Submitted: 22 February, 2024 Accepted: 24 April, 2024 Published: 30 October, 2024 DOI:10.22514/jomh.2024.164

REVIEW

JOMH Journal of Men's Health

Testosterone replacement therapy in adolescents and young men

Alexandra Aponte Varnum[1], Luke van Leeuwen[2], David A. Velasquez[1], Braian Ledesma[1], Nicholas Allen Deebel[3], Jason Codrington[2], Aymara Evans[1], Alejandro Diaz[4], David Miller[1], Ranjith Ramasamy[1,*]

[1]Desai Sethi Urology Institute, Miller School of Medicine, University of Miami, Miami, FL 33136, USA
[2]Miller School of Medicine, University of Miami, Miami, FL 33136, USA
[3]Department of Urology, Wake Forest University School of Medicine, Winston-Salem, NC 27101, USA
[4]Division of Pediatric Endocrinology, Nicklaus Children's, Miami, FL 33155, USA

***Correspondence**
ramasamy@miami.edu
(Ranjith Ramasamy)

Abstract

Guidelines for testosterone replacement therapy (TRT) have been well studied and defined in adults, however, this remains less defined for adolescents and young men. There are a variety of conditions in adolescents and young men that necessitate TRT. These conditions range from genetic etiologies such as Kallmann syndrome and Klinefelter syndrome, to acquired causes such as testicular trauma. Conditions can be broadly classified as hypogonadotropic hypogonadism or hypergonadotropic hypogonadism, depending on whether there are concurrently elevated gonadotropins (follicle-stimulating hormone (FSH) and luteinizing hormone (LH)). The decision to initiate TRT in these cases is multifaceted, contributing to the challenge of formulating clear guidelines. In this review, we utilized online sources such as PubMed and Google Scholar to find relevant literature, using key words such as testosterone therapy, adolescents and hormone replacement and hypogonadism in adolescents. This narrative review explores existing literature on TRT in adolescents and young men, encompassing common etiologies of hypogonadism in this population, available TRT therapies, and management and surveillance protocols. Furthermore, it addresses the evolving field of TRT in transgender youth. This study underscores the necessity for additional clinical investigations to explore emerging TRT therapies and establish clear surveillance guidelines tailored to this population.

Keywords

Testosterone therapy; Hormone replacement; Adolescent male hypogonadism

1. Introduction

According to the 2018 American Urological Association (AUA) guidelines, testosterone deficiency (TD) diagnosis requires two total testosterone level measurements <300 ng/dL along with the presence of clinical signs or symptoms [1]. However, there has been scrutiny regarding the appropriateness of this cut off especially for younger men, with some suggesting a cutoff closer to 400 ng/dL may be more suitable [2]. Signs and symptoms of TD can be categorized as sexual or non-sexual, and they differ in men of different age groups [3]. In older adult men, sexual symptoms of TD include reduced libido, erectile dysfunction, and reduced fertility. Non-sexual symptoms in older adult men tend to be less specific and include decreased motivation and energy, impaired memory and concentration, sleep disturbances, depression, reduced muscle mass, and increased adiposity [3]. In young adult men, these non-sexual symptoms seem to be better predictors of TD than sexual symptoms, with low energy being the symptom with the greatest predictive value of TD, rather than sexual symptoms such as low libido or erectile dysfunction [4]. Diagnosing TD in adolescents poses challenges, signs and symptoms of indicative of syndromes such as Klinefelter or Kallmann syndrome may not manifest until puberty is delayed [5, 6].

Studies have reported that testosterone levels have been declining in young American men, with a report indicating that 22% of those aged 15–39 years have levels below 300 ng/dL [7]. The etiology of TD spans congenital abnormalities (*e.g.*, Kallmann Syndrome, Klinefelter Syndrome), acquired conditions (*e.g.*, testicular trauma, infections), comorbidities (*e.g.*, obesity, diabetes) and substance use (*e.g.*, opioids, anabolic steroids) [8]. TRT in prepubescent males aims to initiate puberty with gradually increasing doses of exogenous T, but this does not prompt testicular volume increase or spermatogenesis [9]. While concerns exist about TRT's impact on growth in short stature or growth hormone-deficient patients, timely and appropriate dosing does not adversely affect adult height [10]. However, the psychological impacts of delayed puberty, including low self-esteem and depression, warrant attention.

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1.1 Hypogonadotropic hypogonadism

Testosterone deficiency can be classified as normogonadotropic hypogonadism, hypogonadotropic hypogonadism or hypergonadotropic hypogonadism. For purposes of this review, we will focus on hypo- and hypergonadotropic hypogonadism. Hypogonadotropic hypogonadism is defined by the insufficient secretion or action of gonadotropin-releasing hormone (GnRH) in the hypothalamus. Adolescent men with this condition have inadequate stimulation of the pituitary hormones LH and FSH leading to low testosterone levels, impaired pubertal development, and infertility. In males with hypergonadotropic hypogonadism, the testes fail to produce adequate testosterone, prompting an increased release of gonadotropins, specifically LH and FSH [11, 12]. This condition may result from a variety of causes including genetic disorders, testicular trauma and infection [12]. Congenital hypogonadotropic hypogonadism is a heterogenous group of disorders characterized by impaired production or action of gonadotropin-releasing hormone (GnRH). Genetic analyses have identified at least 46 genes implicated in the development of congenital hypogonadotropic hypogonadism, though many cases remain undiagnosed with less than 50% identified with a specific gene defect [13, 14]. These genetic alterations have been shown to disrupt the central regulation of reproduction at various levels, including impairing GnRH neurons migration, differentiation, activation, and disrupting neuroendocrine control of GnRH secretion, leading to downstream testosterone deficiency [15]. Acquired hypogonadotropic hypogonadism in adolescent males is characterized by disorders that develop postnatally, affecting the function of gonadotropin-releasing hormone (GnRH) neurons and/or pituitary gonadotroph cells. The most common causes of acquired hypogonadotropic hypogonadism include pituitary tumors (especially prolactinoma), sellar tumors or cysts of the hypothalamus or infundibulum, and infiltrative disorders [16]. Additional causes are vascular, iron overload disorders, pituitary surgery, head trauma, and cranial/pituitary radiation therapy. In contrast, functional hypogonadotropic hypogonadism includes a range of conditions that temporarily suppress the hypothalamic-pituitary-gonadal axis including obesity, chronic illness, nutritional deficiencies, specific medications and stress [16]. In these conditions, the hypothalamic and pituitary structures remain intact and capable of normal function once the external stressors are resolved or removed.

1.2 Hypergonadotropic hypogonadism

Hypergonadotropic hypogonadism in adolescent men is a condition characterized by low testosterone levels due to primary testicular failure. Elevated levels of gonadotropins (LH and FSH) are seen, as the body attempts to stimulate the underperforming testes. Causes can include genetic disorders such as Klinefelter syndrome, myotonic dystrophy, progressive muscular dystrophy, Bloom syndrome, Rothmund-Thomson syndrome, along with testicular trauma, infection, chemotherapy, radiation exposure, autoimmune disorders, and metabolic disorders [17]. Klinefelter syndrome, a common chromosomal disorder causing testicular dysfunction, is characterized by the 47, XXY karyotype. It presents with small, firm testicles, marked gonadal dysfunctions, severely attenuated spermatogenesis, and elevated levels of gonadotropins (LH and FSH) due to primary testicular failure [18]. The degeneration of germ cells begins early in life, as evidenced by fibrosis and hyalinization of seminiferous tubules, along with Leydig cell hyperplasia by puberty [19–21]. Some studies have explored various factors contributing to testicular dysfunction in Klinefelter syndrome (KS), including blood-testis-barrier dysfunction, altered inflammatory mechanisms, and increased apoptosis of Sertoli and Leydig cells [19]. D'Aurora *et al.* [19] identified several of these dysregulated cellular mechanisms through examination of differential gene expression in Sertoli and Leydig cells. The identification of certain gene transcripts being either overexpressed or under expressed has provided valuable insights into the intricate mechanisms leading to testicular failure in KS [19]. In addition to gonadal dysfunction, KS is often associated with neurocognitive and psychosocial impairments, as well as cardiovascular, metabolic and bone disorders [22]. The clinical features of KS are highly variable, and symptoms can become evident in infancy, childhood or adolescence, with many cases diagnosed during adulthood. When the testes are damaged, their ability to produce testosterone can be impaired. This can be caused by cryptorchidism, testicular trauma, testicular torsion, infection, chemotherapy, and radiation exposure. The severity of hypogonadism depends on the extent of the testicular damage [23]. In cases of severe trauma where significant testicular tissue is lost or damaged, the resultant hypogonadism can be permanent [24–26]. In less severe cases, testicular function may recover partially or fully over time. Lastly, autoimmune and metabolic disorders are recognized causes of hypergonadotropic hypogonadism in adolescent males, although these instances are relatively rare compared to other etiologies of hypergonadotropic hypogonadism [27–29].

This comprehensive narrative review endeavors to explore and analyze the existing literature on TRT usage specifically in adolescents and young men aiming to clarify the therapeutic indications, challenges and insights. Our findings contribute to the discourse on TRT's role in meeting the specific health needs of this population, highlighting the necessity for further understanding and research.

2. Methods

Online databases including PubMed, Google Scholar and ResearchGate were utilized to conduct a comprehensive search on current literature. Key words were used to find related literature such as "testosterone therapy", "adolescent hormone replacement" and "male hypogonadism". Articles were assessed for relevance, considering factors such as recent publication dates, applicability to adolescents, and ultimately 66 were selected for inclusion in this non-systematic, narrative review.

3. Approaches to treatment

In adults, the diagnosis requires two morning total testosterone levels below 300 ng/dL, accompanied by clinical symptoms

of hypogonadism. When the total testosterone is borderline in men with clinical signs or symptoms of hypogonadism, free testosterone can be assessed. Some studies suggest a free testosterone <63 pg/mL as a cut off, however the AUA currently lacks definitive guidelines regarding the utility or threshold for employing free testosterone in diagnosing hypogonadism in males [1, 25, 30, 31]. Applying these adult criteria to pediatric and adolescent populations poses challenges, as there are currently no definitive criteria for diagnosing hypogonadism in this age group. Recognizing this gap, Zhu *et al.* [2] analyzed this threshold in their study of men ages 20–44, aiming to ascertain whether a different cutoff level should be employed for young men. Their study involved the examination of testosterone levels in 1486 men, leading to the identification of suspected "normal" ranges for specific age brackets. For instance, they pinpointed a range of 409–558 ng/dL for individuals in the 20–24 age group [2]. In addition to testosterone, assessing LH and FSH levels are imperative to discern the etiology, whether it be hypogonadotropic hypogonadism or hypergonadotropic hypogonadism. This multifaceted approach ensures a more nuanced understanding and tailored diagnosis for young males considering testosterone replacement therapy.

4. Treatment of hypogonadism in adolescents

4.1 Testosterone replacement

When prescribing testosterone replacement therapy (TRT) for primary or secondary hypogonadism in young men, the emphasis is often on long-term usage, distinguishing it from the short-term application often utilized for constitutional delay of growth and puberty (CDGP). In scenarios requiring extended TRT, regular laboratory monitoring becomes essential to ensure the proper titration of testosterone. While comprehensive guidelines have been established for adult men, there remains a noticeable gap in practice guidelines for adolescents. Formulations that have received Food and Drug Administration (FDA) approval for use in children and adolescents are intramuscular testosterone enanthate and subcutaneous testosterone pellets (Table 1) [32]. It is crucial to exercise caution when initiating TRT in adolescents and young males, as it holds the potential to negatively impact spermatogenesis, also with concerns for bone age acceleration and premature closure of the epiphyses.

When discussing intramuscular testosterone formulations, testosterone enanthate (TE) and testosterone cypionate (TC) are commonly utilized to treat male hypogonadism. TE and TC have been studied for its efficacy in treating CDGP, however, the literature on their application in adolescent hypogonadism is comparatively sparse. Earlier clinical trials examining TE for CDGP in boys, such as the study by Richman *et al.* [41], demonstrated a significant rise in mean height velocity, with no notable impact on skeletal age advancement. Sexual maturation indicators, including testicular volume and serum testosterone levels, also exhibited notable increases [32, 41]. More recent studies have supported these early clinical trials, with increased height velocity in participants treated with TE injections every 6 weeks, without significant effects on adult height [42]. To induce puberty in patients with primary hypogonadism, therapy commences at age 11 or 12 with low-dose testosterone cypionate or enanthate, 25 mg subcutaneous/intramuscular (SC/IM) every two weeks or 50 mg once per month. Shorter dosing intervals have demonstrated more stable levels of testosterone and decreased symptoms of hypogonadism [43]. The dose is gradually adjusted every 4–6 months to achieve testosterone levels that correspond to the normal age or pubertal status. Generally, once the testosterone level is between 400 and 700 ng/dL, the dose remains unchanged. These levels are usually reached with a dose of 200–300 mg per month.

Research indicates that men with KS are frequently undertreated with TRT, despite the high prevalence of hypogonadism in KS individuals [44]. While evidence supports the overall benefits of TRT for KS patients, the optimal timing for initiating TRT remains controversial [45]. When FSH levels rise above the normal range most patients maintain normal testosterone production. Thus, testosterone treatment begins only when testosterone levels fall below the normal range for age, typically after age 16. At mid-puberty, if the patient can produce sperm, sperm collection and cryopreservation are recommended, with surgical sperm retrieval offered if necessary. Alternative perspectives advocate for beginning TRT either before puberty or later when clinical signs such as gynecomastia are present [44–46]. While variations in practice persist, TRT remains a crucial intervention in the comprehensive management of KS patients.

In hypogonadotropic hypogonadism cases where future fertility is a concern, treatment starts with FSH injections twice a week for 2–3 months, followed by human chorionic gonadotropin (HCG) three times a week, with doses adjusted by age. This continues until testicular growth and a rise in testosterone to normal levels is observed. Sperm cryopreservation should be offered should sperm be found in the ejaculate. Most patients switch to testosterone injections post-semen collection for convenience and cost. Nonetheless, testosterone injections remain the standard, especially when fertility preservation is not a priority or if FSH/HCG injections are inaccessible.

Testosterone pellets are another prevalent form of TRT. Pellet insertion involves a minor procedure done in office every few months, the benefit is avoiding a daily or weekly medication. Zacharin *et al.* [47] report that the use of testosterone pellets for hypogonadal adolescent boys sustained psychologic serum testosterone levels for approximately 4–6 months. They noted clinical symptom improvement reported by participants along with appropriate bone advancement [47]. Notably, there were no instances of pellet extrusion. Another study investigating testosterone pellet use in adolescents with Klinefelter's observed an increase in serum testosterone levels along with improvement in hypogonadal symptoms. However, they highlighted considerable variations in serum testosterone levels among patients, presenting obstacles in establishing ideal dosing to maintain a target serum testosterone level (Table 1) [34].

Transdermal TRT such as gels and patches are also commonly employed in treating hypogonadism. Patches, however, pose challenges in pediatric use as their dosing is primarily

TABLE 1. Testosterone replacement therapies and common dosing for treatment of hypogonadism in adolescents.

Testosterone Replacement Therapy	Route of Administration	Common dose (for treatment of hypogonadism in adolescents)	Frequency	Adverse Effects and Disadvantages
Testosterone enanthate	Intramuscular or subcutaneous	25–100 mg Increase by 25–100 mg every 6–12 months if necessary (up to 400 mg every 2 to 4 weeks) [9, 32, 33]	Once weekly (for transgender patients), every 2, 3 or 4 weeks for hypogonadism [5, 32]	Injection site irritation Fluctuations in testosterone levels
Testosterone cypionate	Intramuscular or subcutaneous			
Testosterone pellets	Subcutaneous	8–10 mg/kg [5, 32]	Every 3–6 months [34, 35]	Risk of infection, local extrusion, hematoma Difficult to titrate dose
Testosterone undecanoate	Oral	Adult dosing: 40–80 mg 2–3 times daily (Andriol), 158–396 mg twice daily (Jatenzo) [5, 32, 36] Data not available in adolescent population	2 to 3 times daily [5, 32, 37]	Fluctuations in testosterone levels Multiple doses per day
Testosterone gel	Transdermal	1% gel: 0.5 g daily, increase as needed (up to 5 g daily) 2% gel: 10 mg daily [5, 32, 38, 39]	Daily [5, 32, 37]	Skin irritation Need for daily application, risk of secondary transfer
Testosterone patches	Transdermal	14–16 years old: 2.5 mg over 12 hours 17–19 years old: 2.5 mg daily >20 years old: 5 mg daily [5, 32]	Overnight/Daily [32, 37]	Skin irritation Need for daily application
Nasal testosterone gel	Intranasal	Adult dosing: 11 mg per 2 pump actuations (33 mg daily) [40] Data not available in adolescent populations	Three times daily [40]	Nasal irritation Frequent administration

designed for adults, complicating the administration of appropriate doses for children. Nevertheless, its user-friendly nature makes it an attractive choice for TRT in adolescents. In a study by Chioma *et al.* [38], a statistically significant increase in height velocity was observed in boys with constitutional delay of growth and puberty (CDGP) who underwent treatment with either TE or a 2% daily testosterone transdermal gel. Surprisingly, no significant differences were found between TE and testosterone transdermal gel in terms of efficacy. Likewise, Rogol *et al.* [39] explored the use of daily testosterone gel for boys with Klinefelter syndrome or anorchia, revealing a noteworthy rise in serum testosterone to pubertal levels after 6 months of treatment with 1% transdermal gel daily. The most commonly reported side effects included cough, acne and headache [39]. Another study suggested that transdermal testosterone gel might be a more suitable option for boys with hepatic dysfunction, given the gel's reduced first-pass metabolism compared to intramuscular testosterone replacement [48].

Beyond transdermal and intramuscular formulations, alternative formulations such as intranasal testosterone (Natesto) and oral forms of TRT are gaining prominence and may offer benefits in pediatric populations. Nasal gels are considered advantageous due to their potential to preserve spermatogenesis in patients undergoing this form of TRT [3, 32, 49]. To enhance guidelines for dosing and managing TRT in adolescents with hypogonadism, further studies targeted specifically at this population are imperative. As new forms of TRT gain traction, it becomes increasingly important to refine our understanding of their efficacy and safety profiles in pediatric contexts.

4.2 Selective estrogen receptor modulators

Selective estrogen receptor modulators, such as clomiphene citrate and enclomiphene citrate, are frequently employed for

male infertility and more recently for treating male hypogonadism. Clomiphene citrate acts as an estrogen receptor antagonist in the pituitary gland, leading to increased release of LH and FSH, thereby promoting androgen production within the testes [50].

In a comparative analysis of their efficacy in treating hypogonadism compared to TRT, a study revealed similar patient satisfaction levels despite overall lower serum testosterone levels in the clomiphene citrate and testosterone gel groups, compared to those receiving testosterone injections [51]. Krzastek *et al.* [52] retrospectively investigated clomiphene citrate use in treating hypogonadism, revealing that 88% of men were eugonadal when evaluated after 3 years of treatment. Notably, they did not observe a significant difference between those treated for more than 3 years and those treated for less than 3 years [52]. Additionally, few side effects were reported with blurry vision, breast tenderness, and mood changes being the most common [52]. While these findings support their use for treating male hypogonadism, there is limited information regarding their application in adolescents. A significant advantage to these medications lies in their ability to promote increased endogenous production of testosterone, unlike TRT, which suppresses it.

4.3 Selective androgen receptor modulators

Selective androgen receptor modulators (SARMs) have also emerged as a potential alternative to TRT in treating male hypogonadism. Similar to selective estrogen receptor modulators (SERMs), SARMs exhibit tissue-specific agonist or antagonist effects [53]. While initial studies have explored their potential in treating conditions such as cancer-related cachexia, benign prostatic hyperplasia, and prostate cancer, research regarding their efficacy for treating male hypogonadism is limited [53, 54]. Early animal studies have indicated improved sexual function with administration of SARMs [55]. Additionally, their oral formulation and comparatively lower incidence of adverse effects compared to TRT emphasize their potential for further investigation in treating male hypogonadism [53, 54].

4.4 Aromatase inhibitors

Aromatase is a cytochrome P450 enzyme known for catalyzing the conversion of androgens to estrogens [56]. Anastrozole, a type II nonsteroidal inhibitor, binds reversibly to the heme group of cytochrome P450 thereby blocking aromatase and preventing the conversion of testosterone to estradiol [56]. This ultimately results in a reduction of serum estrogen levels while concurrently diminishing the feedback inhibition exerted by estrogen on the pituitary gland. Anastrozole is frequently employed off-label to regulate the testosterone-to-estrogen ratio in men, with some literature alluding to its potential application in the context of male hypogonadism, though the evidence remains somewhat inconclusive [50]. In the context of treating constitutional growth delay and puberty, the use of aromatase inhibitors has been demonstrated to elevate serum concentrations of LH, FSH, inhibin B, and testosterone in comparison to individuals treated with low-dose testosterone [57]. Aromatase inhibitors, due to their effect decreasing estradiol levels and keeping the bone epiphyses open longer, are used in adolescent males with short stature alone or in combination with growth hormone to improve their adult height [58]. Aromatase inhibitors and SERMs have been used to treat pubertal gynecomastia in adolescents [59].

4.5 Adolescent and young male considerations

There are various considerations when selecting options for testosterone therapy (TT) in this age range. The primary goal of TT in adolescents is to parallel normal physiological processes in the development of children and adolescents as accurately as possible [5]. Testosterone also plays a crucial role in bone health and the attainment of peak bone mass during puberty, which can impact long-term osteoporosis risk [60]. Adolescent males are generally prescribed TT for hypogonadism or constitutional delay of growth and puberty (CDGP). For either condition, short courses of low-dose testosterone are administered in a 3-to-6-month window [61]. Permanent hypogonadism, however, requires TT for both induction and sustained maintenance of puberty, with up-titration of dosing in attempts to parallel normal puberty [33]. However, among patients with hypogonadotropic hypogonadism, TT does not induce gonadal maturation or fertility. In this population the use of recombinant FSH first to promote expansion of the Sertoli cell population to optimize capacity for sperm production, followed by human chorionic gonadotropin (HCG) to induce testosterone production, has demonstrated efficacy [62]. After testicular enlargement and normal testosterone levels are obtained, it is possible to obtain sperm to be storage. If a patient and/or family prefers it due to higher costs and easier administration, the patient is then switched to TT. Other alternatives to TT, such as GnRH administration, HCG monotherapy, and clomiphene, exist but their impact on hypogonadal symptoms is debated. Still, TT remains the standard therapy [5].

Many TT options for adults are not readily available for use in the adolescent population. The market has seen the introduction of new generation testosterone therapies for adult use, with enhancements in ease of administration, user-friendliness, and pharmacokinetic effect [9, 40]. New intramuscular formulations, oral formulations, topical gels and creams, buccal patches and nasal preparations have all been developed for the adult population [32]. Unfortunately, this surge in interest for improved testosterone therapies hasn't translated similarly for the adolescent population.

Concerns related to bone health alone do not typically lead to the initiation of TT in adolescents, as the potential benefits and drawbacks on adolescent bone health remain unclear. Defining osteoporosis in children and young adults is a complex task. While there is evidence that TT can enhance bone mass density in hypogonadal adolescent males, it may not fully restore it to normal levels [63, 64]. Previous assumptions that TT accelerates epiphyseal closure have been refuted by studies, indicating that TT, if appropriately administered, does not have an adverse impact on final height [32, 65].

4.6 Surveillance

Monitoring TRT in adolescent males is a critical aspect of ensuring their well-being and addressing specific therapeutic needs. Regular assessments are essential to identify and manage potential adverse effects, as well as to track their growth adequately. The monitoring process should be individualized, considering factors such as the underlying reasons for TRT and the anticipated duration of therapy, which may vary among patients. While established guidelines exist for monitoring TRT in adults [37], there is a scarcity of clear and comprehensive guidelines for adolescents and young men. A study focusing on adolescents undergoing TRT revealed disparities in the evaluation parameters, with 68% of boys having their liver function assessed and 82% having their skeletal age evaluated prior to beginning therapy [66]. At 12 or 18 month intervals, serum testosterone levels, liver function, and blood count were assessed in more than half of the boys [66]. Despite the absence of specific formal guidelines for adolescent males on TRT, adapting existing adult guidelines seems a reasonable approach. It is imperative to tailor these guidelines to the unique needs and reasons for TRT in this population. Consequently, healthcare providers should remain vigilant in their monitoring practices, considering both the general guidelines for TRT and the specific nuances associated with the adolescent age group. Further research and evidence accumulation in this field will contribute to the development of more targeted and comprehensive guidelines for monitoring testosterone replacement therapy in adolescent males [5, 9, 32].

5. Conclusion

The landscape of clinical trials and research in the realm of TRT for adolescents and young men, particularly concerning longer-term treatment, is notably limited. Despite only two forms of TRT being FDA approved for adolescent use, the current market offers a multitude of alternatives, with newer formulations continually emerging. There are several limitations to consider in this study, notably the absence of clinical trials involving adolescent males, which reduces the relevance and currency of available literature for discussion. Moreover, given the absence of consensus regarding treatment strategies for this demographic, navigating and interpreting findings from diverse sources can pose significant challenges. There is a pressing need for increased research in this demographic, especially given the improved side effect profiles observed in some newer formulations, such as the preservation of spermatogenesis and the availability of non-injectable routes of administration. While recognizing the crucial role of testosterone in the development of children and adolescents, it is imperative to acknowledge the associated risks, particularly in young males. Prudent consideration and vigilant monitoring by healthcare providers are essential in the administration of TRT. To address the complexity of this population's treatment, further investigation into refining approaches is crucial. Comparative research on various TRT formulations and alternative testosterone-boosting options like SERMs is warranted to enhance our understanding and optimize therapeutic outcomes.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

RR—Conceptualization; AAV, LL, DAV and JC—Data/research collection and analysis; AAV, LL, NAD, DAV, JC and AE—Writing-original draft; RR, AD, AAV, NAD, DM, BL and DAV—Writing-review and editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

Supported by NIDDK grants R01 DK130991, UE5 DK137308, and Clinician Scientist Development Grant from American Cancer Society to Ranjith Ramasamy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Alexandra Aponte Varnum, Luke van Leeuwen, David A. Velasquez, Braian Ledesma, Nicholas Allen Deebel, Jason Codrington, *et al*. Testosterone replacement therapy in adolescents and young men. Journal of Men's Health. 2024; 20(10): 24-31. doi: 10.22514/jomh.2024.164.