair growth, deepening of the voice). However, during treatment, it could be safe to maintain serum total testosterone level in the mid-normal reference range for pubertal stage [105]. This is why we recommend its periodic laboratory evaluation, ideally at 3 and 6 months after starting treatment and then every 6 months until completion of puberty. Timing of measurement of serum testosterone level may vary, depending on the type of formulation used and if testosterone levels are measured, careful consideration to the collection of samples in relation to the administration of the drug is required. The sample should be collected between injections for intramuscular testosterone enanthate or cypionate and before the next injection for intramuscular TU (to check after the third dose: first 2 injection spaced 6 weeks apart, subsequent given after 12 weeks); for the transdermal testosterone patch, the testosterone level should be checked 3–12 h post-application, 2 weeks after starting treatment; for transdermal testosterone gel, the testosterone level should be checked 2 h post-application, 2 weeks after starting treatment; for oral TU, the testosterone level should be checked 3–5 h after ingestion in the nonfasting state, 2 weeks after starting treatment.

Conclusion

Adolescence represents a crucial period in human life history, the transition between childhood and emerging adulthood, characterized by multiple challenges and developments in the physical and social domains. Testosterone therapy in adolescent boys is primarily aimed at increasing linear growth and pubertal progression, but may also have a positive effect on bone mineral content, muscle function, metabolic profile, and psychological well-being.

Therapy should limit the long-term consequences of early-onset hypogonadism and the psychosocial distress of pubertal delay that may affect teenage behavior, lasting into emerging adulthood. Hypogonadal adolescent males may start on testosterone therapy for several conditions; some may only require testosterone therapy temporarily, while others may need lifetime therapy and the monitoring of therapy will, therefore, depend on the underlying condition. Thus, not only is there a need for clear guidance on how to investigate adolescent males with delayed puberty but there is also a need to have a clear protocol for monitoring boys receiving testosterone therapy, especially in those who may have permanent hypogonadism.

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