Defining Pathological Iron Status in Children with Thalassemia

Bashar Sh. Mustafa
College of Medicine, Ninevah University, Mosul, Iraq
Corresponding author: Bashar.mustafa@uoninevah.edu.iq

Received 27-11-2022 Accepted 18-12-2022

ABSTRACT:

The purpose of this review is to summarize the recent knowledge that has been gathered, allowing a better understanding of iron status in children with thalassemia. Children with thalassemia major typically have severe anemia during the first two stages of life and receive regular red blood cell (RBC) transfusions. The results show that individuals with thalassemia major who are overtly or inadequately transfused have significant body changes that affect physical growth retardation, hostility, weak musculature, leg muscle fitness, extramedullary development of hematopoiesis, and bone expansion, as seen in some developing countries. Cases of thalassemia intermedia occur late and have mild anemia, and cannot tolerate regular blood transfusions. Treatment for thalassemia major includes regular red blood cell transfusions, iron chelating drugs, and bone marrow surgery. In addition, spleen scanning may be necessary in some cases. Also, a bone marrow transplant is the only definitive treatment currently available. The prognosis for patients with beta-thalassemia has improved most over the past 25 years, mostly due to recent medical advances in blood transfusions, iron-chelating drugs, and bone marrow transplants. However, heart disease (heart disease) has been found to remain the leading cause of death in iron-related cases.

Keywords: Thalassemia, pediatric, Iron, Chelating agents, Blood transfusion.

تعريف مستوى الحديد السام عند الأطفال المصابين بالثلاسيميا

الخلاصة:

الغرض من هذه المراجعة هو تلخيص المعرفة الحديثة التي تم جمعها ، مما يسمح بفهم أفضل لحالة الحديد لدى الأطفال المصابين بالثلاسيميا. عادة ما يعاني الأطفال المصابون بالثلاسيميا الكبرى من فقر الدم الوخيم خلال المرحلتين الأوليين من الحياة ويتلقون عمليات نقل منتظمة لخلايا الدم الحمراء .تظهر النتائج أن الأفراد المصابين بالثلاسيميا الكبرى الذين يتم نقلهم الدم لهم بشكل كاف تظهر لديهم تغيرات كبيرة في الجسم تؤثر على تأخر النمو البدني ، والعداء ، وضعف العضلات ، ولياقة عضلات الساق ، وتطور تكون الدم خارج النخاع ، وتوسع العظام ، كما رأينا في بعض البلدان النامية. تحدث حالات الثلاسيميا البينية في وقت متأخر وتؤدي الى فقر الدم الخفيف ولا يمكنها تحمل عمليات نقل الدم المنتظمة. يشمل علاج الثلاسيميا الكبرى عمليات نقل خلايا الدم الحمراء بانتظام والأدوية المخلبة للحديد وجراحة نخاع العظام. بالإضافة إلى ذلك ، قد يكون استئصال الطحال ضروريا في بعض الحالات. أيضا ، زرع نخاع العظم هو العلاج النهائي الوحيد المتاح حاليا. تحسن تشخيص مرضى الثلاسيميا بيتا أكثر على مدى السنوات ال 25 الماضية ، ويرجع ذلك في الغالب إلى التطورات الطبية الحديثة في عمليات نقل الدم ، والأدوية المخلبة للحديد ، وزرع نخاع العظام. ومع ذلك ، فقد وجد أن أمراض القلب لا تزال السبب الرئيسي للوفاة في الحالات المرتبطة بالحديد.

الكلمات المفتاحية: الثلاسيميا، الأطفال، الحديد، عمليات نقل الدم

INTRODUCTION:

Thalassemia is a group of diseases that are inherited in an autosomal recessive manner and involve the loss of a product of structurally normal hemoglobin chains. The clinical picture of thalassemia ranges from fatal to asymptomatic and depends on the degree of genetic defect. The hematological picture usually shows microcytic and hypochromic hemolytic anemia, which is mild compared to the microcytosis of heterozygotes and does not show a decrease in the normal erythrocyte count (2). Recognizing that thalassemia, is indeed mild, is important in terms of hereditary ease, and it is important to distinguish it from iron deficiency. Special examinations are only required in special cases.

The disease picture of thalassemia varies from asymptomatic to fatal and depends on where and how many genes the mutation occurs and what that abnormality is. Especially in endemic areas, a person can inherit from one parent an alpha and from the other beta globin gene or a mutation causing hemoglobinopathy, which increases the variations in symptoms and findings (3). On the other hand, there can be big differences in the clinical picture of people with the same mutation.

Alpha thalassemia manifests already in the fetal period, even the severe forms of beta thalassemia at the earliest at 2-3 months of age (1). The common thing is that the hemoglobin deficiency that occurs as a result of a synthesis disorder leads to hypochromic and microcytosis of red blood cells. Anemia occurs on the one hand as a result of reduced production of red blood cells and on the other hand as a result of increased breakdown.

Thalassemia in minor children is easily confused with mild iron deficiency, but it is already possible to make the distinction with a careful examination of the anamnestic data and the basic blood count. The biochemical indicators of iron status, serum soluble transferrin receptor, and ferritin concentrations help in the differential diagnosis (3) (1). The erythrocyte morphology does not provide decisive additional help, although the abundance of target cells, and poikilocytosis, and basophilic spots in the erythrocytes are more suggestive of thalassemia minor. Although thalassemia is associated with a tendency to accumulate iron, the carrier can still be iron deficient. Biochemical methods are needed to prove it. Serum ferritin concentration is a good measure of iron stores if the patient does not have an infection, inflammation, a tumor, or liver damage. The concentration of soluble transferrin receptors increases in iron deficiency. However, the concentration is also increased in erythrocyte hyperplasia, which limits its discriminating ability in thalassemia. It is useful to know the age-appropriate reference values for hemoglobin concentration and MCV in the thalassemia minor population.

In beta thalassemia major (sometimes called Cooley's anemia), people have severe symptoms of anemia, such as fatigue, weakness, and shortness of breath, and they may also have jaundice, which causes yellowing of the skin and whites of the eyes, ulcers in the skin, and gallstones. Children with beta thalassemia major tend to grow more slowly and reach puberty later than normal cycle (6). Since iron absorption can increase rapidly and frequent blood transfusions are needed (providing, even more, iron), excess iron can accumulate and deposit in the heart muscles, eventually causing iron load disease, heart failure, and early death.

Iron normal physiology:

The physiology of iron metabolism has been well evaluated over the last 20 years. Iron absorption in the stomach is very low. The low pH of gastric secretion, vitamin C, sulfhydryl groups and other reducing agents reduce trivalent iron to bivalent iron in foods. As a matter of fact, iron deficiency anemia (anemia) that develops as a result of the removal of a part of the stomach is quite common in humans (6). Most of the iron is absorbed in the upper parts of the small intestine. $NaHCO_3$ (sodium bicarbonate) released from the pancreas neutralizes the acid pH in the duodenum and converts bivalent iron to trivalent iron. This trivalent iron is reduced to bivalent iron in intestinal epithelial cells (8). Intestinal epithelial cells contain an intracellular iron transporter. Iron A part of it goes from the transporter to the mitochondria. The remainder goes to apoferritin in intestinal epithelial cells and transferrin (siderophyllin), an iron-carrying polypeptide in the blood (5,6). However, ferrokinase and ceruloplasmin are required for the oxidation of divalent iron in plasma to trivalent iron, in other words, or, for iron to combine with transferrin.

In intestinal epithelial cells, the increase in ferritin slows down the absorption of iron, explains that there is enough iron in the stores, prevents excessive iron intake into the body, and protects the cells from toxic effects (4). This phenomenon is also known as a mucosal blockade. Other than intestinal mucosa, ferritin found in the liver, spleen, and bone marrow; is a water-soluble protein. Ferritin is also found in the intestine and plasma from these tissues. Iron absorption is very slow, and only a few milligrams of iron per day are absorbed. Iron absorption is determined by the iron requirement of the organism. Phytic acid in cereals reacts with iron and causes the formation of water-insoluble compounds in the small intestine. Phosphate and oxalates also combine with iron and form compounds that do not dissolve (4) (5).

On the other hand, when iron stores in the body are depleted, red blood cell formation is increased, and in the case of anemia, iron absorption increases and may increase several times. Iron quickly passes into the blood after it is absorbed from the small intestine. Here, it binds to apotransferrin and transfers it to the blood. Iron is transported to the area of the body where it is needed by transferrin in the plasma. The maximum amount of iron that transferrin in plasma can carry is called "iron binding capacity " (6). Transferrin binds strongly to receptors on the (young red blood cells) membrane and is transported, together with bound iron, into erythroblasts by endocytosis. Here transferrin releases iron directly to the mitochondria, where its formation takes place, and hemoglobin is formed (8).

After the red blood cells have completed their lives and are destroyed, the iron here is kept in monocytes and macrophages in the bone marrow, spleen, and liver. Here, free iron is separated and stored mainly in the ferritin pool, or it is used in the bone marrow to form new red blood cells (7). The main iron storage sites in the body are the liver, spleen, intestinal mucosa, and bone marrow. These are followed by the kidney, heart, skeletal muscles and brain. The most important form of storage molecule is ferritin. Hemosiderin is insignificant because it is low. Iron excess accumulates in the body cells in the blood, particularly in hepatocytes, and to a minor amount in the reticuloendothelial cells of the bone marrow (12). In the cell, cytoplasm iron binds with apoferritin to form ferritin which is the key iron in tissues.

Iron metabolism in healthy individuals compared to thalassemia patients:

Human iron metabolism is the set of chemical reactions in the body necessary to maintain iron homeostasis at the systemic and cellular levels. Iron is essential for the body and can be toxic. Controlling and maintaining iron levels in the body is an important component of many aspects of human health and disease (9). Iron deficiency states are the main reason for a decrease in working capacity, and an increase in susceptibility to viral diseases, especially in children, and they cause growth and developmental retardation in children.

Normally, the body of a healthy adult person contains about 3-5 g of iron, so an iron can be classified as a trace element. Iron is distributed unevenly in the body. The body has the ability to maintain its iron balance by regulating iron absorption. When the body's iron stores are scarce, iron absorption is enhanced. If, on the other hand, the iron stores are full, information is sent to the small intestine via hormones that the absorption of iron must be reduced (10).

However, iron deficiency is one of the features accompanying beta-thalassemia in patients with thalassemia. If they are respected and treated quickly, the prognosis is good. Several studies suggest that it is necessary to accurately assess the position of iron between beta thalassemia and iron deficiency. Beta-thalassemia major causes hemolytic anemia, poor growth, and body abnormalities during immaturity. Many sick children have to receive regular blood transfusions for life (11). Intermediate beta thalassemia is milder than beta thalassemia major and tolerates occasional blood transfusions. A bone marrow transplant is effective for some children with beta thalassemia major. Cases of thalassemia have a normal life expectancy. Major cases of beta thalassemia often die from complications of heart iron overload conditions up to 30 times. If detected early, it should be treated immediately (9,12).

Iron Status in HBS/B versus HBS/S:

Sickle cell disease (Hb-SS in its most common form) is the most common sickle cell disease. It blocks the blood vessels in the body and causes severe pain. It can also cause problems like organ and tissue damage. Other common sickle cell disorders are called Hb-SC disease and sickle cell thalassemia (6).

Sickle cell anemia is a hereditary blood disorder. This species is really dangerous for babies and small children. People with this disorder have abnormal red blood cells throughout their lives (8). Changes in these cells cause them to take on a "sickle" shape. "Red blood cells (red blood cells) are very fragile and sometimes hard. They can get stuck in blood vessels and block blood flow. This can cause unexpected pain throughout the body. This can damage and overburden body organs (13).

Research shows that children with sickle cell disease can be infected with their own blood. Penicillin can help you die from this disease. Taking penicillin twice a day helps the bacteria grow in the blood and kills them before they can cause a serious infection in the body (15). Children with sickle cell disease may have age-related pain. This condition is more common in older children, but it can also occur in infants. The pain is usually in the bones and sometimes in the abdomen. This pain is not dangerous (7). The pain usually goes away after a few hours or days. Over-the-counter medications such as acetaminophen and ibuprofen often provide pain relief (7).

Meanwhile, the hemoglobin in red blood cells carries oxygen through the body's channels. In another condition called sickle cell beta-thalassemia (Sβ0 thalassemia), red blood cells are made from abnormal hemoglobin. This condition is called

hemoglobin S (sickle cell hemoglobin). This causes the red blood cells to become smaller and lighter in color (6).

Symptoms of RLS depend on the type and severity of the disease. The real problem is when the color channels in the body don't get enough oxygen to survive.) Children with RLS may have a slightly enlarged spleen, which is fine (14).

Blood transfusion frequency and duration in thalassemia:

In moderate to severe thalassemia cases, red blood cell transfusions are drug-dependent. The purpose of this treatment is to provide patients with normal hemoglobin and healthy red blood cells. Red blood cells live only about 120 days. Therefore, blood transfusions may be needed to maintain a healthy red blood cell status (16). However, if people complain of hemoglobin H or beta-thalassemia intermedia, they may need a blood transfusion if needed, but not always. For example, blood may be needed if there is severe anemia or an infection that causes fatigue. Patients with thalassemia major need regular blood transfusions (usually every 2-4 weeks). These transfusions help maintain normal hemoglobin and red blood cell levels. Blood transfusions can help patients feel better, enjoy a normal life, and grow into adults. This treatment is necessary. However, they carry a great risk in terms of transfusion-transmitted infections (Syphilis, Hepatitis, AIDS). However, these tests are carried out with great care in blood banks (13).

A sample is taken from the blood bank for analysis at the blood center. If the fever drops easily and no other problems are detected, the blood transfusion is continued slowly. If it is evaluated that the fever may be due to other causes, blood transfusion is not continued and other necessary treatments are applied. In order to prevent a simple fever reaction, the blood, ABO,and Rh (D) blood groups and cross-comparison should be appropriate (17). It would be more appropriate for late-onset thalassemia major and thalassemia intermedia cases to receive subgroup-appropriate blood cells regarding ABO and Rh (D).

In thalassemia patients, before the first blood transfusion, a test is performed for these blood-transmissible microbes. As long as the blood transfusion is continued, these tests are repeated in the patient's blood at 6-month intervals. When small, hemoglobin levels drop to 9-10 g/dL at longer intervals (like 4-6 weeks) and blood transfusions are performed. However, over time, the need for more frequent blood transfusions occurs and may become more frequent, up to 2-4 weeks. This is not because the disease progresses, but because as body mass increases with growth, blood consumption increases in parallel. Similarly, while 1 unit (250 mL) of blood (or even less than 1 unit at the beginning of 15-20 ml/kg body weight) is given at the beginning, 2 units and even rarely 3 units of blood can be given consecutively as the body mass increases (12) (16). The most common problems during blood transfusion are fever and chills. In this case, the blood transfusion is stopped. Normal serum and antipyretics are given through your vein. Controls are made regarding the blood given. Blood pressure is measured. The patient will be asked if they have any complaints other than fever, chills, and body aches. If necessary, a blood given to you is given by passing through the leukocyte filter. Although this process significantly prevents the fever reaction, it can still sometimes develop.

Treatment options for iron overload in thalassemia patients:

Excess iron is an important cause of thalassemia. Furthermore, in non-transplanted subjects, iron overload occurs secondary to increased intestinal deposition of therapeutic iron. Iron overload is the most

common cause of death and organ damage. Iron overload occurs when iron intake is increased for a prolonged period, either following blood transfusion or due to increased iron intake through the digestive tract (18). Both factors are present in thalassemia. The main cause of iron overload in thalassemia major is transfusion drugs, while increased gastrointestinal absorption is more prominent in transfusion-independent thalassemia. When transfusing blood regularly for a thalassemia patient, excess iron is unavoidable because the body cannot remove excess iron. Iron accumulation is toxic and dangerous to many tissues and can lead to heart disease (heart failure), cirrhosis, liver cancer, growth retardation, and many hormonal disturbances.

Children with beta-thalassemia major should receive as few blood transfusions as possible to prevent iron overload. However, the elimination of abnormal hemopoiesis by periodic transfusions of erythrocyte mass can be effective in patients with serious pathogens. To prevent or reduce hemochromatosis, excess (blood transfusion) iron must be removed (for example, with chelation therapy). Splenectomy can reduce the need for blood transfusions in patients with splenomegaly (10). Transplantation of allogeneic stem cells can be effective, but it requires the presence of a histological donor. In addition, the method carries a high risk of complications, including lethal, ones, and the need for long-term immunosuppressive therapy limits its use. Phlebotomy is a simple method of removing excess iron in most cases, which prolongs survival but does not prevent the development of liver cancer. After the diagnosis, about 500 ml of blood (about 250 mg of iron) is expressed weekly until the serum iron concentration is normalized and transferrin saturation is less than 50% (14). Weekly phlebotomy may be needed for several years. When the iron level is normalized, further phlebotomy is performed to keep the transferrin saturation level below 30%. Treatment of diabetes, cardiac dysfunction, erections, and other secondary manifestations is carried out in the presence of indications.

Also, chelation therapy is essential to balance the rate of iron accumulation during transfusion by increasing urinary iron excretion and/or chelation. However, if chelation is delayed or ignored, it is important that the iron be removed earlier than that. This is because iron is also essential for basic physiological purposes. The main problem with chelation is balancing the benefits of chelation with the negative benefits of excessive chelation (15). When iron status worsens, therapy should be adjusted to avoid excessive chelation. Another major challenge with chelation therapy is ensuring regular adherence throughout therapy, as shorter interruptions can have devastating consequences. While the tolerance of individual pawns is important to achieve this, other factors such as brain health, family support, and social support can also affect commitment and fear.

Difference between Transfusion-Dependent Thalassemia and Non-Transfusion Dependent Thalassemia:

Depending on the circumstances of the transfusion, thalassemia can be divided into two categories: "transfusion-dependent" thalassemia and "transfusion-independent" thalassemia. Laboratory and clinical cases should be taken into account when deciding whether to initiate blood transfusion if thalassemia is proven. Blood transfusions should be given in accordance with the blood transfusion guidelines for thalassemia cases. Facial changes, growth retardation, fractures, or signs of extramedullary hematopoiesis should be included in regular blood transfusions, in fact, if the hemoglobin level is less than 7 g/dl, at least two blood tests should be done every two weeks, or if the

hemoglobin is more than 7 g/dl one daily test is required (19) . For thalassemia, consider patients with severe anemia (hemoglobin status below 5 g/dL) regardless of transfusion. Except for severe cases of anemia, hemoglobin status should not be used as an indicator for starting blood transfusion therapy. If development is delayed, facial skeletal changes, progressive splenomegaly, decreased exercise tolerance, delayed secondary laboratory testing, and decreased quality of life, cases should be included in a routine blood transfusion program (11,13). Extending the red blood cell antigen assay before the first blood transfusion helps to resolve immunization problems that occur later. The RBC products used must be at least 14 days old and present leukopenia. ABO-Rh (D) and Rh (C,c,E,e) should be applied to Kell-compatible blood.

Non-transfusion-dependent (NTDT) thalassemia is less severe than its transfusion-dependent counterpart. NTDT includes three clinically distinct forms: beta-thalassemia (β-TI, hemoglobin E / beta-thalassemia) and alpha-thalassemia. In addition, NTDT thalassemia is rarer. NTDT cases were less severe than transfusion-induced thalassemia cases. One difference between NTDT and TDT is that the NTDT view is usually older than the TDT view. The clinical features of NTDT cases have been found to correlate with the severity of the usual anemia: the lower the hemoglobin locus, the greater the likelihood of body scarring, growth retardation, and even progressive splenomegaly. NTDT cases may present with perinatal hemolytic encephalopathy or high fever, leading to a misdiagnosis of TST and the initiation of a regular transfusion program (17). In addition, some cases of NTDT in adulthood are asymptomatic. They may be misdiagnosed during a routine test or tests, have mild or moderate symptoms of anemia, or have symptoms and complications associated with iron overload and typical anemia. Insights from NTDT may help avoid unnecessary blood transfusions and transfusion-related complications and ultimately lead to monitoring and dressing programs that help improve the quality of life of the unborn with complications. The view of NTDT can be determined primarily by genotype, but is essentially a clinical view.

In children with beta thalassemia, supportive treatment is required for life. Supportive treatment includes regular blood transfusions every month, chelation therapy to prevent iron accumulation, and treatment of complications that may develop. Gene therapy is not yet successful. If bone marrow transplantation is performed at an early age (<6 years), better results are obtained and a transfusion-free life is ensured.

It is used to treat a number of blood disorders in non-elderly patients, including beta-thalassemia major, sickle cell anemia and other hemolytic anemias, Diamond-Blackfan anemia, and other skeletal disorders (20). Typical transfusions include 10–15 ml/kg of packed red cells every 3–5 weeks to maintain hemoglobin levels at 9–10 g/dL in children with thalassemia and to maintain hemoglobin S status in children <30. People with sickle cell disease.

Iron overload, studied in clinical trials, is an adverse clinical consequence of repeated blood transfusions that can lead to severe organ damage, morbidity, and mortality if not treated appropriately (18). The threat of decreased anterior pituitary iron levels due to growth retardation and impaired sexual development in children with transfusion-related disorders. Iron chelation is important for removing excess iron from the body, but the effectiveness and success of the treatment largely depend on the patient's preferences (19). Desferrioxamine is a well-known and proven drug for a long time. Adherence to oral iron sequestrants and deferiprone may improve adherence.

CONCLUSION:

Iron pathology coexisted in thalassemia patients, treating or overcoming such condition is required to avoid complication. Blood transfusion is important part of thalassemia treatment and the outcome will be iron overload resulted from red blood cells catabolized iron content. Chelating agents are indicated to prevent iron complications.

REFERENCES:

1. Huart J, Bouquegneau A, Lutteri L, Erpicum P, Grosch S, Résimont G, et al. Proteinuria in COVID-19: prevalence, characterization and prognostic role. Journal of nephrology. 2021 Apr;34(2):355-64. https://doi.org/10.1007/s40620-020-00931-w
2. Beard JL, Dawson H, Piñero DJ. Iron metabolism: a comprehensive review. Nutrition Reviews. 1996 Oct 1;54(10):295-317. https://doi.org/10.1111/j.1753-4887.1996.tb03794.x
3. Biswas B, Naskar NN, Basu K, Dasgupta A, Basu R, Paul B. Malnutrition, its attributes, and impact on quality of life: an epidemiological study among β-thalassemia major children. Korean journal of family medicine. 2021 Jan;42(1):66. doi: 10.4082/kjfm.19.0066
4. Biswas B, Naskar NN, Basu R, Dasgupta A, Paul B, Basu K. Knowledge of the caregivers of thalassemic children regarding thalassemia: A cross-sectional study in a tertiary care health facility of eastern India. Iraqi Journal of Hematology. 2018 Jul 1;7(2):49. DOI: 10.4103/ijh.ijh_1_18
5. Cianciulli P. Treatment of iron overload in thalassemia. Pediatric endocrinology reviews: PER. 2008 Oct 1;6:208-13.
6. Cohen AR, Galanello R, Pennell DJ, Cunningham MJ, Vichinsky E. Thalassemia. ASH Education Program Book. 2004;2004(1):14-34. https://doi.org/10.1182/asheducation-2004.1.14
7. Darvishi-Khezri H, Karami H, Naderisorki M, Zahedi M, Razavi A, Kosaryan M, et al. Moderate to severe liver siderosis and raised AST are independent risk factors for vitamin D insufficiency in β-thalassemia patients. Scientific Reports. 2020 Dec 3;10(1):1-8. https://doi.org/10.1038/s41598-020-78230-4
8. Elsayh KI, Mohammed WS, Zahran AM, Saad K. Leukocytes apoptosis and adipocytokines in children with beta thalassemia major. Clinical and experimental medicine. 2016 Aug;16(3):345-50. https://doi.org/10.1007/s10238-015-0361-6
9. Finch CA, Huebers H. Perspectives in iron metabolism. New England Journal of Medicine. 1982 Jun 24;306(25):1520-8. DOI: 10.1056/NEJM198206243062504
10. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. The Journal of nutrition. 2001 Feb 1;131(2):649S-68S. https://doi.org/10.1093/jn/131.2.649S
11. He T, Gatehouse PD, Smith GC, Mohiaddin RH, Pennell DJ, Firmin DN. Myocardial T measurements in iron-overloaded thalassemia: An in vivo study to investigate optimal methods of quantification. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine. 2008 Nov;60(5):1082-9. https://doi.org/10.1002/mrm.21744
12. Kohgo Y, Ikuta K, Ohtake T, Torimoto Y, Kato J. Body iron metabolism and

pathophysiology of iron overload. International journal of hematology. 2008 Jul;88(1):7-15. https://doi.org/10.1007/s12185-008-0120-5

13. Gasche C. Iron physiology and pathophysiology in humans. Gastroenterology. 2013 Feb 1;144(2):464-5. https://doi.org/10.1053/j.gastro.2012.12.019
14. Comensoli L, Bindschedler S, Junier P, Joseph E. Iron and fungal physiology: a review of biotechnological opportunities. Advances in applied microbiology. 2017 Jan 1;98:31-60. https://doi.org/10.1016/bs.aambs.2016.11.001
15. Neufeld EJ. Update on iron chelators in thalassemia. Hematology 2010, the American Society of Hematology Education Program Book. 2010;2010(1):451-5. https://doi.org/10.1182/asheducation-2010.1.451
16. Sheikh MA, Shakir MU, Shah M. The assessment of nutritional status of children with beta thalassemia major with body mass index. Pak J Med Health Sci. 2017;11:262-5.
17. Sultan S, Irfan SM, Ahmed SI. Biochemical markers of bone turnover in patients with β-thalassemia major: A single center study from Southern Pakistan. Advances in hematology. 2016;2016. https://doi.org/10.1155/2016/5437609
18. Taher AT, Saliba AN. Iron overload in thalassemia: different organs at different rates. Hematology 2014, the American Society of Hematology Education Program Book. 2017;2017(1):265-71. https://doi.org/10.1182/asheducation-2017.1.265
19. Walker EM, Walker SM. Effects of iron overload on the immune system. Annals of Clinical & Laboratory Science. 2000 Oct 1;30(4):354-65.
20. Walter PB, Fung EB, Killilea DW, Jiang Q, Hudes M, Madden J, et al. Oxidative stress and inflammation in iron-overloaded patients with β-thalassaemia or sickle cell disease. British journal of haematology. 2006;135(2):254-63. https://doi.org/10.1111/j.1365-2141.2006.06277.x