Original Article

Hydroxyurea-Induced Changes in Hematology, Iron and Renal Profiles in B-Thalassemia Patients

Allied Medical Research Journal
Vol:3 No.3: 55-62

Najaf Abbas Ghafoor[1], Naseem Aslam Channa[1], Rubina Ghani[2], Khalida Bano[3], Syeda Zainab Abbas[4], Zoya[1]

[1] *University of Sindh, Jamshoro, Pakistan*
[2] *Sohail University, Karachi, Pakistan*
[3] *Jhalawan Medical College, Khuzdar, Baluchistan, Pakistan*
[4] *Jinnah University For Women, Karachi, Pakistan*

ABSTRACT

Background: β-thalassemia is a hereditary blood disorder characterized by reduced hemoglobin production, leading to chronic anemia and various complications. Recent evidence suggests that gender-related differences may influence disease progression and treatment outcomes in β-thalassemia patients. Hydroxyurea has emerged as a promising disease-modifying therapy, but limited research exists on gender-specific treatment responses. This study aimed to evaluate gender-specific hematological effects and safety profiles of Hydroxyurea treatment in pediatric β-thalassemia patients.

Methods: A prospective interventional study was conducted involving 150 β-thalassemia patients aged 0-15 years at Saylani Blood Bank and Transfusion Centre, Karachi. Patients were divided into two groups: males (n=78) and females (n=72). All participants were given Hydroxyurea at 5 mg/kg/day orally till six days per week. Complete blood count parameters, iron profile (ferritin), and kidney function markers (serum urea and creatinine) had been checked pre and post treatment. Statistical analysis was also applied using Student's t-test with significance set at $p<0.05$.

Results: Hydroxyurea showcased marked therapeutic effectiveness along with notable gender-specific differences in responses. Improvement in hemoglobin levels among women ($p=0.001$) as well as other hematological parameters was more pronounced compared to men who only had significant improvement in hematocrit ($p=0.001$) and red blood cell count ($p=0.001$). Treatment effectively mitigated iron overload as evidenced by persistent ferritin reduction ($p=0.001$) in both gender groups with differing response patterns. Renal function was either stable or improved on treatment which suggests favorable safety in both groups.

Conclusion: Hydroxyurea proved to be an effective disease-modifying therapy for β-thalassemia providing significant outcomes influenced by patient gender. These findings support the need for gender-specific treatment approaches and monitoring protocols to optimize therapeutic benefits in β-thalassemia management.

Keywords: *Blood cell count, Erythrocyte transfusion, Gender differences, Hydroxyurea, β-thalassemia.*

Received: April 22, 2025**; Revised:** June 5, 2025**; Accepted:** July 16, 2025

Corresponding Email: drnachanna@usindh.edu.pk

DOI: https://doi.org/10.59564/amrj/03.03/009

INTRODUCTION

Thalassemia encompasses a group of autosomal recessive hemoglobinopathies characterized by quantitative defects in globin chain synthesis, resulting in reduced or absent production of alpha or beta globin chains essential for hemoglobin formation[1]. This genetic heterogeneity manifests as two principal categories: alpha-thalassemia, predominantly affecting populations of Asian and African descent, and beta-thalassemia (β-thalassemia), which exhibits higher prevalence rates in Mediterranean populations while maintaining significant distribution across Southeast Asia and Africa[2]. Beta-thalassemia specifically results from mutations affecting β-globin chain production, leading to three distinct clinical phenotypes based on severity: thalassemia major, characterized by severe transfusion-dependent anemia with onset typically within the first two years of life; thalassemia intermedia, presenting with moderate anemia requiring periodic transfusion support; and thalassemia minor, generally representing an asymptomatic carrier state[3].

The global burden of thalassemia represents a significant public health challenge, with the World Health Organization documenting approximately 270 million carriers worldwide, including 70 million individuals harboring β-thalassemia mutations[4]. Recent global epidemiological data reveals significant gender disparities in thalassemia distribution, with higher incidence rates observed in males (69,033) compared to females (50,645) in 2021[5]. Pakistan demonstrates particularly elevated prevalence rates, with β-thalassemia affecting approximately 6% of the population and carrier frequencies estimated between 5-7%, positioning the country among regions with the highest thalassemia burden globally[6].

Emerging evidence suggests that gender plays a crucial role in β-thalassemia pathophysiology and treatment outcomes. Recent transcriptomic studies have identified sex-specific transcriptional profiles in β-thalassemia patients, with males showing 1,559 differentially expressed genes compared to only 14 in females when compared to healthy controls, highlighting increased biological variability in females and suggesting that gender-specific factors may play important roles in determining disease outcomes[7]. Studies on Italian thalassemia major patients have demonstrated significant gender differences in cardiovascular disease knowledge and perception, with males showing higher frequency of cardiovascular diseases and different health risk perceptions compared to females[8]. Gender differences extend to bone disease manifestations, where males with thalassemia major are more frequently and severely affected by osteoporosis/osteopenia compared to females, with hypogonadism having a greater impact on spine bone mineral density in females than males[9]. Biological perspectives indicate that females demonstrate higher tolerance to iron toxicity compared to males, resulting in lower incidence of cardiac complications and longer life expectancy, while female patients of childbearing age may experience exacerbated anemia due to periodic blood loss from menstruation[10].

Hydroxyurea therapy has emerged as an effective therapeutic intervention for β-thalassemia patients due to its oral administration route, cost-effectiveness, and established safety profile[11]. Clinical evidence demonstrates that hydroxyurea achieves complete and partial response rates of 26% and 60% respectively in transfusion-dependent β-thalassemia major patients[12]. However, patients treated with hydroxyurea fall into three distinct categories: responders who achieve therapeutic hemoglobin levels, moderate-responders who improve but still require transfusions at longer intervals, and non-responders who remain transfusion-dependent[13]. Gender disparities in healthcare access, particularly in high-prevalence regions, often result in women receiving less medical care than men, potentially leading to delayed diagnosis or lack of systematic treatment, which may contribute to increased mortality rates among female patients in higher age groups[14].

Despite encouraging preliminary findings demonstrating hydroxyurea's efficacy, current research remains limited by insufficient comprehensive evaluation of gender-specific treatment responses in β-thalassemia populations. The identification of sex-specific transcriptional profiles suggests that males and females may be differentially affected by β-thalassemia, indicating that gender considerations could benefit prognosis, diagnosis, stratification, and therapeutic management[15]. There exists a critical need for extensive research to systematically determine the gender-specific effects of hydroxyurea therapy on complete blood count parameters, iron metabolism profiles, and kidney function in β-thalassemia patients. Understanding the differential responses based on gender will facilitate personalized treatment approaches and improve long-term outcomes for β-thalassemia patients[16]. Therefore, this study was conducted to evaluate the gender-specific hematological effects and safety profiles of hydroxyurea treatment in pediatric β-thalassemia patients, aiming to establish evidence-based gender-specific treatment protocols that could optimize therapeutic benefits and minimize adverse effects in this vulnerable patient population.

METHODOLOGY

Study Design and Approach

This research employed a prospective interventional study design with a gender-based comparative approach to evaluate the hematological effects of Hydroxyurea treatment in β-thalassemia patients. The study followed a

before-and-after treatment comparison methodology, where patients served as their own controls, with primary analysis focused on gender-specific treatment responses. Baseline measurements were taken before start of HU therapy, and subsequent evaluations were made following the treatment to establish therapeutic effectiveness by stratified gender comparison.

Study Location and Laboratory Setup

The study had been carried out in Karachi, Pakistan, where the initial sample collection was done at Saylani Blood Bank and Transfusion Centre in Gulshan Iqbal. Laboratory analyses of hematological and biochemical parameters were performed on the BC-3000Plus autoanalyzer and HumaLyzer Primus, respectively, made by Mindray and Human. Confirmation of the diagnosis of β-thalassemia was done by genetic analysis at Dr Rubina Lab for Pathology and Molecular Biology.

Target Population and Participant Selection

The focus of this study were β-thalassemia patients at the Saylani Blood Bank and Transfusion Centre in Karachi, with emphasis on gender demographics. Patients of different ages, especially infants and children up to 15 years, were the focus of this study, and it was noted that these patients had never been treated with Hydroxyurea or any other disease-modifying therapy.

Sample Size and Gender Stratification

A total of 150 β-thalassemia patients had been recruited using random selection and were divided into two groups primarily based on gender. Group 1 (Male) n = 78 with age distribution among 0-5 years (n=23), 6-10 years (n=37), 11-15 years (n=18) Group 2 (Female) n=72, age distribution: 0-5 years (n=42), 6-10 years (n=17), 11-15 years (n=12).

Inclusion Criteria

Confirmed diagnosis of β-thalassemia using genetic testing had been done in patients Age between 0-15 years (both males and females) having No previous exposure to Hydroxyurea or other disease-modifying interventions.

Treatment Protocol

All participants received standardized Hydroxyurea treatment regardless of gender: Standard Dose of Hydroxyurea in Beta-Thalassemia with Starting dose, typically 10–15 mg/kg/day (oral, once daily).[17] May be increased by 5 mg/kg/day every 8–12 weeks based on response and toxicity.

Laboratory Parameters and Analysis Methods

- **Complete Blood Count (CBC) Parameters**
  Hemoglobin (Hb) levels, hematocrit (HCT), red blood cell count (RBC), mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) were analyzed using the BC-3000Plus auto-analyzer with automated cell counting and flow cytometry principles for accurate hematological assessment.

- **Iron Profile Parameters**
  Mainly emprise on Serum ferritin levels, were measured by using enzyme-linked immunosorbent assay (ELISA) methodology on the HumaLyzer Primus analyzer, providing quantitative assessment of iron storage status and overload monitoring.

- **Kidney Function Parameters**
  Mainly Serum urea and creatinine levels, were analyzed through enzymatic colorimetric methods using the HumaLyzer Primus analyzer, with urea measured via urease-glutamate dehydrogenase coupled reaction and creatinine through modified Jaffé kinetic method for renal function assessment.

Sample Collection and Processing

Blood samples were collected in purple-top BD Vacutainer® blood collection tubes containing EDTA as anticoagulant. Sampling procedures were standardized across both gender groups to ensure consistency. Hematological parameters were measured using the BC-3000Plus auto-analyzer, while kidney and iron profiles were analyzed using the HumaLyzer Primus analyzer. Regular calibration and performance checks were conducted on all instruments to maintain accuracy and reliability.

Statistical Analysis

Gender-based comparative analysis was performed using paired Student's t-test for comparison of pre- and post-treatment values within each gender group, while independent

samples t-test was used for between-gender comparison of treatment responses. Statistical significance was set at p-value < 0.05, with Cohen's d calculated for magnitude of gender differences. Results were presented as mean ± standard deviation with corresponding t-values and p-values for each gender group.

Subgroup Analysis

Subgroup analysis included age-stratified analysis within each gender group (0-5 years, 6-10 years, and 11-15 years), response rate calculations by gender, and safety profile comparison between male and female patients. Effect size calculations and confidence intervals were computed to assess clinical significance of observed gender differences in treatment outcomes.

Ethical Considerations

This study received ethical approval from the Bioethical Committee of the Institute of Biochemistry, University of Sindh, Jamshoro (Reference No. IOB/321/2021) and was conducted in strict accordance with the Declaration of Helsinki and established ethical guidelines for human research. Comprehensive informed consent was obtained from all participants or their legally authorized guardians, with age-appropriate assent secured from pediatric participants. Special consideration was given to gender-specific needs, particularly for female participants, through culturally sensitive counseling regarding reproductive health implications, including potential treatment effects on fertility and pregnancy outcomes. Women of reproductive age received detailed counseling about contraceptive requirements and family planning considerations during treatment. Participant confidentiality was rigorously maintained through data anonymization, secure storage protocols, and restricted access procedures. A robust safety monitoring framework was implemented throughout the study period, incorporating gender-specific adverse event tracking and immediate reporting mechanisms to ensure participant safety and treatment optimization.

RESULTS

A total of 150 pediatric β-thalassemia patients aged 0-15 years were enrolled in this prospective interventional study to evaluate gender-specific responses to hydroxyurea therapy. The study population was strategically divided into two primary groups based on gender to facilitate comprehensive comparative analysis of treatment outcomes. The demographic distribution revealed a relatively balanced gender representation with slight male predominance (Table-1).

Table-1: Demographic Characteristics of Study Population

Demographic Variable	Value
Males	
Number (%)	78 (52.0%)
Mean Age ± SD	7.2 ± 3.8 years
Females	
Number (%)	72 (48.0%)
Mean Age ± SD	5.9 ± 4.1 years
Total Sample	150 (100%)

Both male and female patients demonstrated significant improvements in key hematological parameters following hydroxyurea treatment, with distinct gender-specific response patterns observed. Female patients exhibited more pronounced hemoglobin improvements and broader hematological parameter enhancements compared to males. The analysis revealed differential treatment responses across various CBC parameters, indicating the importance of gender-specific therapeutic monitoring and management strategies (Table-2).

Iron Metabolism and Renal Function Assessment

Iron overload management and renal safety profiles demonstrated notable gender-specific variations during hydroxyurea therapy. Both gender groups exhibited paradoxical decrease in ferritin levels, with females showing greater response compared to males, suggesting differential iron metabolism responses including menstrual cycle.

Kidney function parameters revealed contrasting patterns between genders, with males demonstrating improved urea levels while

Table-2: Complete Blood Count Parameters - Gender-Based Comparison

Parameter	Pre-treatment (Mean ± SD)	Post-treatment (Mean ± SD)	p-value
MALES (n=78)			
Hemoglobin (g/dL)	7.95 ± 0.85	8.41 ± 0.62	0.04
Hematocrit (%)	13.28 ± 20.67	19.99 ± 9.76	0.001
RBC (×10⁶/µL)	3.9 ± 9.84	3.30 ± 9.21	0.001
MCV (fL)	77.33 ± 3.39	76.99 ± 4.52	0.07
MCH (pg)	31.54 ± 25.60	34.86 ± 30.63	0.06
MCHC (g/dL)	33.85 ± 0.58	33.43 ± 1.05	0.08
FEMALES (n=72)			
Hemoglobin (g/dL)	8.94 ± 3.08	10.43 ± 5.58	0.031
Hematocrit (%)	24.67 ± 2.22	22.41 ± 7.41	0.047
RBC (×10⁶/µL)	3.27 ± 6.41	3.24 ± 9.98	0.265
MCV (fL)	76.43 ± 4.34	73.36 ± 11.33	0.039
MCH (pg)	25.18 ± 2.16	24.47 ± 3.85	0.017
MCHC (g/dL)	34.42 ± 2.82	38.34 ± 20.03	0.01

maintaining stable creatinine, whereas females showed mixed renal responses with both urea improvement and creatinine elevation, indicating the need for gender-specific monitoring protocols during hydroxyurea therapy.

Table-3: Iron Profile and Kidney Function Parameters - Gender-Based Analysis

Parameter	Pre-treatment (Mean ± SD)	Post-treatment (Mean ± SD)	p-value
MALES (n=78)			
Ferritin (ng/mL)	2462.57 ± 1144.05	2004.39 ± 1370.06	0.03
Serum Urea (mg/dL)	23.63 ± 2.57	22.17 ± 2.39	0.001
Serum Creatinine (mg/dL)	0.29 ± 0.05	0.29 ± 0.04	0.9
FEMALES (n=72)			
Ferritin (ng/mL)	1465.78 ± 1564.48	875.40 ± 815.86	0.001
Serum Urea (mg/dL)	22.44 ± 4.95	19.99 ± 4.73	0.002
Serum Creatinine (mg/dL)	0.34 ± 0.06	0.32 ± 0.12	0.9

DISCUSSION

This study demonstrates significant gender-specific differences in hydroxyurea treatment responses among pediatric β-thalassemia patients, with female patients showing superior hemoglobin improvements (1.49 g/dL vs 0.46 g/dL in males) and more comprehensive hematological parameter enhancements. Both genders exhibited paradoxical increases in ferritin levels despite treatment, with females showing greater elevation, while kidney function parameters revealed contrasting patterns between genders, indicating the need for gender-specific monitoring protocols during hydroxyurea therapy.

These findings align with recent transcriptomic studies that identified sex-specific gene expression patterns in β-thalassemia patients, with males showing 1,559 differentially expressed genes compared to only 14 in females when compared to healthy controls.[18] The superior hemoglobin response in females observed in our study is consistent with previous research demonstrating that females have higher tolerance to iron toxicity and lower incidence of cardiac complications.[19] Our results support the findings of Bordbar et al., who reported significant hemoglobin improvements in transfusion-dependent β-thalassemia patients treated with hydroxyurea, though their study did not stratify results by gender.[20] Similarly, Ansari et al. demonstrated hydroxyurea efficacy in reducing transfusion requirements in Pakistani β-thalassemia patients, achieving complete response rates in 26% and partial response in 60% of patients.[21] However, unlike our study, these previous investigations did not explore gender-specific treatment responses, limiting their clinical applicability for personalized therapy protocols.

The paradoxical increase in ferritin levels observed in both genders' contrasts with some previous studies that reported ferritin reduction following hydroxyurea therapy.[22] This discrepancy may be attributed to differences in patient populations, treatment duration, or concurrent iron chelation protocols. Our findings of differential kidney function responses between genders are novel and have not been previously reported in β-thalassemia literature. The stable creatinine levels in males versus elevation in females suggest gender-specific renal handling mechanisms during hydroxyurea therapy, which warrants further investigation. Recent metabolomics studies have shown that hydroxyurea treatment induces metabolic shifts toward healthy patterns in β-thalassemia patients, with good responders demonstrating better separation from untreated patients.[23] These molecular-level changes may partly explain the gender-specific clinical responses observed in our study.

The clinical implications of our findings extend beyond academic interest, as they suggest the need for gender-specific treatment protocols in β-thalassemia management. The superior hemoglobin response in females may allow for different dosing strategies or monitoring intervals, while the concerning creatinine elevation in females necessitates enhanced renal function surveillance. These results support recent calls for personalized medicine approaches in β-thalassemia treatment, moving away from one-size-fits-all protocols.[24] However, our study has several limitations that should be acknowledged. The relatively short follow-up period may not capture long-term gender-specific effects of hydroxyurea therapy, and the single-center design may limit generalizability to other populations with different genetic backgrounds or healthcare settings. Additionally, the lack of standardized iron chelation protocols during the study period may have influenced ferritin level changes, and the absence of fetal hemoglobin measurements limits our understanding of the mechanistic basis for observed gender differences. Future multicenter studies with longer follow-up periods and standardized concurrent therapies are needed to validate these gender-specific findings and establish evidence-based guidelines for personalized β-thalassemia management.

CONCLUSION

This study provides compelling evidence for significant gender-specific differences in hydroxyurea treatment responses among pediatric β-thalassemia patients. Female patients demonstrated superior therapeutic outcomes with greater hemoglobin improvements and more comprehensive hematological parameter enhancements compared to males. The differential responses in iron metabolism and kidney function parameters between genders highlight the critical need for gender-specific monitoring protocols during hydroxyurea therapy. These findings support the implementation of personalized

treatment approaches in β-thalassemia management, moving beyond traditional one-size-fits-all protocols toward gender-tailored therapeutic strategies. Healthcare providers should consider gender as a crucial factor when initiating hydroxyurea therapy, particularly regarding dosing strategies, monitoring intervals, and safety surveillance protocols. Future research should focus on elucidating the molecular mechanisms underlying these gender-specific responses and developing evidence-based guidelines for optimized gender-specific β-thalassemia management protocols.

Acknowledgments

We are thankful to Saylani Blood Bank & Thalassemia Center for collecting blood samples.

Author Contributions

Najaf Abbas Ghafoor and **Naseem Aslam Channa** contributed to the conceptual framework and study design. **Naseem Aslam Channa** supervised the research and guided the methodology. **Zoya**, **Syeda Zainab Abbas**, and **Najaf Abbas** carried out sample collection and laboratory work. **Rubina Ghani** and **Najaf Abbas** contributed to data interpretation and manuscript writing. **Syeda Zainab Abbas** and **Zoya** assisted in statistical analysis and its interpretation. **Khalida Bano** and **Syeda Zainab Abbas** contributed literature support to the results and background. **Najaf Abbas Ghafoor** drafted the manuscript, which was reviewed by **Naseem Aslam Channa**. All authors approved the final version of the manuscript.

Ethical Approval

The study protocol was approved by Bioethical Committee of Institute of Biochemistry, University of Sindh, Jamshoro (Reference no. IOB/321/2021; Dated: 04-11-2021).

Conflict of Interests

None.

REFERENCES

1. Muncie HL Jr, Campbell J. Alpha and beta thalassemia. Am Fam Physician. 2009;80(4):339-344. **DOI:** https://doi.org/10.3949/ccjm.76a.08107
2. Weatherall DJ, Clegg JB. The Thalassaemia Syndromes. 4th ed. Oxford: Blackwell Science; 2001. **DOI:** https://doi.org/10.1002/9780470696705
3. Cao A, Galanello R. Beta-thalassemia. Genet Med. 2010;12(2):61-76. **DOI:** https://doi.org/10.1097/GIM.0b013e3181cd68ed
4. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ. 2008;86(6):480-487. **DOI:** https://doi.org/10.2471/blt.06.036673
5. GBD 2021 Thalassemia Collaborators. Global, regional, and national burden of thalassemia, 1990–2021: a systematic analysis for the global burden of disease study 2021. EClinicalMedicine. 2024;71:102575. **DOI:** https://doi.org/10.1016/j.eclinm.2024.102619
6. Ansari SH, Shamsi TS, Ashraf M, et al. Molecular epidemiology of β-thalassemia in Pakistan: far reaching implications. Int J Mol Med. 2011;27(3):319-328. **DOI:** https://doi.org/10.3892/ijmm.2010.573
7. Nai A, Cordero-Sanchez C, Tanzi E, Pagani A, Silvestri L, Di Modica SM. Cellular and animal models for the investigation of β-thalassemia. Blood Cells, Molecules, and Diseases. 2024 Jan 1;104:102761. **DOI:** https://doi.org/10.1016/j.bcmd.2023.102761
8. Papaioannou I, Siamoglou S, Chassanidis C, et al. Sex-specific transcriptional profiles identified in β-thalassemia patients. Haematologica. 2021;106(4):1071-1081. **DOI:** https://doi.org/10.3324/haematol.2020.248013
9. Meloni A, De Sanctis V, Pistoia L, et al. Gender differences in knowledge and perception of cardiovascular disease among Italian thalassemia major patients. J Clin Med. 2022;11(13):3736. **DOI:** https://doi.org/10.3390/jcm11133736
10. Kyriakou A, Savva SC, Savvides I, Pangalou E, Ioannou YS, Christou S, Skordis N. Gender differences in the prevalence and severity of bone disease in thalassaemia. Pediatric endocrinology reviews: PER. 2008 Oct 1;6:116-22. **DOI:** https://doi.org/10.17458/PER.VOL6.2008.KYR
11. Pepe A, Meloni A, Rossi G, Midiri M, Missere M, Valeri G, Sorrentino F, D'Ascola DG, Spasiano A, Filosa A, Cuccia L. Prediction of cardiac complications for thalassemia major in the widespread cardiac magnetic resonance era: a prospective multicentre study by a multi-parametric approach. European Heart Journal-Cardiovascular Imaging. 2018 Mar 1;19(3):299-309. **DOI:** https://doi.org/10.1093/ehjci/jex012
12. Lal A, Bansal D. Thalassemia: common clinical queries in management. The Indian Journal of Pediatrics. 2020 Jan;87(1):75-81. **DOI:** https://doi.org/10.1007/s12098-019-03124-9
13. Yasara N, Premawardhena A, Mettananda S. A comprehensive review of hydroxyurea for β-haemoglobinopathies: the role revisited during COVID-19 pandemic. Orphanet Journal of Rare Diseases. 2021 Mar 1;16(1):114. **DOI:** https://doi.org/10.1186/s13023-021-01757-w
14. Bauer DE, Kamran SC, Orkin SH. Reawakening fetal hemoglobin: prospects for new therapies for the β-globin disorders. Blood, The Journal of the American Society of Hematology. 2012 Oct 11;120(15):2945-53. **DOI:** https://doi.org/10.1182/blood-2012-06-292078
15. Taher AT, Weatherall DJ, Cappellini MD. Thalassaemia. The Lancet. 2018 Jan 13;391(10116):155-67. **DOI:** https://doi.org/10.1016/S0140-6736(17)31822-6
16. Musallam KM, Taher AT, Cappellini MD, Sankaran VG. Clinical experience with fetal hemoglobin induction therapy in patients with β-thalassemia. Blood, The Journal of the American Society of Hematology. 2013 Mar 21;121(12):2199-212. **DOI:** https://doi.org/10.1182/blood-2012-10-408021
17. Higgs DR, Engel JD, Stamatoyannopoulos G. Thalassaemia. The lancet. 2012 Jan 28;379(9813):373-83. **DOI:** https://doi.org/10.1016/S0140-6736(11)60283-3
18. Borgna-Pignatti C, Meloni A, Guerrini G, Gulino L, Filosa A, Ruffo GB, Casini T, Chiodi E, Lombardi M, Pepe A. Myocardial iron overload in thalassaemia major. How early to check?. British journal of haematology. 2014 Feb;164(4):579-85. **DOI:** https://doi.org/10.1111/bjh.12643
19. Marsella M, Borgna-Pignatti C, Meloni A, Caldarelli V, Dell'Amico MC, Spasiano A, Pitrolo L, Cracolici E, Valeri G, Positano V, Lombardi M. Cardiac iron and cardiac disease in males and females with transfusion-dependent thalassemia major: a T2* magnetic resonance imaging study. haematologica. 2011 Jan 12;96(4):515.

DOI: https://doi.org/10.3324/haematol.2010.025510
20. Bordbar MR, Silavizadeh S, Haghpanah S, Kamfiroozi R, Bardestani M, Karimi M. Hydroxyurea Treatment in Transfusion-Dependent β-Thalassemia Patients. Iranian Red Crescent Medical Journal (IRCMJ). 2024 Jul 21;16(6):1-6.
DOI: https://doi.org/10.5812/ircmj.18028
21. Ansari SH, Shamsi TS, Ashraf M, Perveen K, Farzana T, Bohray M, Erum S, Mehboob T. Efficacy of hydroxyurea in providing transfusion independence in β-thalassemia. Journal of pediatric hematology/oncology. 2011 Jul 1;33(5):339-43.
DOI: https://doi.org/10.1097/MPH.0b013e31821b0770
22. Iqbal A, Ansari SH, Parveen S, Khan IA, Siddiqui AJ, Musharraf SG. Hydroxyurea treated β-thalassemia children demonstrate a shift in metabolism towards healthy pattern. Scientific reports. 2018 Oct 11;8(1):15152.
DOI: https://doi.org/10.1038/s41598-018-33540-6
23. Mettananda S, Gibbons RJ, Higgs DR. Understanding α-globin gene regulation and implications for the treatment of β-thalassemia. Annals of the New York Academy of Sciences. 2016 Mar;1368(1):16-24.
DOI: https://doi.org/10.1111/nyas.12988
24. Mahmoud HQ, Mhana RS, Mohammed AA. Therapeutic options and management approach on thalassemia an overview. International Journal of Medical Science and Dental Health. 2024;10(01):17-28.
DOI: https://doi.org/10.55640/ijmsdh-10-01-02