International Journal of General Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Trans Dermal Testosterone Compared to Intramuscular Testosterone for Young Males with Delayed Puberty: A PRISMA Guided Systematic Review

Mosleh Jabari

Department of Endocrinology, College of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia

Correspondence: Mosleh Jabari, Department of Endocrinology, College of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia, Email dr.mosleh.jabari@gmail.com

Background: Challenges in selecting the right formulation of testosterone (TE) for young males with delayed puberty (DP) arise from the fact that there is limited evidence based guidelines in recommending the most efficient and safe formulation of TE.

Objective: To evaluate the existing evidence and systematically review the interventional effects of transdermal TE to other modes of TE administration for the treatment of DP among young and adolescent males.

Methods: All types of methodologies published in English were searched from the data sources including MEDLINE, Embase, Cochrane Reviews, Web of Science, AMED and Scopus from 2015 till 2022. Boolean operators with keywords "types of TE", "modes of TE administration", "DP", "transdermal TE", "constitutional delay of growth and puberty, (CDGP)" "adolescent boys" and "hypogonadism" to optimize the search results. The main outcomes of concern were optimal serum TE level, body mass index, height velocity, testicular volume, pubertal stage (Tanner), The secondary outcomes included in this study were adverse events and patient satisfaction.

Results: After screening 126 articles, 39 full texts were reviewed. Only five studies could be included after careful screening and rigid quality assessments. Most studies were at high or unclear risk of bias with short duration and follow up periods. Only one study was a clinical trial covering all the outcomes of interests.

Conclusion: This study points out the favorable effects of transdermal TE treatment for DP in boys, while the existence of the vast gap in research needs to be acknowledged. Despite the utmost demand in an appropriate TE treatment for young males with DP, scarce efforts and trials are being undertaken to provide clear clinical guidance of treatment. Quality of life, cardiac events, metabolic parameters, coagulation profiles are important aspects of the treatment are overlooked and under evaluated in most studies.

Systematic Review Registration: PROSPERO CRD 42022369699.

Keywords: delayed puberty, transdermal testosterone, testosterone treatment, hypogonadism, constitutional delay of growth, DP, TT

Introduction

Rationale

The clinical absence of first signs of pubertal developmental milestones is defined as delayed puberty (DP) in boys and girls.[1] Functional delay in the production of gonadotropin-releasing hormone (GnRH) from the hypothalamus considered responsible for DH.[2] CDGP due to individual genetic variations, malnutrition, chronic illness and other functional defects can be the underlying case for DP.[3] DP can present with socio physiological burden for patients and their families.

Diagnosis for DP among boys are based on the assessment of clinical signs and symptoms and a low testosterone (TE) concentrations in serum in the morning on at least two occasions (< 10.4 nmol/L).[4,5] In conditions like hypogonadism, where enough hormones for masculine growth and development during puberty (TE) or enough sperm or both[6] are

Received: 4 November 2022
Accepted: 3 February 2023
Published: 27 February 2023

not produced due to congenital or acquired conditions external hormonal treatments are required.[7] Based on causes of DP like CDGP or hypogonadism for young boys, chemically synthesized TE has been used since 1935 as a common clinical intervention, targeting genital maturation, adequate secondary sexual characteristics developments, attainting the optimal muscular and bone growth.[8,9]

The typical clinical approach for adolescent males with CDGP or hypogonadism is the prescription for Testosterone Replacement Therapy (TRT). Currently various choices of interventions for TE replacement and management for adults are available, including intramuscular (IM), subcutaneous, oral and transdermal preparations,[10–15] but the right tittered choice and mode of administration of TE for young adults are not available.[16–18] Pitfalls in the use of TE usages for adolescents have disclosed multitudes of risks, associated behavioral deviations in the pre pubertal group and below target height line achievement with non-advancement of one's age which has generated a warning for its usage.[19–21] Earlier short acting esters of TE like Sustanon®, were used as IM preparations that have been used for many years for the treatment of pubertal TE deficiency.[22] Studies report the safety and efficacy of short-term use of TE Enanthateor oral TE undecanoate in inducing puberty and increasing growth in young males with CDGP.[23,24]

Though the long-term safety and efficacy of Transdermal testosterone therapy (TRT) for puberty completion and maintenance have not been established, reliable evidence on the use of Transdermal testosterone (TT) for adolescent boys to induce and maintain puberty are emerging.[25–27] It is optimal that all kinds of TE therapies for young males are administered and monitored to better mimic the physiologic pubertal development. A critical lack of scientific evidence based guidelines for prescribing transdermal TE for adolescent boys hinders achieving this and the current TRT regimens are based on consensus and expert opinion.

The US Food and Drug Administration has currently approved only IM TE esters (TE enanthate) and subcutaneous TE for DP, while no preparation is approved for long-term use in the adolescent age.[17,28–32] In adult males with hypogonadism several TE formulations like transdermal nasal, subcutaneous, and oral formulation have been are recently developed with improved pharmacokinetic profile and to ease the administration route increasing patient compliance.[33–36] These formulations are not approved for pediatric age, although some of them are used as off-label regimens.[37–40] Pediatric uses of exogenous TE has been reported for the treatment of microphallus in infants and the management of diminished or absent mini puberty.[41–43].

Critically limited evidences are available in support of the use of TT in the long term use boys with DP. Current practices lacks evidence based guidelines and the recommendations in selecting the route of administration and in the ideal preference of monitoring of the TE dose are based on expert opinions and consensus. It is of paramount importance clinically to identify and utilize an effective, safe, convenient to use and cost effective regimen of TE treatment which optimally mimics the physiological situation, as the majority of boys diagnosed with DP require longer periods of treatment.

TT for young males has not yet been a topic of any meta-analysis or a systematic review to this date and thus this review has a highlighted an importance in providing guidelines and evidence to the current TT treatment requirements to treat DP. Hence this study aims to compare the TT intervention to other types of TE interventions recommended to treat the symptoms of DP among young males.

In this study, a PRISMA guided systematic review is undertaken including randomized-controlled trials (RCTs) and non-randomized studies with an objective to evaluate the TT treatment options involving young male population diagnosed with DP. The review question formulated for this review is as follows. Participants (P): Boys younger than 19 years, Intervention (I): TT preparations for DP for young boys. Comparisons(C): Injectable TEs and oral TE. Outcomes (O): Serum TE levels, bone mineral density, height velocity and pubertal growth, adverse effect and quality of life.

Objectives

Using a broad set of eligibility criteria and an inclusive search strategy this systematic review sought to evaluate the existing evidence and systematically review the interventional effects of TT to other modes of TE administration for the treatment of DP among young and adolescent males.

Methods

Protocol and Registration

Detailed eligibility criteria and methods of analysis were specified in advance and documented in a published review protocol.[44] This review conforms to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[45] and is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD 42022369699). The institutional review board ruled out the need for an ethical approval for a systematic review.

Inclusion and Exclusion Criteria

The full text articles retrieved were assimilated that were relevant after review of the titles and abstracts. Final eligibility assessment was done independently for full text articles and all studies were individually appraised.

Inclusion criteria for the studies were (1) Methodologies of clinical trials without limitation on intervention design features, systematic reviews, meta-analysis, case reports and series, cross sectional studies on young and adolescent boys with DP (below 18 years) from 2015 until 2022, comparing TT to other modes of TE treatment. (2) Studies which included at least 3 of the following post-interventional outcomes helpful to assess the DP related clinical presentations: Serum TE levels, body mass index, bone mineral density, LSH, FSH and adverse effects. Studies on adults, studies on women, trans genders, animal studies, narrative reviews letters to editor, editorials, commentaries, and abstracts only available were excluded. Table 1 summarizes the inclusion and exclusions criteria designed for this study.

Table 1 describes these criteria.The Figure 1 illustrates the PRISMA flow diagram for the studies selected in the search process and eligibility appraisal.

Information Sources and Search Strategy

Based on the study eligibility criteria, a search strategy was designed consisting of a systematic, computer-assisted, literature search of existing evidence from several online databases like MEDLINE, Embase, Cochrane Reviews, Web of

Table 1 The Inclusion and Exclusion Criterias for the Study Selection

	Inclusion Criteria	Exclusion Criteria
Participants	Young boys and adolescent boys (Below 18 years)	Adult, women and animal studies
Intervention	Studies with Transdermal testosterone As interventional treatment for DP	Other hormones used for masculinity and transgender needs. Studies that involve testosterone Intervention other than transdermal testosterone
Comparison	Studies comparing Transdermal Testosterone to IM testosterone as interventional treatment for DP	Studies with patients did not any interventions, insufficient raw data
Outcomes	Studies which observed and stated interventional outcomes.	Studies that have not adequately defined post-interventional outcomes of the treatment,
Study designs	All methodologies of clinical trials, Systematic reviews, meta-analysis, And case series	Conference proceedings, commentaries, letter to editors, narrative reviews.
Language	English publications	Non English publication without English translations available.
Availability	Full texts available	Abstracts only available, Author duplicate publications
Time	From 2015 till 2022	Dated before 2015

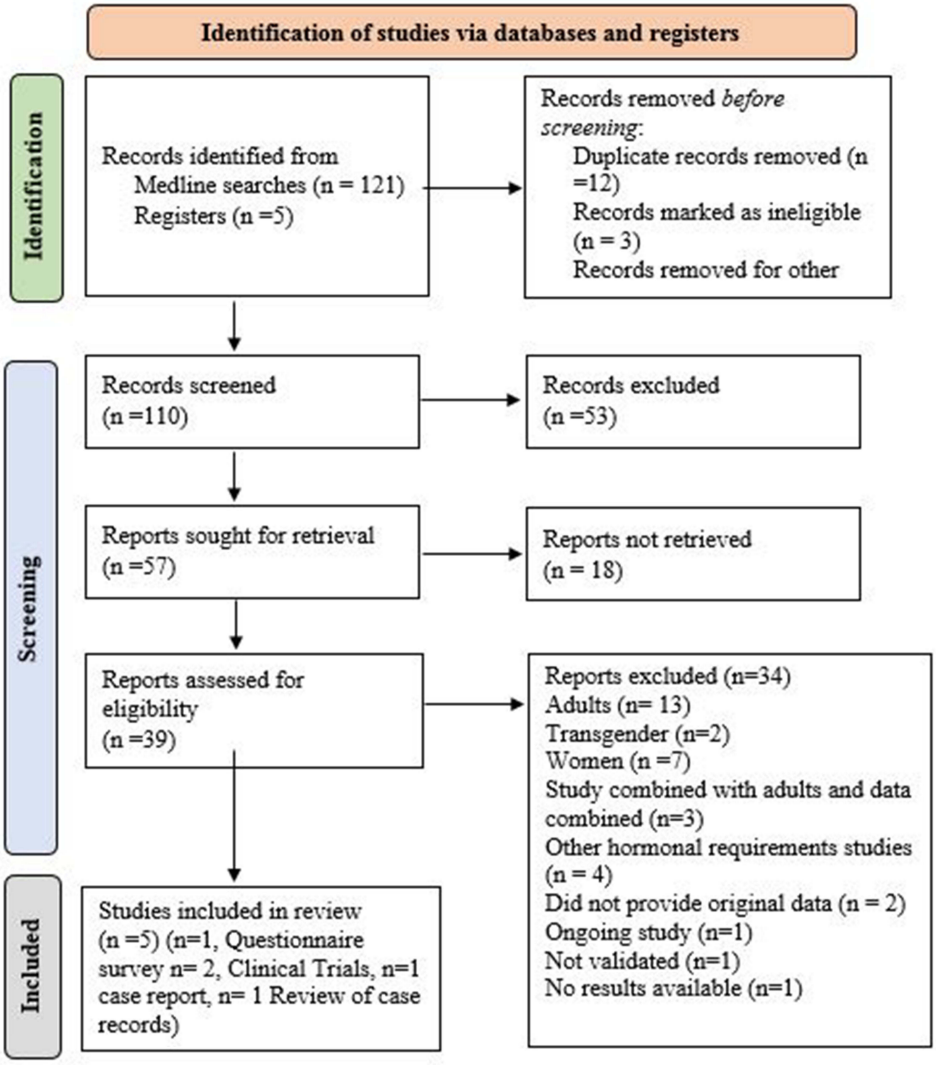

Figure 1 PRISMA Flowchart elaborating on study retrieval and inclusion in this study.
Notes: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10). Creative Commons.[45]

Science, the Allied and Contemporary Medicine (AMED) for articles published between 2015 to 2022. Boolean logics with keywords "types of TE", "modes of TE administration", "DP", "TT", "CDGP", "adolescent boys" and "hypogonadism", "androgens", hypogonadal boys, IM TE injections, to which relevant subheadings like "administration & dosage", modes of administration (buccal, cream, gel, implant, injections, oral, patch, transdermal) were applied in combination to optimize the search results.

Study Selection

The selected studies were independently identified, selected, and appraised. To avoid possible selection bias, grey literatures including published and unpublished thesis, was obtained by searching Web of Science, ProQuest Dissertations and clinicaltrials.gov. The reference sections of retrieved original articles and reviews were scanned for studies that might have been missed in the primary searches. Studies were filtered with regard to study design and methodological features, main and secondary reported outcomes evaluated under this study. Eligibility was tracked and arranged with EndNote (Version 5.0 Thompson Reuters, 2011).

Data Collection Process

Data extraction for all variables was independently completed and assessed using a customized data extraction spreadsheet. Search results were combined and duplicates were deleted. The selected titles and abstracts were reviewed, and full-text reports were retrieved of those that were potentially relevant, and later classified as included or excluded. Data from the included studies were extracted into the predesigned spreadsheet.

Data Items

Full-data extraction was done for study design details including the publication details, methodological attributes, and post interventional outcomes featured in the study, TE duration and preparation used, remarks of the included study, participant demographics. Table 2 and Table 3 and are illustrative of this data extraction and synthesis.

A meta-analysis was ruled out due to the heterogeneous nature of the limited amount of studies which are available. This there was no further statistical analysis involved and the review was summarized narratively after the explicit quality assessment process. This directs to a key research gap of the lack of evidence in this topic and contributes to the medical decisions based on weaker scientific support.

The review was themed into main outcomes and secondary outcomes. Main outcomes of concern were the achievement of optimal serum TE levels, height velocity, bone mineral density and pubertal growth. The secondary outcomes evaluated were adverse events and quality of life.

Risk of Bias in Individual Studies

Due to the heterogeneous nature of the included studies, Mixed Methods Appraisal Tool (MMAT)

2018[46] was used to appraise the quality of the different study designs included in this study. The

MMAT, consists of a checklist which appraises the methodological quality of included studies in systematic reviews, qualitative, quantitative, and mixed methods studies.[47] Checklists for nonrandomized and mixed method designs were used. Each study was screened with 2 questions and further a 5 assessments criteria check list to answered with Yes, No, cannot tell was used. A total score of 7 constitutes a Yes response to the screening and assessment criteria.[48] Subsequently the spreadsheet was updated for the final review and summarization of the included studies.

Summary Measures and Additional Analyses

A tabular as well as narrative summary of all study design features, participant details, outcome variables of interests are presented in this review. The outcomes of interests were compared between the IM TE dose and TT dose.

Results

Study Selection

This systematic review search ended only with 5 studies included from an initial hit of 126 studies Following the removal of duplicates, 110 studies were screened (titles and abstracts) to identify and 39 articles were assessed for full eligibility and only 5 studies were included in this systematic review. Full-text review led to the removal of 34 articles. The PRISMA flow diagram of study selection procedure is shown in Figure 1. A total of 842 participants were included from these included studies and Table 4 provides the summary of the attributes included studies. Out of the included studies one was a questionnaire based survey,[49] two were clinical trials,[50,51] and one a retrospective case reports review[52] one a case report.[53] This is an explicit manifestation of the dire insufficiency of clinical trials and on young males with TE requirements.

Study Characteristics

A summary of the attributes included studies included studies are comprehensively presented in Table 4.

Table 2 Main Outcome Comparison and Descriptions

Study	Serum Testosterone (ng/dl)		BMI (kg/m^2)		HV (cm/Year)		Testicular Volume (mL)		Bone Age		Pubertal Growth	
	IM	Trans Dermal Gel	IM	Trans Dermal Gel	IM	Trans Dermal Gel	IM	Trans Dermal Gel	IM	Trans Dermal Gel	IM	Trans Dermal Gel
Stancampiano, 2021[49]	Less increase reported compared to Transdermal	Reports as increased	Less increase reported compared to Transdermal	Reports as increased	Less increase reported compared to Transdermal	Reports as increased	Less increase reported compared to Transdermal	Reports as increased	Less increase reported compared to Transdermal	Reports as increased	From II To IV	From II to IV
Mastromattei, 2020[50]	Increased	Significantly increased	Increased	Increased	Increased	Significantly increased	Increased	Significant testicular enlargement		Remarkably higher	From II To IV	From II to IV
Chioma 2018[51]	From 66.4 (mean) to 157.1	From 66.4 (mean) to 94.3	From 18.5 to 19.5	From 18.5 to 19.2	From 4.7 to 9.4	From 4.7 9.2	From 5.8 To 6.9	From 5.8 to 6.7	From 12.3 to 13.4	From 12.3 to 13.5	From II To IV	From II to IV
Herald 2018[52]	Reports as increased	Reports as increased	Reports as increased	Reports as increased more than IM	Reports as increased	Reports as increased more than IM	Reports as increased	Reports as increased comparable to IM	Reports as increased	Reports as increased more than IM	From II To IV	From II to IV
Contreras 2017[53]	NA	173	From 19.16 to 0.16	From 33.28 to 32.13	Increased by 4.9	Increased by 7.3	Not reported	Not reported	NA	NA	From II to IV	From II to IV

Table 3 Adverse Events and Patient Satisfaction on Transdermal Testosterone Treatment for Young and Adolescent Boys with Delayed Puberty

Study	Adverse Events	Quality of Life and Patient Satisfaction
Stancampiano, 2021[49]	Acne or oily skin, aggressive behavior with IM testosterone	Not reported
Mastromattei, 2020[50]	Not reported	Not reported
Chioma 2018[51]	No significant side effects for both IM and transdermal testosterone	Not reported
Herald 2018[52]	Raised transaminases, increased aggression with IM testosterone	Not reported
Contreras 2017[53]	Erythema associated with IM testosterone	All of the treated boys reported satisfaction with both types of treatment regimens.All of the patients tolerated the treatments well.

Abbreviation: IM, Intramuscular.

Risk of Bias Within Studies

The methodological quality of the included articles are shown in the Table 5. Of the included reports, only 2 studies were rated as moderately strong, and the other 3 studies were moderately weak, respectively.

Synthesis of Results

Due to the high heterogeneous nature of the included studies a meta-analysis was excluded and therefore progressed with a narrative synthesis.

Participant Details

In total, this review represents 842 participants, 40.02% (n = 337) were identified as having CDGP, where 20.19% (n=170) had hypogonadism and 0.83% (n=7) had hypogonadotropic hypogonadism. The mean age of the participants were 14.84 and the duration of the TE treatment were all short term with a mean of 6 months.

Main Outcomes

The main outcomes of concern were optimal serum TE level, body mass index, height velocity, testicular volume, pubertal stage (Tanner).

Serum Testosterone Level

Raising Serum TE to an optimal level is the utmost goal of TE treatment, which alleviates the symptoms of DP. The transdermal TE gel treatment is shown to be promising than IM TE for young boys with DP[50,51] and suggests it to be an alternative to other modes of TE treatments. It can be seen that both gel and IM TE preparations are able to achieve desirable levels of TE within a short duration with minimal fluctuations.[50–53] Studies on adult men[54–57] have reported an average level of TE levels are reported by the weekly usage of short acting IM TE. Women and girls studies[32,58–61] reports the favorable pharmacokinetic profile of transdermal gel compared to achieve an optimal peak of TE level.

The limited amount of evidences available in selecting TT against other modes of TE is evident in the sparse amount of studies included in this study. It is evident that there exists, a critical need for explicit clinical guidance that can be applied to monitor the safety as well as efficacy of transdermal therapy in this age group. Table 2 which is descriptive of all the main outcomes covered in this study.

Pubertal Growth

Evaluation of BMI (kg/m^2) testicular volume, testicular volume, bone mineral density, pubertal stages as per tanner stages, were included to identify the growth. Table 5 is inclusive of these observed outcomes from the included study.

Table 4 Summary of the Attributes Included Studies

Study	Methodology	Participant Data		T Preparation Used		Duration of Testosterone	Reported Outcomes	Remarks
		n	Mean Age	Intra Muscular	Transdermal Gel			
Stancampiano, 2021[49]	Questionnaire Survey	162 with hypogonadism	14.7	Sustanon®, a blend of intramuscular testosterone esters (T decanoate 40%, T phenylproprionate 24%, T isocaproate 24%, T proprionate	Tostrex 2% testosterone gel	Varied	LVT, blood count, bone age and BMD	It is stated that the testosterone replacement therapy in boys is currently varied and suggests that the standardization of practice may lead to more effective assessment of treatment outcomes.
Mastromattei, 2020[50]	Retrospective trial	246 with CDGP	12.2	50mg enanthate testosterone(Testoviron) every 4 weeks for 3 months	10mg 2% (Tostrex 2%) daily or 3 months	6 months	HV (cm/year), Serum Testosterone (ng/dl), FSH (UI/l), LH (UI/l)	The study validated that TTG to be more effective to induce growth spurt, better tolerated and with a more physiological effect on pubertal induction compared to IMTT in CDGP population
Chioma 2018[51]	Retrospective observational	73 with CDGP with hepatic dysfunction	14.7	50mg enanthate testosterone(Testoviron) every 4 weeks for 3 months	10mg 2% (Tostrex 2%) daily or 3 months	6 months	HV (cm/year), BMI (kg/m^2), Pubarche according to Tanner, TV(mL) Bone age, Serum Testosterone (ng/dl) FSH, (UI/l) and LH (UI/l)	Reports the efficacy of short-term testosterone gel treatment to induce growth spurt with improvement on height velocity approaching to pubertal values.
Herald 2018[52]	Multicenter retrospective review of case records	358 (constitutional in 17, chronic disease in 10, organic hypogonadism 7, multiple pituitary hormone deficiency in 6, and isolated hypogonadotropic hypogonadism in 6.	14.2	1 g testosterone undecanoate as Nebido and the rest (95%) were on varying doses of testosterone enanthate as Sustanon (median starting dose 100mg	2% topical testosterone solution, 40 mg once daily	9 months	Bone age, LVT and Hematocrits	Results are inconclusive and highlights the effectives of transdermal gel and notes that testosterone therapy for hypogonadism in boys is rare and may be associated with adverse events.
Contreras 2017[53]	Case report	3 (1 with primary gonadal failure, 1 with congenital pan hypopituitarism and 1 with craniopharyngioma)	16.5	50 mg enanthate testosterone every 4 weeks.	2% topical testosterone solution, 60 mg once daily	9 months	BMI (kg/m^2) Tanner Staging, Serum Testosterone (ng/dl), FSH (UI/l), LH (UI/l)	Advocates the promising effect of TT gel and recommends it as an alternative agent for IM usages for pubertal induction among adolescent patients with hepatic dysfunction.

Table 5 Quality Assessment of the Included Studies Using Mixed Methods Appraisal Tool (MMAT)

	1.Qualitative				4. Qualitative Descriptive				5. Mixed Methods			Total Points	Overall Quality Score
Study	**1.1**	**1.2**	**1.3**	**1.4**	**4.1**	**4.2**	**4.3**	**4.4**	**5.1**	**5.2**	**5.3**		
Stancampiano, 2021[49]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	8/11	Moderate Strong
Mastromattei, 2020[50]	Yes	Yes	No	Yes	Yes	Yes	Cannot tell	Yes	Yes	Yes	No	8/11	Moderate Strong
Chioma 2018[51]	No	Yes	No	No	Yes	Yes	Cannot tell	Yes	Yes	Yes	Yes	7/11	Moderate Weak
Herald 2018[52]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	7/11	Moderate Weak
Contreras 2017[53]	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	7/11	Moderate Weak

It can be seen that all the included studies[49–53] reported the comparable efficacy of TT treatment in all the included main outcome observations.The heterogeneous nature of outcome reporting and the extremely limited availably of clinical trials makes it hard to make a definite statement.

TE changes the BMI and the included studies[51–53] reports TT to be at par with IM TE preparations. Though from a limited amount to studies, BMI increase was apparent in all types[49–53] of TE treatment. Clinical trials should be initiated to cover the anthropometric parameters, metabolic changes, changes in fat mass, lean body mass, and muscle strength comparing transdermal approach to other modes of TE treatment. It is noteworthy that in all studies with the transdermal gel approach[49–53] bone age is reported to be a gradual and progressive increase during treatment more apparently.

Secondary Outcomes

Secondary outcomes included in this review were the adverse events of the interventions and the reported patient satisfaction.

Adverse Events and Patient Satisfaction

Only one study[53] assessed the effect of TE therapy on patient satisfaction. Increase aggression and mood swings was reported by a study,[52] whereas the other studies does not significantly draws notice to any adverse effects. The impact of TE therapy on quality of life among boys with DP is difficult to quantify due to the significant heterogeneity in study population, study duration, and the measures to identify it. One study[49] reports acne or oily skin, aggressive behavior with IM TE and erythema was reported[53] for a patient under IM TE treatment, while there no significant adverse events reported on TT by the other included studies. It is evident that clear conclusion cannot be derived from such limited sources on the different formulations for young boys with DP. Table 3 briefs all these observations.

Strengths and Limitations

This review has explicitly followed the PRISMA protocols and presented a transparent review, drawing on recommendations and highlighting the research gaps found. In addition, the breadth of the study inclusion criteria has ensured a comprehensive coverage of the TE intervention under review. A rigorous use of screening process, data abstraction, and quality appraisal increases the strength of conclusions has been ensured in this study. Based on these this review support the evidence of the use of TT for the clinical management of DP in boys.

A potential limitation of this review is the volume of included literature included in this study. Although short term TE preparations are being marketed on a high scale, there is a clear lack of scientific evidence and support for the

consumption and prescription of these products. Due to the high volume of research con ducted with mixed samples of adults and adolescents an inability to obtain segregated data from the articles is highlighted here.

Considering the various TE preparations and modes of administration used in the literature as well as the different participant samples, this review has a great deal of clinical heterogeneity. Variation in response to the intervention was infrequently reported. Consequently, complete statistical analysis and quantitative integration of the data cannot be assimilated.

Recommendations for Future Research

Future studies recruiting sufficient sample population with longer follow up periods should be considered. These studies should report unified measurements of outcome measurements. Finally, further research exploring the potential mechanisms mediating the transdermal preparations pharmacokinetics is warranted to better understand the interventional outcomes. Such mechanisms include, but are not limited to, vascular indices of health and function as well as patient satisfaction.

Conclusion

Positive treatment effects of TE for adult men, women and transgender are well-researched and has been explored. This study exposes the critical lack of experimental researches, meta-analysis for comparing TT delivery with other TE administration routes for young males with DP. It is very imminent that there should be clinical trials undertaken in this field as there are many new combination of TE dosages and administration routes emerging in the market. These new preparations of TE should be according to the patient's preference, cost, availability, and formulation-specific properties for the young boys with clinically evident DP.

In conclusion, though both transdermal gel andIM TRT appear to be effective preparations for the treatment of DP in young males, TT shows more promising in the mode of administration and in better outcomes of serum TE elevation and hence recommended for treating DP among young boys. However, any clinical recommendations on TT treatment needs more clinical trial and meta analyses and thus this study only provides a clinical support and not a guideline. The research gap identified needs to be filled by future clinical trials comparing TT with other modes of TE administration for young males with DP.

Patient and Public Involvement

This study being a systematic literature review, the patients selected were recruited by the researchers of the included studies. All the patient and families related aspects involved in design and implementation of the interventions were priori addressed by the authors of the selected studies.

Data Sharing Statement

This review has utilized the published data from the included studies and thus a full dataset is not openly available.

Informed Consent

For this type of study, formal consent is not required.

Funding

No fund or sponsorship in any form was obtained from any organization for carrying out this study.

Disclosure

The author has no conflict of interest to disclose.

References

1. Jin H-Y, Lim J-S, Lee Y, et al. Growth, puberty, and bone health in children and adolescents with inflammatory bowel disease. *BMC Pediatr*. 2021;21(1). doi:10.1186/s12887-021-02496-4
2. Wu H-M, Chang H-M, Leung PCK. Gonadotropin-releasing hormone analogs: mechanisms of action and clinical applications in female reproduction. *Front Neuroendocrinol*. 2021;60:100876. doi:10.1016/j.yfrne.2020.100876

3. Witchel SF, Plant TM. Neurobiology of puberty and its disorders. *Human Hypothal Neuroendocr Disord*. 2021;463–496. doi:10.1016/b978-0-12-820683-6.00033-6
4. Matsumoto AM. Diagnosis and Evaluation of Hypogonadism. *Endocrinol Metab Clin North Am*. 2022;51(1):47–62. doi:10.1016/j.ecl.2021.11.001
5. Persani L, Bonomi M, Cools M, et al. Endo-ERN Expert opinion on the differential diagnosis of pubertal delay. *Endocrine*. 2021;71(3):681–688. doi:10.1007/s12020-021-02626-z
6. Jayasena CN, Anderson RA, Llahana S, et al. Society for endocrinology guidelines for testosterone replacement therapy in male hypogonadism. *Clin Endocrinol*. 2021;96(2):200–219. doi:10.1111/cen.14633
7. Federici S, Goggi G, Quinton R, et al. New and consolidated therapeutic options for pubertal induction in hypogonadism: in-depth review of the literature. *Endocr Rev*. 2021;43(5):824–851. doi:10.1210/endrev/bnab043
8. Grinspon RP, Castro S, Brunello FG, et al. Diagnosis of Male central hypogonadism during childhood. *J Endocr Soc*. 2021;5(11). doi:10.1210/jendso/bvab145
9. Harrington J, Palmert MR. An approach to the patient with delayed puberty. *J Clin Endocrinol Metab*. 2022;107(6):1739–1750. doi:10.1210/clinem/dgac054
10. Ehrensaft D, Tishelman AC. Take the T out, Put the T in: gender-affirming hormones in youth. *Andrology*. 2021;9(6):1698–1706. doi:10.1111/andr.13055
11. Grannis C, Leibowitz SF, Gahn S, et al. Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys. *Psychoneuroendocrinology*. 2021;132:105358. doi:10.1016/j.psyneuen.2021.105358
12. Desai A, Yassin M, Cayetano A, et al. Understanding and managing the suppression of spermatogenesis caused by Testosterone Replacement Therapy (TRT) and Anabolic–Androgenic Steroids (AAS). *Ther Adv Urol*. 2022;14:175628722211050. doi:10.1177/17562872221105017
13. Corona G, Vena W, Pizzocaro A, et al. Testosterone supplementation and bone parameters: a systematic review and meta-analysis study. *J Endocrinol Invest*. 2022;45(5):911–926. doi:10.1007/s40618-021-01702-5
14. Lanier NE, Nguyen CM, Mihalopoulos NL, et al. 54. Adolescent transgender boys: effects of 2 years of testosterone therapy. *J Adolesc Health*. 2022;70(4):S29. doi:10.1016/j.jadohealth.2022.01.167
15. Al Samahy O, Othman D, Gad D, et al. Efficacy of topical testosterone in management of scrotal hypoplasia and agenesis. *J Pediatr Urol*. 2021;17(4):515.e1–515.e8. doi:10.1016/j.jpurol.2021.02.014
16. Cohen J, Nassau DE, Patel P, et al. Low testosterone in adolescents & young adults. *Front Endocrinol*. 2020;10. doi:10.3389/fendo.2019.00916
17. Kresch E, Patel M, Lima TF, Ramasamy R. An update on the available and emerging pharmacotherapy for adults with testosterone deficiency available in the USA. *Expert Opin Pharmacother*. 2021;22(13):1761–1771. doi:10.1080/14656566.2021.1918101
18. Patel M, Muthigi A, Ramasamy R. JATENZO®: challenges in the development of oral testosterone. *Int J Impot Res*. 2021;34(7):721–724. doi:10.1038/s41443-021-00461-4
19. Figueiredo MG, Gagliano-Jucá T, Basaria S. Testosterone therapy with subcutaneous injections: a safe, practical, and reasonable option. *J Clin Endocrinol Metab*. 2021;107(3):614–626. doi:10.1210/clinem/dgab772
20. Suarez AMC, Israeli JM, Kresch E, et al. Testosterone therapy in children and adolescents: to whom, how, when? *Int J Impot Res*. 2022;34(7):652–662. doi:10.1038/s41443-021-00525-5
21. Zacharin MR, Warne GL. Treatment of hypogonadal adolescent boys with long acting subcutaneous testosterone pellets. *Arch Dis Child*. 1997;76(6):495–499. doi:10.1136/adc.76.6.495
22. Vogiatzi M, Tursi JP, Jaffe JS, et al. Testosterone use in adolescent males: current practice and unmet needs. *J Endocr Soc*. 2020;5(1). doi:10.1210/jendso/bvaa161
23. Pastuszak AW, Gittelman M, Tursi JP, et al. Pharmacokinetics of testosterone therapies in relation to diurnal variation of serum testosterone levels as men age. *Andrology*. 2021;10(2):209–222. doi:10.1111/andr.13108
24. Abildgaard J, Petersen JH, Bang AK, et al. Long-term testosterone undecanoate treatment in the elderly testosterone deficient male: an observational cohort study. *Andrology*. 2021;10(2):322–332. doi:10.1111/andr.13124
25. Shankara Narayana N, Ly LP, Jayadev V, et al. Optimal injection interval for testosterone undecanoate treatment of hypogonadal and transgender men. *Endocr Connect*. 2021;10(7):758–766. doi:10.1530/EC-21-0109
26. White WB, Dobs A, Carson C, et al. Effects of a novel oral testosterone undecanoate on ambulatory blood pressure in Hypogonadal Men. *J Cardiovasc Pharmacol Ther*. 2021;26(6):630–637. doi:10.1177/10742484211027394
27. Ahmad SW, Molfetto G, Montoya D, et al. Is oral testosterone the new frontier of testosterone replacement therapy? *Cureus*. 2022;14(8). doi:10.7759/cureus.27796
28. Khodamoradi K, Khosravizadeh Z, Parmar M, et al. Exogenous testosterone replacement therapy versus raising endogenous testosterone levels: current and future prospects. *F&S Rev*. 2021;2(1):32–42. doi:10.1016/j.xfnr.2020.11.001
29. Hashim PH, Kinnear HM, Cruz CD, et al. Pharmacokinetic comparison of three delivery systems for subcutaneous testosterone administration in female mice. *Gen Comp Endocrinol*. 2022;327:114090. doi:10.1016/j.ygcen.2022.114090
30. Barbonetti A, D'Andrea S, Francavilla S. Testosterone replacement therapy. *Andrology*. 2020;8(6):1551–1566. doi:10.1111/andr.12774
31. Ghosh T, Abraham W, Jasti B. Transdermal and topical drug delivery systems. In: *Theory and Practice of Contemporary Pharmaceutics*. CRC Press; 2004:423–455.
32. Zeng J, Xie T-F, Huang T, et al. Preparation and in vitro and in vivo evaluation of a testosterone film forming gel for the treatment of hypoactive sexual desire disorder in women. *AAPS Pharm Sci Tech*. 2022;23(3). doi:10.1208/s12249-021-02201-9
33. Dubey R, Pothuvan U. Transdermal patches: an emerging mode of drug delivery system in Pulmonary arterial hypertension. *J Drug Deliv Ther*. 2021;11(4–S):176–186. doi:10.22270/jddt.v11i4-S.4925
34. Farooqui H, Upadhyay P, Upadhyay S. Transdermal patches approach towards self-nano-emulsifying drug delivery system (SNEDDS) using essential oil as penetration enhancer. *Micro Nanosyst*. 2022;14(4):314–340. doi:10.2174/1876402914666220221105304
35. Al Hanbali OA, Khan HM, Sarfraz M, Arafat M, Ijaz S, Hameed A. Transdermal patches: design and current approaches to Painless Drug Delivery. *Acta Pharmaceutica*. 2019;69(2):197–215. doi:10.2478/acph-2019-0016
36. Mani SB, Clavijo RI. Medical treatment of hypogonadism in men. *Urol Clin North Am*. 2022;49(2):197–207. doi:10.1016/j.ucl.2021.12.008
37. Smurawa TM, Congeni JA. Testosterone precursors: use and abuse in pediatric athletes. *Pediatr Clin North Am*. 2007;54(4):787–796. doi:10.1016/j.pcl.2007.05.002

38. Malik RD, Liu DB. Survey of pediatric urologists on the preoperative use of testosterone in the surgical correction of hypospadias. *J Pediatr Urol*. 2014;10(5):840–843. doi:10.1016/j.jpurol.2014.02.008
39. Funderburgh LJ, Zipf W, Sotos JF. [PDF] direct measurement of testosterone in a pediatric center, with use of a radioimmunoassay kit and unextracted serum.: semantic scholar. *Clin Chem*. 1983;29(10):1796–1798. doi:10.1093/clinchem/29.10.1796
40. Arisaka O, Hoshi M, Kanazawa S, et al. Systemic effects of transdermal testosterone for the treatment of microphallus in children. *Pediatr Int*. 2001;43(2):134–136. doi:10.1046/j.1442-200x.2001.01353.x
41. Rey RA, Grinspon RP. Androgen treatment in adolescent males with hypogonadism. *Am Jo Men's Health*. 2020;14(3):155798832092244. doi:10.1177/1557988320922443
42. Takeuchi H, Okubo H. Clinical efficiency of combination therapy using testosterone replacement therapy, phosphodiesterase 5 inhibitors and Kampo herbal medicine for EUGONADAL patients with late-onset hypogonadism syndrome. *Exp Ther Med*. 2021;22(4). doi:10.3892/etm.2021.10608
43. Lee J, Brock G, Barkin J, et al. The my-T study: patient satisfaction and preference comparing topical and nasal testosterone therapies. *Can Urol Assoc J*. 2019;13(11). doi:10.5489/cuaj.5680
44. Schiavo JH. Prospero: an international register of systematic review protocols. *Med Ref Serv Q*. 2019;38(2):171–180. doi:10.1080/02763869.2019.1588072
45. Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10). doi:10.1136/bmj.b2700
46. Hong QN, Pluye P, Fàbregues S, et al. Improving the content validity of the mixed methods appraisal tool: a modified e-delphi study. *J Clin Epidemiol*. 2019;109:111. doi:10.1016/j.jclinepi.2019.01.012
47. Harrison R, Jones B, Gardner P, Lawton R. Quality Assessment with diverse studies (Quads): an appraisal tool for methodological and reporting quality in systematic reviews of mixed- or multi-method studies. *BMC Health Serv Res*. 2021;21(1):1–20.
48. Lizarondo L, Stern C, Apostolo J, et al. Five common pitfalls in mixed methods systematic reviews: lessons learned. *J Clin Epidemiol*. 2022;148:178–183. doi:10.1016/j.jclinepi.2022.03.014
49. Stancampiano MR, Lucas-Herald AK, Russo G, et al. Testosterone therapy in adolescent boys: the need for a structured approach. *Horm Res Paediatr*. 2019;92(4):215–228. doi:10.1159/000504670
50. Mastromattei S, Todisco T, Chioma L, et al. Efficacy of short-term induction therapy with low-dose testosterone as a diagnostic tool in the workup of delayed growth and puberty in boys. *J Endocrinol Invest*. 2022;45(12):2377–2384. doi:10.1007/s40618-022-01879-3
51. Chioma L, Papucci G, Fintini D, et al. Use of testosterone gel compared to intramuscular formulation for puberty induction in males with constitutional delay of growth and puberty: a preliminary study. *J Endocrinol Invest*. 2017;41(2):259–263. doi:10.1007/s40618-017-0726-7
52. Lucas-Herald AK, Mason E, Beaumont P, et al. Single-centre experience of testosterone therapy for boys with hypogonadism. *Horm Res Paediatr*. 2018;90(2):123–127. doi:10.1159/000490738
53. Contreras MF, Raisingani M, Prasad K, Franklin B, Shah B. Transdermal testosterone gel for induction and continuation of puberty in adolescent boys with hepatic dysfunction. *J Pediatr Endocrinol Metabol*. 2017;30(1). doi:10.1515/jpem-2016-0201
54. Johansen N, Lindén Hirschberg A, Moen MH. The role of testosterone in menopausal hormone treatment. What is the evidence? *Acta Obstet Gynecol Scand*. 2020;99(8):966–969. doi:10.1111/aogs.13819
55. Lin L-T, Li C-J, Tsui K-H. Serum testosterone levels are positively associated with serum anti-mullerian hormone levels in infertile women. *Sci Rep*. 2021;11(1):6336.
56. Diem SJ, Greer NL, MacDonald R, et al. Efficacy and safety of testosterone treatment in men: an evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med*. 2020;172(2):105. doi:10.7326/M19-0830
57. Nolan BJ, Proietto J, Sumithran P. Single-Center Real-life experience with testosterone treatment in adult men with Prader–Willi syndrome. *Am J Med Genet A*. 2022;188(9):2637–2641. doi:10.1002/ajmg.a.62770
58. Madsen MC, van Dijk D, Wiepjes C, et al. M. Erythrocytosis in a large cohort of trans men using testosterone: a long term follow up study on prevalence, determinants, and the effect of years of exposure. *J Endocr Soc*. 2021;5(Supplement_1):A726–A726. doi:10.1210/jendso/bvab048.1477
59. Bhasin S, Lincoff AM, Basaria S, et al. Effects of long-term testosterone treatment on cardiovascular outcomes in men with hypogonadism: rationale and design of the Traverse Study. *Am Heart J*. 2022;245:41–50. doi:10.1016/j.ahj.2021.11.016
60. Salamin O, Nicoli R, Langer T, et al. Longitudinal evaluation of multiple biomarkers for the detection of testosterone gel administration in women with normal menstrual cycle. *Drug Test Anal*. 2021;14(5):833–850. doi:10.1002/dta.3040
61. Donaldson M, Kriström B, Ankarberg-Lindgren C, et al. Optimal pubertal induction in girls with Turner syndrome using either oral or transdermal estradiol: a proposed modern strategy. *Horm Res Paediatr*. 2019;91(3):153–163. doi:10.1159/000500050