


Guideline

Guideline for the Diagnosis and Management of Growth and Puberty Disorders in Patients with Transfusion-Dependent Thalassemia

Fariba Ghassemi¹, Mohammad E. Khamseh², Negin Sadighnia¹, Mojtaba Malek³, Nahid Hashemi-madani², Neda Rahimian², Pooya Faranoush¹, Ali Elahinia¹, Vahid Saeedi¹, Dorsa Fallah Azad¹, Mohammad Faranoush¹ 

¹ Pediatric Growth and Development Research Center, Institute of Endocrinology Iran University of Medical Sciences Tehran Iran

² Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences (IUMS), Tehran, Iran

³ Research Center for Prevention of Cardiovascular Disease, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences (IUMS), Tehran, Iran



Scan and read the
article online

Citation Ghassemi F, Khamseh ME, Sadighnia N, Malek M, Hashemi-madani N, Rahimian N, Faranoush P, Elahinia A, Saeedi V, Fallah Azad D, Faranoush M. Guideline for the diagnosis and management of growth and puberty disorders in patients with transfusion-dependent thalassemia. Iran J Blood Cancer. 2024 March 25;16(1): 43-52.



Article info:

Received: 6 Jan 2024

Accepted: 3 Mar 2024

Published: 25 Mar 2024

Keywords:

Guideline
Growth
Puberty
Transfusion Dependent Thalassemia
Iron Chelators

Abstract

Introduction: Thalassemia, particularly α and β types, are characterized by mutations causing varied clinical manifestations such as anemia, skeletal deformities, and iron accumulation. Patients with transfusion-dependent thalassemia (TDTs) often face growth and puberty complications, which are influenced by the disease's type and severity. These disruptions not only result from chronic anemia, iron chelation therapy, and endocrinopathies but also significantly impact the patient's quality of life.

Methods: A comprehensive guideline was formulated through a systematic literature review and stakeholder engagements. The protocol emphasizes diagnosing and managing growth and puberty disorders in TDT patients, integrating consistent monitoring, documentation, and patient-specific assessments.

Results: The guideline proposes a detailed monitoring schedule from birth to adulthood, focusing on growth velocity norms and referral criteria to pediatric endocrinologists. It outlines protocols for hormone treatments in cases of delayed or arrested puberty, with distinctions for boys and girls. The treatment approach is multidisciplinary, combining growth monitoring, hormone therapy, and potential surgical interventions. The complexities demand continuous management, with treatment plans tailored to individual patient needs.

Conclusions: The research provides a pivotal national protocol for addressing growth and puberty anomalies in TDT patients, aiming to enhance their well-being and standardize care. The emphasis on proactive, individualized strategies will bolster healthcare outcomes and reduce associated costs.

* Corresponding Author:

Mohammad Faranoush

Affiliation: Pediatric Growth and Development Research Center, Institute of Endocrinology Iran University of Medical Sciences
Tehran Iran

E-mail: faranoush47@gmail.com

1. INTRODUCTION

Thalassemia, a subset of hemoglobinopathies, arises from diminished or absent synthesis of specific globin chains. Depending on the affected chain, thalassemias are categorized as α , β , γ , δ , $\delta\beta$, or $\epsilon\gamma\delta\beta$. The α and β thalassemia, resulting from mutations in the primary polypeptide chains (α or β) of the adult hemoglobin molecule (Hb A, $\alpha_2\beta_2$), hold the most clinical significance (1-4). In these variants, an imbalanced alpha-to-beta chain ratio induces the accumulation of surplus chains, instigating premature degradation of erythroid precursors in both the bone marrow (ineffective erythropoiesis) and the bloodstream (hemolysis). Consequently, this imbalance produces symptoms ranging from varying anemia levels and extramedullary hematopoiesis to potential skeletal deformities, growth restrictions, and iron accumulation (5, 6). Based on clinical manifestations and transfusion needs, thalassemia syndromes are phenotypically categorized into transfusion-dependent thalassemia (TDTs) and non-transfusion-dependent thalassemia (NTDTs). TDTs necessitate regular transfusions for survival, encompassing conditions such as β thalassemia major and severe Hb E/ β thalassemia, among others. Without sustained transfusion support, morbidity escalates, and lifespan diminishes (7, 8). Approximately 50% of children and adolescents with TDT exhibit growth and puberty disruptions (9). In adolescents and adults with thalassemia major, the prevalence of hypogonadism is 38% in females and 43% in males (10). Delayed puberty is defined as the absence of complete pubertal development in girls by the age of 13, and in boys by the age of 14 years old. Hypogonadism is a condition characterized by insufficient production of sex hormones, such as testosterone in males and estrogen in females, by the gonads (testes in males or ovaries in females). This hormonal deficiency can result in various physical and developmental challenges. In boys, hypogonadism is identified by the lack of testicular enlargement, typically measured as less than 4 ml (11, 12). Testicular enlargement plays a crucial role in puberty, and its absence may cause delays or incompleteness in sexual maturation, impaired muscle development, and other related issues (13). Likewise, in girls, hypogonadism is indicated by the absence of breast development by the age of 16. Breast development, fueled by estrogen, is a fundamental aspect of female puberty. The absence of this development can lead to delays or incompleteness in sexual maturation, including the non-appearance of menstruation and other associated concerns (14). Distinctive manifestations encompass hindered linear growth, lag in skeletal maturity, insufficient weight gain, craniofacial alterations, atypical body proportions, and delayed onset of

puberty. These outcomes arise from a complex interplay of underlying factors (15, 16), including chronic anemia, which reduces oxygen supply to tissues, causing nutritional deficits and cardiac strain, hindering growth (17, 18). The hypermetabolic state resulting from ineffective erythropoiesis can induce growth failure and bone demineralization due to increased metabolic demands (16). Nutrient deficiencies, linked to a hypermetabolic state or chelating agents, in vital nutrients like zinc, folate, and vitamins E and D can hamper growth (16, 19). Iron chelation therapy, while vital for managing iron overload, can lead to growth failure by disrupting endocrine functions and causing malnutrition (20). Moreover, The buildup of iron in the body raises labile iron levels and disrupts the Reactive Oxygen Species (ROS) system, resulting in oxidative stress and causing harm and impairment to cells (21, 22). Endocrinopathies, such as hypogonadism affecting 70-80% of thalassemia major patients, primarily due to iron deposits in the gonads or pituitary, can impact growth. Complications also include hypothyroidism, growth hormone deficiency, and parathyroid issues, often from chronic iron overload or chelation, affecting growth (10). Chronic liver diseases impact growth by affecting nutrient absorption, protein synthesis, and causing hormonal imbalances (23, 24). Additionally, psychological stress can suppress growth hormone secretion and reduce adherence to essential medical treatments (25). The mechanism of growth and puberty defects in thalassemia patients is summarized in **Figure 1**.

For effective management of growth disorders in patients with TDT, healthcare providers must adopt an integrated approach, swiftly identifying and addressing contributory factors. Due to the significant healthcare costs and the preventable nature of many complications, meticulous patient monitoring, strict adherence to treatments, and early problem identification are vital (16). This proactive strategy enhances patient well-being and reduces healthcare costs. This enhances patients' quality of life and curtails treatment expenses (7).

Established national guidelines promise uniform care, prompt interventions, and an emphasis on preventative measures. Creating and applying these guidelines are pivotal for refining patient outcomes and bolstering the effectiveness of healthcare systems. Consequently, this research endeavors to formulate a comprehensive national protocol for diagnosing and addressing growth and puberty anomalies in patients with TDT.

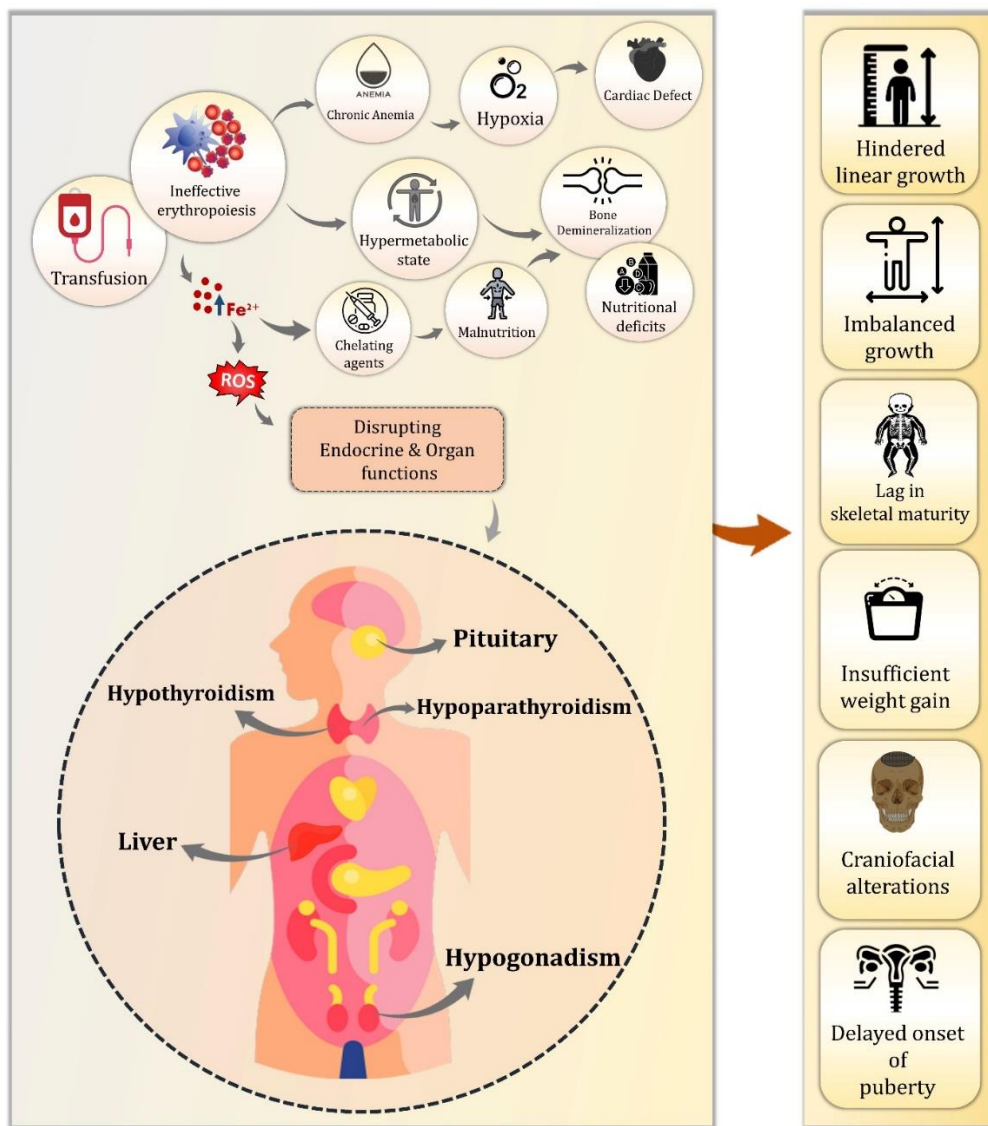


Figure 1. The mechanism of growth and puberty defects in thalassemia patients.

2. METHODS

2.1. Study Design and Objective

This study was conceived to design a comprehensive, evidence-based national guideline to systematically address the myriad of growth and puberty disorders observed in TDT patients.

2.2. Literature Review

A systematic review of available literature was undertaken. We focused on diagnosing and managing growth and

puberty impairments and multifaceted underlying causes in TDT.

2.3. Stakeholder Engagement and Guideline Development

A multidisciplinary team of specialists, including hematologists, endocrinologists, nutritionists, and pediatricians, were consulted. Their insights were instrumental in framing evidence-based recommendations. Central to this was the development of individualized treatment regimens catering to the unique needs of TDT patients.

2.4. Monitoring, Adherence, and Early Detection

Given the implications on the healthcare system and the vital role of early detection, mechanisms were established for rigorous patient monitoring. This involves ensuring treatment adherence, instituting appropriate screenings, and facilitating timely intervention upon detecting disorders.

2.5. Guideline Dissemination and Review

The developed guideline will be disseminated extensively to healthcare professionals and other relevant stakeholders to ensure maximum efficacy. Recognizing the dynamic nature of clinical science, a provision for periodic review and updating of the guideline has been incorporated.

3. ADDRESSING GROWTH ABNORMALITIES IN PATIENTS WITH TDT

3.1. Principles of Growth Rate Screening

To ensure comprehensive evaluation in TDT care, it is important to involve a healthcare professional experienced in TDT care. Consistent and regular monitoring of growth and development should be conducted. This includes documenting growth parameters such as height, weight, and head circumference. Additionally, determining bone age can be done using a left wrist radiograph (26). During assessments, it is crucial to consider patient-specific medical history, disease severity, nutritional status, and iron overload. The results obtained from screenings should inform the development of an individualized treatment strategy tailored to the specific needs of the patient (7, 27).

3.2. Monitoring Schedule

To assess growth and development, it is recommended to refer to the appropriate ethnically adjusted charts from birth. These assessments should be continued every 3-6 months until the end of the growing period, which is typically until 18 years for females and 21 years for males (28).

3.3. Key Milestones

To ensure accurate tracking of growth and development, it is important to record the parents' height during the first visit. For children under two years, measure the recumbent length every 1-3 months. For children over two years, measure standing height every three months (29). Additionally, measure sitting height every six months to

assess for truncal shortening associated with chelator toxicity (30). It is also important to track head circumference and weight every three months. Evaluating growth velocity should be done biannually every three months. Lastly, assess puberty progression using the Tanner classification system every three months (31).

3.4. Growth Velocity Norms:

- 0 to 6 months - 2.5 cm/month
- 7 to 12 months - 1.25 cm/month
- 12 to 24 months - Usually >10 cm/year
- Age two to four years - 5.5 to 9 cm/year.
- Age four to six years - 5 to 8.5 cm/year.
- Age six years to puberty:
 - 4 to 6 cm/year for boys.
 - 4.5 to 6.5 cm/year for girls.

3.5. Referral Criteria to a pediatric endocrinologist for patients with TDT

Common indicators of growth impediments include short stature, which refers to height registering below the 3rd percentile, adjusted for gender and age following national growth standards (32). Another indicator is diminished growth velocity, characterized by annual growth progression measured in centimeters, falling beneath the 10th percentile when categorized by age and sex according to established growth velocity benchmarks (33). Additionally, indicators of potential pituitary hormone insufficiencies, such as gonadotropins, growth hormone, and central hypothyroidism, should be considered. Manifestations suggestive of underlying etiologies contributing to growth impediments can include nutritional insufficiencies, persistent hepatic disorders, or enduring cardiac insufficiency (34).

3.6. Laboratory Screening for GH deficiency

Standard examinations comprise biochemical analysis, thyroid function assessments involving thyroid-stimulating hormone (TSH) and free thyroxine (FT4), bone age determination through X-ray imaging of the wrist and hand, and evaluation of bone mineral density (BMD) (35).

In cases of short stature, it is recommended to measure the levels of IGF-1 (insulin-like growth factor 1) and GFBP3 (insulin-like growth factor-binding protein 3). If the results of IGF-1 or GFBP3 are abnormal or if growth velocity is reduced, it is advised to conduct two growth hormone (GH) stimulation tests (36).

Evaluating the hypothalamic-pituitary-gonadal axis (hypogonadotropic hypogonadism) in individuals with

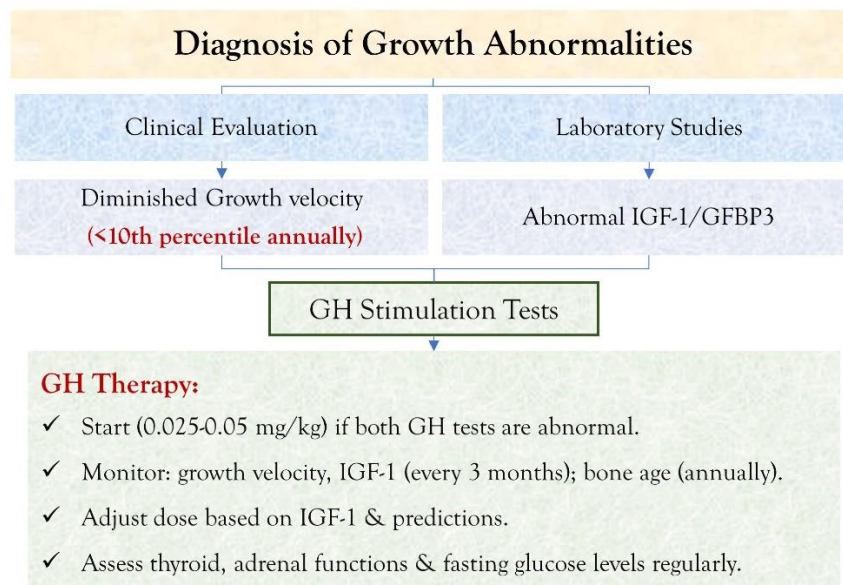


Figure 2. Addressing Growth Abnormalities in Transfusion-dependent Thalassemia

thalassemia major and delayed puberty/hypogonadism highlights the subsequent characteristics: Reduced basal secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). A diminished LH/FSH response to gonadotropin-releasing hormone (GnRH) and irregular disturbance of the spontaneous pulsatile pattern of LH and FSH secretion. Lower baseline levels of sex steroids, including estradiol and testosterone. In specific cases, there is a decline in testosterone secretion in response to human chorionic gonadotropin (HCG). Performing a pelvic ultrasound to evaluate the dimensions of the ovaries and uterus in females (10, 37).

3.7. Treatment and Follow-Up

3.7.1. Growth Hormone Therapy

In case of abnormal results in both GH stimulation tests, start with a daily dose of (0.025-0.05) mg/kg. Continue the treatment as long as the patient demonstrates a positive response (38).

3.7.2. Follow-Up

To ensure effective growth hormone (GH) therapy in patients with transfusion-dependent thalassemia (TDT), the following steps should be taken: Monitor growth velocity and IGF-1 levels every three months to assess treatment response. Adjust the GH dose based on IGF-1 levels, growth response, and growth prediction models. Evaluate bone age annually to monitor skeletal maturation.

Regularly assess thyroid and adrenal functions before and after starting GH therapy due to potential pituitary hormone disruptions in TDT. Perform regular assessments of fasting blood glucose levels before and during the treatment course to monitor the potential risk of exacerbating insulin resistance and developing Type 2 diabetes after initiating GH therapy (39, 40).

4. ADDRESSING PUBERTY DISORDERS

4.1. Diagnosis of Delayed Puberty

Delayed puberty and hypogonadism are the most apparent clinical complications of hemosiderosis in transfusion-dependent thalassemia (TDT) (2, 41). To ensure effective growth hormone (GH) therapy in patients with TDT, the following measures should be implemented: Monitor growth velocity and IGF-1 levels every three months to evaluate the response to treatment. Adjust the GH dose based on IGF-1 levels, growth response, and growth prediction models. Evaluate bone age annually to assess skeletal maturation. Regularly assess thyroid and adrenal functions before and after starting growth hormone therapy due to the potential pituitary hormone disruptions in TDT. Perform regular assessments of fasting blood glucose levels before and during the treatment course to monitor the potential risk of exacerbating insulin resistance and developing Type 2 diabetes after initiating GH therapy (39, 42).

4.2. Tanner staging system

- (both males and females)
 - Stage 1: No hair
 - Stage 2: Downy hair
 - Stage 3: Scant terminal hair
 - Stage 4: Terminal hair that fills the entire triangle overlying the pubic region.
 - Stage 5: Terminal hair that extends beyond the inguinal crease onto the thigh (43).
- **Male External Genitalia Scale**
 - Stage 1: Testicular volume < 4 ml or long axis < 2.5 cm
 - Stage 2: 4 ml-8 ml (or 2.5-3.3 cm long), 1st pubertal sign in males
 - Stage 3: 9 ml-12 ml (or 3.4-4.0 cm long)
 - Stage 4: 15-20 ml (or 4.1-4.5 cm long)
 - Stage 5: > 20 ml (or > 4.5 cm long) (44)
- **Female Breast Development Scale**
 - Stage 1: No glandular breast tissue palpable
 - Stage 2: Breast bud palpable under areola (1st pubertal sign in females)
 - Stage 3: Breast tissue palpable outside areola; no areolar development
 - Stage 4: Areola elevated above the contour of the breast, forming a “double scoop” appearance.
 - Stage 5: The areolar mound recedes back into a single breast contour with areolar hyperpigmentation, papillae development, and nipple protrusion (45).

4.3. Hormonal Treatment Protocols

The management of delayed or arrested puberty and of hypogonadotropic hypogonadism requires consideration of various factors, such as the age of onset, the degree of iron overload, the extent of hypothalamic-pituitary-gonadal axis impairment, the presence of chronic liver disease, and the psychological consequences of hypogonadism (46, 47).

- For boys:
 - Objective: to mimic the normal adolescent development of boys with delayed puberty due to hypogonadism.
 - Initial treatment: starting from 13 years of age, administer testosterone enanthate (or another long-acting testosterone ester) intramuscularly at a dose of 50 mg per month for approximately nine months (range: 6-12 months).

- Subsequent treatment: over the next 3-4 years, gradually increase the dose to the adult replacement dose of 200 mg every 2-3 weeks.
- Initiate replacement therapy in boys with suspected hypogonadotropic hypogonadism by the time their bone age reaches 14 years or less (48).
- Monitoring includes complete blood count (CBC) for all patients and prostate-specific antigen (PSA) for those above 40 years.
- Modify testosterone dose based on hematocrit levels. If the hematocrit level exceeds 54%, the medication should be discontinued for 1-3 months, and the patient should be evaluated for hematocrit increase. If there is no other cause for elevated hematocrit, testosterone can be readministered at a lower dose after hematocrit correction (49).
- For girls:
 - Objective: to simulate the normal adolescent development of girls with ovarian failure.
 - With a firmly established diagnosis of hypogonadism, begin hormonal substitution therapy at 12-13 years of age.
 - Pre-treatment evaluation should include a lipid profile and vascular thrombosis history.
 - Initial treatment: administer ethinyl estradiol 2.5-5 µg orally daily for six months (50).
 - If spontaneous puberty or breakthrough bleeding does not occur within six months from the end of treatment, ethinyl estradiol is re-introduced in gradually increasing dosages (2.5-5 µg daily) every 6 months to a maximum dose of 50 µg of ethinyl estradiol or 0.675 mg of Conjugated estrogen (51).
 - After 12 months of therapy (or sooner if breakthrough bleeding occurs), begin cyclic therapy:
 - Estrogen: for the first 21 days of each month.
 - Progestogen (e.g., medroxyprogesterone acetate 5 mg orally) from the 12th to the 21st day of each month.
 - Gradually increase the dose of estrogen over the next 2-3 years to conjugated estrogen 0.6-1.25 mg or ethinyl estradiol 10-20 mg daily for the first 21 days of each month or estradiol patch (52, 53) .

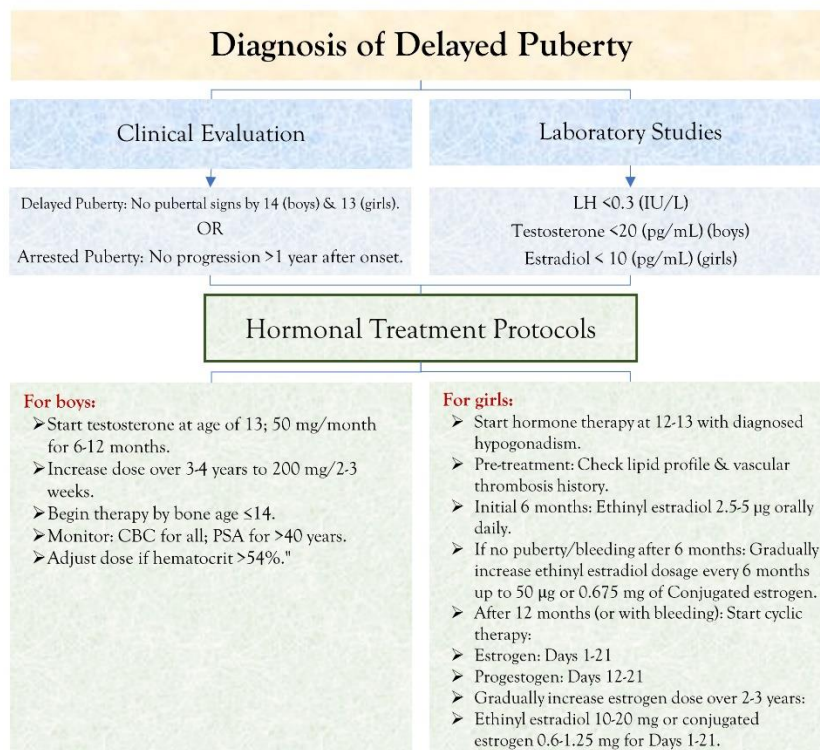


Figure 3. Addressing Puberty Disorders in Transfusion-Dependent Thalassemia

5. FOLLOW-UP AND ANNUAL SCREENING

The following tests and assessments are recommended for evaluating various aspects: Serum thyroid stimulating hormone (TSH) and free thyroxine (FT4) should be measured to assess thyroid function. Additionally, serum levels of calcium, ionized calcium, inorganic phosphate, magnesium, and alkaline phosphatase should be evaluated to assess mineral and bone metabolism. An X-ray of the wrist and hand is recommended to determine bone age. In cases where growth velocity is abnormal, it is advisable to conduct two growth hormone (GH) provocation tests to assess GH secretion (54).

6. RECOMMENDATIONS FOR PREVENTION OF GROWTH AND PUBERTY ABNORMALITIES IN TDT

Ensure meticulous administration of blood transfusions and consistently maintain hemoglobin levels above nine g/dL. Administer iron chelators correctly and aim to keep ferritin levels under 1000 ng/mL to prevent iron overload (55). Opt for using advanced iron chelators that present reduced skeletal side effects for improved treatment outcomes. Address and rectify nutritional imbalances to support overall health and optimize treatment efficacy (56).

Prescribe zinc supplements when a zinc deficiency is detected to address specific nutritional needs and promote well-being (57) (Figure 2, 3).

5. PHYSICIANS AUTHORIZED BY MEDICAL UNIVERSITIES FOR THALASSEMIA CARE AND MEDICATION PRESCRIPTION

- Subspecialists in Pediatric/Adult Hematology and Oncology
- Subspecialists in Pediatric/Adult Endocrinology
- Pediatric Medicine Specialists
- Specialists in Internal Medicine
- General Medical Practitioners

8. CONCLUSION

Thalassemia patients, especially those with TDT, face significant growth and puberty challenges. The presented guideline, derived from comprehensive research and expert input, offers a structured approach for diagnosing, managing, and preventing these challenges, promoting better health outcomes and improved quality of life for Transfusion-Dependent Thalassemia patients.

Conflict of interest

The authors have no financial or personal relationships that could influence or bias their work, or the recommendations provided in the guidelines.

Acknowledgment

The authors would like to thank the Ministry of Health and Medical Education for their support and assistance.

References

- Shafique F, Ali S, Almansouri T, Van Eeden F, Shafi N, Khalid M, Khawaja S, Andleeb S, Hassan MU. Thalassemia, a human blood disorder. *Braz J Biol.* 2021;83:e246062.
- Faranoush M, Faranoush P, Heydari I, Foroughi-Gilvae MR, Azarkeivan A, Parsai Kia A, Sadighnia N, Elahinia A, Zandi A, Rezvany MR, Hashemi-Madani N, Ziaee A, Nekouian R, Rohani F. Complications in patients with transfusion dependent thalassemia: A descriptive cross-sectional study. *Health Science Reports.* 2023;6(10):e1624.
- Ehsanipour F, Faranoush P, Foroughi-Gilvae MR, Sadighnia N, Fallahpour M, Motamedi M, Zandi A, Safaei Z, Zandi A, Faranoush M. Evaluation of immune system in patients with transfusion-dependent beta-thalassemia in Rasoul-e-Akram Hospital in 2021: A descriptive cross-sectional study. *Health Science Reports.* 2022;5(6):e871.
- E. Khamseh M, Malek M, Hashemi-madani N, Ghassemi F, Rahimian N, Ziaee A, Foroughi-Gilvae MR, Faranoush P, Sadighnia N, Elahinia A, Rezvany MR, Faranoush M. Guideline for the diagnosis and treatment of diabetes mellitus in patients with transfusion-dependent thalassemia. *Iranian Journal of Blood and Cancer.* 2023;15(4):293-303.
- Taher AT, Weatherall DJ, Cappellini MD. *Thalassaemia.* *Lancet.* 2018;391(10116):155-67.
- Hashemi-madani N, Rahimian N, Khamseh ME, Faranoush P, Malek M, Ghasemi F, Sadighnia N, Foroughi-Gilvae MR, Alavi SM, Mashayekhnia MJ, Bashizade M, Roudaki Sarvendani MR, Ebrahimi E, Faranoush M. Guideline for the diagnosis and treatment of hypothyroidism and hypoparathyroidism in patients with blood transfusion-dependent thalassemia. *Iranian Journal of Blood and Cancer.* 2023;15(2):89-96.
- Farmakis D, Porter J, Taher A, Domenica Cappellini M, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. *Hemasphere.* 2022;6(8):e732.
- Faranoush P, Elahinia A, Ziaee A, Faranoush M. Review of endocrine complications in transfusion-dependent thalassemia. *Iranian Journal of Blood and Cancer.* 2023;15(4):212-35.
- Angastiniotis M, Lobitz S. Thalassemias: An Overview. *Int J Neonatal Screen.* 2019;5(1):16.
- Srisukh S, Ongphiphadhanakul B, Bunnag P. Hypogonadism in thalassemia major patients. *J Clin Transl Endocrinol.* 2016;5:42-5.
- Front Matter of Volume II. In: Jameson JL, De Groot LJ, de Kretser DM, Giudice LC, Grossman AB, Melmed S, Potts JT, Weir

GC, editors. *Endocrinology: Adult and Pediatric* (Seventh Edition). Philadelphia: W.B. Saunders; 2016. p. i.

12. Grinspon RP, Castro S, Brunello FG, Sansó G, Ropelato MG, Rey RA. Diagnosis of Male Central Hypogonadism During Childhood. *J Endocr Soc.* 2021;5(11):bvab145.

13. Dwyer AA. Psychosexual effects resulting from delayed, incomplete, or absent puberty. *Curr Opin Endocr Metab Res.* 2020;14:15-21.

14. Campbell C, Mallappa A, Wisniewski AB, Silovsky JF. Chapter 6 - Sexual Behavior of Prepubertal Children. In: Bromberg DS, O'Donohue WT, editors. *Handbook of Child and Adolescent Sexuality.* San Diego: Academic Press; 2013. p. 145-70.

15. Arab-Zozani M, Kheyrandish S, Rastgar A, Miri-Moghaddam E. A Systematic Review and Meta-Analysis of Stature Growth Complications in β -thalassemia Major Patients. *Ann Glob Health.* 2021;87(1):48.

16. Bain B. 2021 Guidelines For The Management of Transfusion Dependent Thalassaemia (TDT), 4th Edition. Capellini MD, Farmakis D, Porter J and Taher A (Eds). *Thalassaemia International Federation, 2021, ISBN-13 978-9963-717-18-7. British Journal of Haematology.* 2023;200(4):532-.

17. Manne N, Yadav SK, Gupta BK, Singhal S, Dubey A. Prevalence of hypoparathyroidism, growth retardation in patients of β -thalassemia major. *Age.* 2020;10:25yrs.

18. HASHEMI-JOKANDAN E, KHALAJI A, ABDOLLAHZADEH A, SEPARHAM A. Pulse pressure and inferior wall ST-segment elevation myocardial infarction: investigating mortality, hospital major cardiovascular events, and long-term prognosis.

19. Aslanabadi N, Jangioskouei N, Jafari N, Pakmehr A, Khalaji A, Esmailnejad A, Moslemi M, Khabbazi S. Association of serum vitamin D levels with coronary artery angiographic findings; A cross-sectional study. *Journal of Preventive Epidemiology.* 2023;8(1).

20. Shash H. Non-Transfusion-Dependent Thalassemia: A Panoramic Review. *Medicina.* 2022;58(10):1496.

21. Faranoush P, Jahandideh A, Nekouian R, Mortazavi P. Evaluation of the in vitro and in vivo effect of liposomal doxorubicin along with oncolytic Newcastle disease virus on 4T1 cell line: Animal preclinical research. *Veterinary Medicine and Science.* 2023;9(3):1426-37.

22. Faranoush M, Faranoush P, Heydari I, Foroughi-Gilvae MR, Azarkeivan A, Parsai Kia A, Sadighnia N, Elahinia A, Zandi A, Rezvany MR. Cover Image, Volume 6, Issue 10. *Health Science Reports.* 2023;6(10):e1641.

23. Issam Mohammad I, S. Al-Doski F. Assessment of Liver Functions in Thalassaemia. *Tikrit Journal of Pharmaceutical Sciences.* 2023;8(1):87-95.

24. Nouri-Vaskeh M, Khalili N, Khalaji A, Behnam P, Alizadeh L, Ebrahimi S, Gilani N, Mohammadi M, Madinehzadeh SA, Zarei M. Circulating glucagon-like peptide-1 level in patients with liver cirrhosis. *Archives of Physiology and Biochemistry.* 2023;129(2):373-8.

25. Tarım H, Öz F. Thalassemia Major and Associated Psychosocial Problems: A Narrative Review. *Iran J Public Health*. 2022;51(1):12-8.
26. Manzoor Mughal A, Hassan N, Ahmed A. Bone age assessment methods: a critical review. *Pak J Med Sci*. 2014;30(1):211-5.
27. De Sanctis V, Soliman AT, Elsedfy H, Skordis N, Kattamis C, Angastiniotis M, Karimi M, Yassin MADM, El Awwa A, Stoeva I, Raiola G, Galati MC, Bedair EM, Fiscina B, El Kholly M. Growth and endocrine disorders in thalassemia: The international network on endocrine complications in thalassemia (I-CET) position statement and guidelines. *Indian Journal of Endocrinology and Metabolism*. 2013;17(1):8-18.
28. Ahmad N, Sutan R, Tamil AM, Hajib N. Growth patterns and nutritional status of small for gestational age infants in Malaysia during the first year of life. *Child Health Nurs Res*. 2021;27(4):317-27.
29. de Onis M, Branca F. Childhood stunting: a global perspective. *Maternal & Child Nutrition*. 2016;12(S1):12-26.
30. Tubman VN, Fung EB, Vogiatzi M, Thompson AA, Rogers ZR, Neufeld EJ, Kwiatkowski JL. Guidelines for the Standard Monitoring of Patients With Thalassemia: Report of the Thalassemia Longitudinal Cohort. *J Pediatr Hematol Oncol*. 2015;37(3):e162-9.
31. De Sanctis V, Soliman AT, Elsedfy H, Skordis N, Kattamis C, Angastiniotis M, Karimi M, Yassin MA, El Awwa A, Stoeva I, Raiola G, Galati MC, Bedair EM, Fiscina B, El Kholly M. Growth and endocrine disorders in thalassemia: The international network on endocrine complications in thalassemia (I-CET) position statement and guidelines. *Indian J Endocrinol Metab*. 2013;17(1):8-18.
32. Ghadiany M, Tabarrae M, Salari S, Haghghi S, Rezvani H, Ghasemi SN, Karimi-Sari H. Adding oral pioglitazone to standard induction chemotherapy of acute myeloid leukemia: a randomized clinical trial. *Clinical Lymphoma Myeloma and Leukemia*. 2019;19(4):206-12.
33. Heltshe SL, Borowitz DS, Leung DH, Ramsey B, Mayer-Hamblett N. Early attained weight and length predict growth faltering better than velocity measures in infants with CF. *Journal of Cystic Fibrosis*. 2014;13(6):723-9.
34. Carsote M, Vasiliu C, Trandafir AI, Albu SE, Dumitrascu MC, Popa A, Mehedintu C, Petca RC, Petca A, Sandru F. New Entity-Thalassemic Endocrine Disease: Major Beta-Thalassemia and Endocrine Involvement. *Diagnostics (Basel)*. 2022;12(8).
35. Safaroghli-Azar A, Bashash D, Kazemi A, Pourbagheri-Sigaroodi A, Momeny M. Anticancer effect of pan-PI3K inhibitor on multiple myeloma cells: Shedding new light on the mechanisms involved in BKM120 resistance. *European journal of pharmacology*. 2019;842:89-98.
36. Barffour MA, Bernstein RM, Hinnouho GM, Wessells KR, Arnold CD, Kounnavong S, Hess SY. Insulin-like Growth Factor 1 (IGF1), IGF Binding Protein-3 (IGFBP3) and Growth Response to Daily Zinc Supplementation: A Randomized Trial in Rural Laotian Children. *Nutrients*. 2023;15(11).
37. Soliman AT, elZalabany MM, Ragab M, Abdel Fattah M, Hassab H, Rogol AD, Ansari BM. Spontaneous and GnRH-provoked gonadotropin secretion and testosterone response to human chorionic gonadotropin in adolescent boys with thalassaemia major and delayed puberty. *J Trop Pediatr*. 2000;46(2):79-85.
38. Ngim CF, Lai NM, Hong JY, Tan SL, Ramadas A, Muthukumarasamy P, Thong MK. Growth hormone therapy for people with thalassaemia. *Cochrane Database Syst Rev*. 2020;5(5):Cd012284.
39. Ngim CF, Lai NM, Hong JY, Tan SL, Ramadas A, Muthukumarasamy P, Thong MK. Growth hormone therapy for people with thalassaemia. *Cochrane Database Syst Rev*. 2017;9(9):Cd012284.
40. Ngim CF, Lai NM, Hong JYH, Tan SL, Ramadas A, Muthukumarasamy P, Thong MK. Growth hormone therapy for people with thalassaemia. *Cochrane Database of Systematic Reviews*. 2020(5).
41. De Sanctis V, Soliman AT, Daar S, Di Maio S, Yassin MA, Canatan D, Vives Corrons JL, Elsedfy H, Kattamis A, Kattamis C. The experience of a tertiary unit on the clinical phenotype and management of hypogonadism in female adolescents and young adults with transfusion dependent thalassemia. *Acta Biomed*. 2019;90(1):158-67.
42. Farmakis D, Porter J, Taher A, Domenica Cappellini M, Angastiniotis M, Eleftheriou A, Taskforce* ftTG. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. *HemaSphere*. 2022;6(8):e732.
43. Ge H, Wang X, Yuan X, Xiao G, Wang C, Deng T, Yuan Q, Xiao X. The epidemiology and clinical information about COVID-19. *European Journal of Clinical Microbiology & Infectious Diseases*. 2020;39(6):1011-9.
44. Lei J, Kusov Y, Hilgenfeld R. Nsp3 of coronaviruses: Structures and functions of a large multi-domain protein. *Antiviral research*. 2018;149:58-74.
45. Dawood AA. Mutated COVID-19 may foretell a great risk for mankind in the future. *New microbes and new infections*. 2020;35:100673.
46. De Sanctis V, Soliman AT, Yassin MA, Di Maio S, Daar S, Elsedfy H, Soliman N, Kattamis C. Hypogonadism in male thalassemia major patients: pathophysiology, diagnosis and treatment. *Acta Biomed*. 2018;89(2-s):6-15.
47. Bozzola M, Bozzola E, Montalbano C, Stamati FA, Ferrara P, Villani A. Delayed puberty versus hypogonadism: a challenge for the pediatrician. *Ann Pediatr Endocrinol Metab*. 2018;23(2):57-61.
48. Casale M, Baldini MI, Del Monte P, Gigante A, Grandone A, Origa R, Poggi M, Gadda F, Lai R, Marchetti M, Forni GL. Good Clinical Practice of the Italian Society of Thalassemia and Haemoglobinopathies (SITE) for the Management of Endocrine Complications in Patients with Haemoglobinopathies. *Journal of Clinical Medicine*. 2022;11(7):1826.
49. Cervi A, Balitsky AK. Testosterone use causing erythrocytosis. *Cmaj*. 2017;189(41):E1286-e8.
50. Esmaili S, Safaroghli-Azar A, Pourbagheri-Sigaroodi A, Salari S, Gharehbaghian A, Bashash D. Activation of PPAR γ intensified the effects of arsenic trioxide in acute promyelocytic leukemia through the suppression of PI3K/Akt pathway:

Proposing a novel anticancer effect for pioglitazone. *The International Journal of Biochemistry & Cell Biology*. 2020;122:105739.

51. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis*. 2010;5:11.

52. Vidal A, Dhakal C. Association of Beta-Thalassaemia and Hypogonadotropic Hypogonadism. *Case Rep Obstet Gynecol*. 2022;2022:4655249.

53. Tenbergen G, Wittfoth M, Frieling H, Ponseti J, Walter M, Walter H, Beier KM, Schiffer B, Kruger TH. The neurobiology and psychology of pedophilia: recent advances and challenges. *Frontiers in human neuroscience*. 2015;9:344.

54. Asad ZT, Ghazanfari M, Naleini SN, Sabagh A, Kooti W. Evaluation of serum levels in T3, T4 and TSH in beta-thalassemic

patients referred to the Abuzar hospital in Ahwaz. *Electron Physician*. 2016;8(7):2620-4.

55. Shah N, Mishra A, Chauhan D, Vora C, Shah NR. Study on effectiveness of transfusion program in thalassemia major patients receiving multiple blood transfusions at a transfusion centre in Western India. *Asian J Transfus Sci*. 2010;4(2):94-8.

56. Cianciulli P. Iron chelation therapy in thalassemia syndromes. *Mediterr J Hematol Infect Dis*. 2009;1(1):e2009034.

57. Pinto VM, Forni GL. Management of Iron Overload in Beta-Thalassemia Patients: Clinical Practice Update Based on Case Series. *Int J Mol Sci*. 2020;21(22).