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Clinical Complications of Beta-Thalassemia Major

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Abstract

Beta thalassemia syndrome (β-TM) syndrome is a group of hereditary blood disorders that are mainly characterized by reduction or absence of β-globin chain synthesis. Without iron chelation therapy (ICT) the regular blood transfusion would increase the iron stores to several times. Endocrine glands are vulnerable to iron overload causing endocrine dysfunction. Iron deposition within the parathyroid gland causes hypoparathyroidism particularly after ten years of age. Pancreatic islets are very susceptible to oxidative damage due to iron overload; their high divalent metal expression makes them highly susceptible to iron-catalyzing oxidative stress. The pathogenicity of osteopathy in β-TM is multifactorial comprising environmental (diet and lifestyle), iatrogenic (medicines), genetic and acquired factors (expansion of bone marrow, hemochromatosis, deficiency of growth hormone, hepatitis and hypogonadism). The increase in blood transfusion and RBCs break down in addition to iron accumulation and deposition are the main factors causing splenomegaly. Liver disease is one of the major complications affecting patients with β-TM.Liver damage is multifactorial with iron overload is considered the main causative factor, as well as hepatitis C (HCV) and hepatitis B (HBV) infections which are acquired on recurrent blood transfusions. The free radicals of deposited iron overcome the cellular antioxidant mechanisms resulting in peroxidative cellular injury. As a result, iron overload is the leading cause of left ventricular cardiomyopathy development.

Keywords: Beta-thalassemia major, Iron overload, Endocrinopathies

المضاعفات الناتجة عن مرض الثلاسيميا الكبرى

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الخلاصة

الثلاسيميا الكبرى-نوع بيتا هي مجموعة من اضطرابات الدم الوراثية التي تتميز بشكل رئيسي بقلة أو انعدام توليف سلسلة غلوبين-بيتا. بدون العلاج المكبل للحديد (ICT) فإن نقل الدم المنتظم من شأنه أن يزيد من مخازن الحديد عدة مرات. الغدد الصماء عرضة للفرط الزائد للحديد مما يسبب اختلال وظائف الغدد الصماء. ترسب الحديد داخل الغدة جنب الدرقية يسبب قلة في هرمون الباراثايرويد وخاصة بعد عشر سنوات من العمر. خلايا بيتا في البنكرياس معرضة بشدة للأضرار التأكسدية بسبب الفرط الزائد للحديد ؛ إن وجود التعبير المعدني الثنائي التكافؤعلى الخلايا يجعلهم أكثر عرضة للإجهاد المؤكسد المحفّز للحديد. التسبب في مرض هشاشة العظام في الثلاسيميا الكبرى يكون متعدد العوامل و التي تشمل العوامل البيئية (النظام الغذائي ونمط الحياة) ، الادوية، العوامل الوراثية والمكتسبة (توسع نخاع العظم ، الصباغ الدموي ، نقص هرمون النمو ، التهاب الكبد ونقص الغدد التناسلية). يعد نقل الدم وزيادة تحطم كرات الدم الحمراء بالإضافة إلى تراكم الحديد وترسبه من العوامل الإضافية لتضخم الطحال ، يعد اعتلال الكبد أحد المضاعفات الرئيسية التي تؤثر على المرضى الذين يعانون من الثلاسيميا الكبرى حيث يكون متعدد العوامل ومن اهم هذه العوامل هو زيادة فرط الحديد ويعتبر المسبب الرئيسي لذلك ، بالاضافة الى التهاب الكبد نوع (C) والتهابات الكبد نوع (B) التي تكتسب في عمليات نقل الدم المتكررة. تتغلب الجذور الحرة للحديد الناتجة عن فرط الحديد على آليات مضادات الأكسدة الخلوية مما يؤدي إلى تحطم مؤكسد لخلايا القلب. نتيجة لذلك ، يعتبر الحمل الزائد للحديد هو السبب الرئيسي لاعتلال عضلة القلب.

الكلمات المفتاحية:الثلاسيميا الكبرى-نوع بيتا ، الفرط الزائد للحديد ،الغدد الصماء .

Introduction

Beta thalassemia major is a group of hereditary blood disorders that are mainly characterized by reduction or absence of β-globin chain synthesis, resulting in a reduction of hemoglobin in red blood cells (RBCs), decreased production of RBCs and consequently anemia [(1,2)]. Thalassemia disease was first described by Thomas B. Cooley in 1925[(2,3)]. The β globin synthesis is normally regulated by two β genes; one on each copy of chromosome 11[(4)]. Thalassemia is an autosomal recessive genetic condition, caused by point mutation within or near β-gene. Such mutations result in either absence of the β globin (β^0-thalassemia) or reduction in synthesis of the β globin(β^+-thalassemia)[(5)]. B-thalassemia is clinically classified into three major types: 1-) Thalassemia minor (β-thalassemia carrier/trait): this type is heterozygous with a mild clinical phenotype since one normal copy of the beta globin chain is present (e.g. β+/β, β0/β). 2-) β-thalassemia intermedia: a heterogeneous genetic mutation that still allows for some β-globin chain formation (β+/β0, β+/β+). Patients develop symptoms later than in thalassemia major most often between 2-6 years of age with heterogeneous clinical findings that are similar but milder than β-thalassemia major (β-TM).

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Although patients are capable of surviving without regular transfusion, development and growth are retarded. 3-) β-thalassemia major (Cooley's anemia): refers to a severe phenotype which occurs when patients are homozygous or compounds heterozygous for β chain mutation (severe β+/β+, β+/β0,β0/β0), patients commonly present with symptoms within the first two years of life [3,11,14]. The reduction or absence of the β-globin chains results in a relative excess of α-globin chains, which when unpaired are unstable and precipitate in the erythroid precursors in the bone marrow, consequently there is ineffective erythropoiesis and the mature cells that reach the circulation have a shortened lifespan[6]. The cornerstone management for patients with β-TM is based on lifelong transfusion and iron chelation. The aims of transfusion are to correct anemia and suppress ineffective erythropoiesis[7]. The iron-loading rate from the blood transfusion in transfusion-dependent thalassemias (TDT) is about ten times the rate in non-transfusion-dependent thalassemias (NTDT); a unit processed from 420ml of donor blood contains approximately 200mg of iron. In β-TM the equivalent of 100-200 ml of blood per kg body weight per year is transfused, this means iron accumulation in mg is equivalent to 116-232mg/kg/ year, or 0.32-0.64 mg/kg/day. Without iron chelation therapy (ICT) the regular blood transfusion would increase the iron stores to several times the normal levels [11,26].Iron overload results in severe complications including cardiac disease, osteopathy and endocrine complications [11, 26]. The Non-transferrin-bound iron (NTBI) and labile plasma iron (LPI) circulate in plasma and are deposited in susceptible cells in which NTBI rather than using transferrin receptor, enters cells through the voltage-dependent Ca^{+2} channel (Figure 1). Myocardial iron overload causes death from cardiomyopathy and heart failure in the second decade of life, Pituitary damage causes growth retardation, hypogonadism and delayed puberty, endocrine complications include diabetes, hypoparathyroidism and hypothyroidism, and liver disease ending with cirrhosis and hepatocellular carcinoma[8,9].

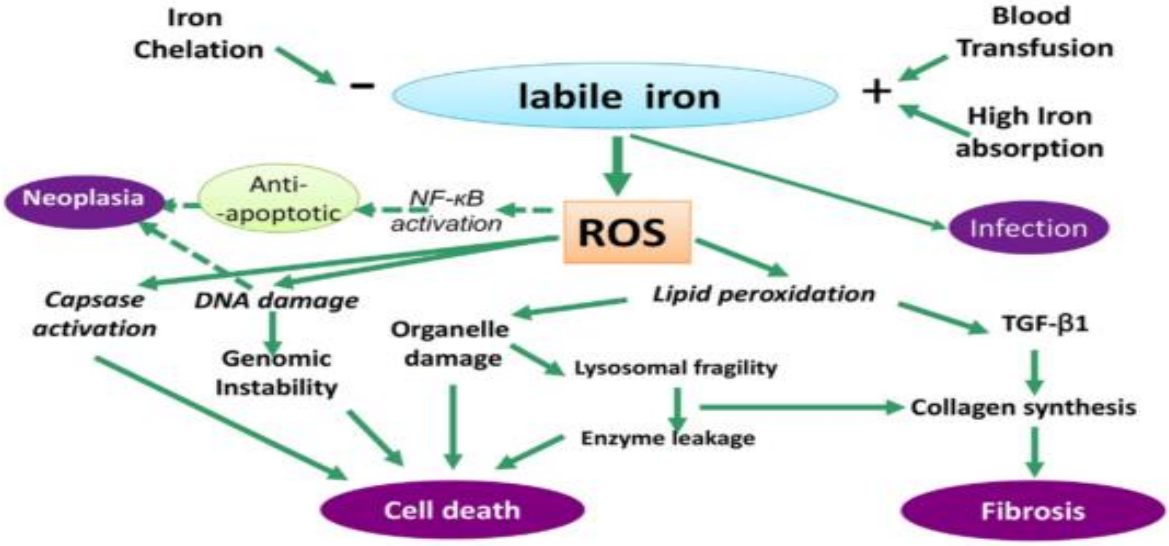

Figure 1. Pathologic mechanisms and consequences of iron overload [10].

Clinical complications of β-thalassemia major

growth retardation

Endocrine glands are susceptible to excess iron causing endocrine dysfunction (significantly Hypogonadotropic hypogonadism HH) which is a common complication in β-TM that requires recognition and treatment. Patients with the β-TM present with a delay in growth and puberty and reduction of the average height. Growth failure pathogenesis is multifactorial: including iron overload, chronic anemia and hypoxia, zinc and folic acid deficiency, chronic liver disease, intensive use of chelating agents, endocrinopathies and growth hormone-insulin like growth factor-1(GH-IGF-1) axis dysregulation[11]. Normal growth of children is disrupted by anemia, iron overload and ineffective erythropoiesis. However, maintenance of Hb above 9 with adequate chelation therapy makes β-TM patients growing as normal as their non-Thalassemic peers[11].Zinc is a trace element that has an important role in the synthesis of fat, enzymes, immune system, and RBCs' survival and its deficiency causes membrane fragility[12]. Despite zinc deficiency and hyperzincuria due to chelation therapy in β-TM patients, there is no significant difference between those with or without growth impairment regarding zinc concentrations in the body[13]. Folic acid deficiency results in complications such as anorexia, growth failure and GIT disorders besides megaloblastic anemia. Folic acid deficiency is more severe among β-TM patients; however, microcytosis of thalassemia may mask the hematological characteristics of folic acid deficiency. Folic acid in a dose of 1mg/day should

be given to thalassemic patients with deficiency states[14].Intensive Chelation therapy, mainly deferoxamine (DFO) when given as early as 2-5 years may have deleterious effects on growth, it has been found that DFO inhibits cell proliferation, DNA synthesis, mineral deposition, and collagen formation; all of which result in shortening of the spinal height and consequent truncal shortening[11,15].

Hypogonadism

Hypogonadism is the most common reported endocrinopathy; caused by iron deposition in the pituitary gland, gonads or both. It has been shown that gonadotropes require much more iron than other anterior pituitary cells, and are most affected by iron-overload resulting in declined levels of LH (luteinizing hormone) and FSH (follicular stimulating hormone)[16].The direct effect of NTBI on testes and ovaries is still unknown; however, ovaries reserve is still preserved in most females with thalassemia even if they were amenorrheic since they can still ovulate after hormonal treatment. Males testes on histological examination from autopsies revealed testicular interstitial fibrosis and hyperpigmentation of undifferentiated seminiferous tubules with a diminished number of Leydig cells[17].Anterior pituitary gland iron deposition occurs in the first decade of life, but the clinical manifestations appear only around puberty in which firstly only a diminished gonadotropin reserve and intact gonadotropin pulse is demonstrated, but, later the reserve of the gonadotropin is dramatically diminishing that may result in irreversible damage of the hypothalamic-pituitary-gonadal (HPG) axis[16].

Hypothyroidism

Thyroid dysfunction frequently occurs in β-TM but its prevalence and severity depend on the age of the studied populations, ferritin levels, duration, frequency of blood transfusion, and dose and type of chelating agent used[18]. T3 (triiodothyronine) and T4 (thyroxine) levels are regulated strictly by hypothalamic-pituitary-thyroid axis. Thus, hypothyroidism may be central or primary depending on the iron deposition in hypothalamus, pituitary or thyroid gland. Thyroid hormones affect many systems including cardiovascular, nervous, reproductive, and digestive systems. Thyroid function should be monitored in all patients with β-TM as they are considered hypertransfused, and in those who receive suboptimal chelation therapy. Patients with an elevated TSH (thyroid stimulating hormone) level should be followed up yearly, and a proper chelation therapy can prevent and reverse iron overload-induced hypothyroidism, L-thyroxin should be instituted in hypothyroid β-TM patients with moderate to severe iron overload[19].

Hypoparathyroidism

The secretion of the parathyroid hormone (PTH) takes place by the parathyroid gland and functions in calcium homeostasis together with vitamin D and Calcitonin, PTH maintains calcium levels within normal range by facilitating its absorption from the gastrointestinal tract, or by phosphorous excretion and calcium reabsorption from the kidney; or by bone resorption. PTH also plays a role in the conversion of vitamin D to its active form (1, 25 dihydroxycholecalciferol) in the kidneys[20].Patients with β-TM undergoing frequent transfusions, which causes iron deposition within the parathyroid gland with a resultant hypoparathyroidism particularly after ten years of age; as a consequence of that low PTH and vitamin D ensue. Hypoparathyroidism is also a leading cause of hypocalcemia, and several neurological complications may evolve such as tetany, seizures, and paresthesia[21,22].Patients with β-TM require a yearly screening for hypoparathyroidism to estimate hypocalcemia associated problems. Thalassemia patients in their second decade of life require supplementation with calcium and vitamin D to prevent complications such as neurological complications and fractures, and to maintain normal bone growth[23].

Diabetes mellitus (DM)

DM constitutes 20-30% of endocrine complications worldwide in patients with β-TM[24]. Pancreatic islets are very susceptible to oxidative damage due to iron overload; their high divalent metal expression makes them highly susceptible to iron-catalyzing oxidative stress. Another proposed mechanism of glucose abnormalities in β-TM is autoimmunity against antigens of the β-cells, in which iron deposition within these cells provides an environment that triggers an autoimmune reaction against β-cells and consequently destroying them. Zinc deficiency is a common problem in β-TM, and it has been shown that zinc deficiency results in exacerbation of inability of the pancreas to secrete sufficient amount of insulin in response to glucose load in β-TM patients, also iron deposition within parenchymal tissues such as the pancreas induces inflammation, recent studies demonstrated elevated levels of circulating IL-1α (interleukin-1alpha), TNF-α (tumor necrosis factor alpha) and IL-6 (interleukin -6) in β-TM patients which explains the progressive and gradual deterioration of these cells[25].According to the UK and international thalassemia management guidelines recommend regular screening by annual oral glucose tolerance test (OGGT) around puberty or 10 years when a family history is presented. This allows for a proper treatment of hyperglycemia or intensification of iron chelation therapy which would improve glycemic control or prevents future diabetes development[26].Patients with β-TM are aimed at preventing, detecting and managing diabetes-related

complications comprising macrovascular complications (cardiovascular, cerebrovascular and peripheral vascular diseases), and microvascular complications (diabetic retinopathy, nephropathy, and neuropathy)[26].The use of HbA1c for assessing glycemic control in thalassemia patients with hemoglobinopathies is less accurate; hence an alternate method for assessment that is not affected by abnormal hemoglobin variants is the use of fructosamine levels measurement which depends on serum protein glycosylation[25].

Bone diseases

Osteopenia and osteoporosis (OP) affect about 40-50% of patients with β-TM and are responsible for a vast majority of morbidity in this population with an increased risk for pathological fractures. The pathogenicity of osteopathy in β-TM is multifactorial comprising environmental (diet and lifestyle), iatrogenic (medicines), genetic and acquired factors (expansion of bone marrow, hemochromatosis, deficiency of GH or IGF-1, hepatitis and hypogonadism[27]. The pathogenesis of osteopathy is summarized by the following points:

1- Role of receptor activator of nuclear factor-κB, receptor activator of nuclear factor-κB ligand, and osteoprotegerin (RANK/RANKL/OPG) system: Physiologically two distinct cell types are in charge of the maintenance and renewal of the bone: the osteoblasts which are responsible for bone formation and the osteoclasts which are responsible for bone resorption and remodeling. In β-TM, the "aging" process of the bone begins as early as in childhood due to the gradual development of an imbalance between enhanced osteoclastic resorption and insufficient osteoblastic formation[28]. The essential pathway that links osteoclast-mediated bone resorption with osteoblast-mediated bone formation consists of a paracrine system that comprises receptor activator of nuclear factor-κB ligand (RANKL), its receptor activator of nuclear factor-κB (RANK), and a soluble protein osteoprotegerin (OPG). RANKL is produced by osteoblasts and their precursors, binds to the RANK receptor, promoting osteoclast differentiation and proliferation. OPG functions as a decoy receptor to block the action of RANKL. This system provides a balance between bone formation and resorption and through which a wide variety of biological mediators like (hormones, cytokines, and growth factors) affect bone homeostasis[29]. It has been found that RANKL which enhances osteoclastic function is elevated in β-TM patients, while OPG and OPG/RANKL ratio were reduced, associated with low bone mineral density (BMD) this gives evidence that OPG/RANKL system plays a vital role in the pathogenesis of osteoporosis in β-TM, moreover cytokines levels (interleukin-1α, TNF-α, and interleukin-6) were elevated in β-TM in which these inflammatory cytokines inhibit growth plate proliferation and differentiation, increase apoptosis and result in reduction of matrix synthesis. Circulating IL-1α concentrations were found to correlate with RANKL serum levels indicating an association between these cytokines and altered bone turnover in β-TM patients[28,30].

2- Genetic factors: The genetic factors play a significant role in the pathogenesis of osteopenia and osteoporosis in β-TM accounting for 70% of the variance in (BMD). Polymorphisms of several genes affecting BMD have been identified most important are collagen type I A1 (COLIA1), transforming growth factor-beta 1 (TGF- β1) and vitamin D receptor (VDR). In a study of Thalassemia male patients with (COLIA1) gene polymorphism associated with more severe osteoporosis of the spine and the hip and there was a failure of improvement of spinal OP using bisphosphonate therapy. TGF- β1 is the most available growth factor in human bones, and it is produced by osteoblasts has the main function of inhibiting osteoclasts proliferation and activity and stimulates proliferation and differentiation of pre-osteoblasts. Polymorphisms of this gene have been studied and play a role in lowered BMD and susceptibility to osteoporotic spine fractures. Polymorphism of VDR gene have found to be associated with short stature and lowered lumbar spine and femoral neck BMD in thalassemia patients[30].

3-Bone marrow expansion: As mentioned above that ineffective erythropoiesis results in erythroid hyperplasia and marrow expansion secondary to extramedullary hematopoiesis[31]. This results in expansion of the medulla, thinning of cortical bone and resorption of cancellous bone causing a generalized loss of BMD[30].

4-Endocrine complications: Hypogonadism: in transfusion-dependent thalassemia hypogonadism results primarily from pituitary failure and to a lower extent of gonadal failure[16]. Hypogonadism is associated with lower BMD in β-TM[32]. Generally, low estrogen and progesterone concentrations result in a decrease in the inhibition of osteoclast activity and bone formation. Low testosterone levels result in the reduction of its direct stimulatory effect on the proliferation and differentiation of osteoblasts[33]. GH-IGF dysfunction: GH and IGF have an anabolic effect on which is very important during adolescence for the acquisition of bone mass and during adult life for maintaining skeletal architecture[30]. Defective GH-IGF axis causes a decrease in osteoblast proliferation and bone matrix and increases in osteoclasts activation and subsequent bone loss[33]. Hypoparathyroidism: vitamin D and calcium deficiency increase bone turnover by stimulating PTH production; consequently increased PTH stimulates osteoclastogenesis and subsequent bone resorption to maintain normal circulating calcium concentrations. Hypothyroidism: chondrogenesis and bone mineralization are regulated by T3; T3

augments osteocalcin and collagen synthesis, increase proliferation and differentiation of osteoblasts. In adult life T3 is an anabolic hormone that is necessary for growth to stimulate peak bone mass accrual. Nevertheless, it regulates BMD and bone turnover; i.e., hypothyroidism is a leading cause for growth retardation and bone deformation[30]. Diabetes mellitus: insulin stimulate osteoblasts proliferation and maintains endochondral bone growth, insulin deficiency is a known risk factor for the development of osteoporosis[30].

5-Iron overload and Deferoxamine (DFO) toxicity: Deposition of iron in the bones impairs osteoid maturation and inhibits mineralization locally, this occurs by a mechanism that includes incorporation of iron into calcium hydroxyapatite crystals which consequently affects their growth[34]. DFO is responsible for bone growth and metabolism disorders. It exerts a direct effect by interfering with bone growth and by altering bone metabolism due to chelation of trace metals. DFO exerts deleterious effects on osteoblasts through inhibition of DNA synthesis, osteoblasts proliferation, differentiation of osteoblastic precursors, and in patients receiving high doses it enhances osteoblasts apoptosis[35].

6-Reduced physical activity: Patients with β-TM have a reduced physical activity either due to the complication of the disease or overprotection of the parents who do not encourage their children to make any muscular activity; in either case, this results in increased osteoclastic function and/or reduced osteoblastic activity after which bone destruction ensues[33,34].

Thalassemia facies

The majority of craniofacial manifestations in β-TM are due to hemolytic anemia, hypoxia and ineffective erythropoiesis with a resultant bone marrow hyperplasia and expansion. These include frontal bossing, larger cheekbones, depressed nasal bridge, and protruding maxilla. Craniofacial changes give a distinctive "chipmunk" – like appearance[36,37] (Figure 2).

Figure 2. The facial appearance of a child with β-TM[1].

Splenomegaly

The Spleen is the major organ of Hb catabolism of the old RBCs. In β-TM, there is an increased rate of hemopoiesis to compensate for anemia, causing an increase in production of abnormal RBCs and consequent clearance, as well as other changes such as extramedullary hemopoiesis resulting in splenomegaly. The increase in blood transfusion and RBCs break down in addition to iron accumulation and deposition are additional factors for splenomegaly[38]. Hypersplenism is problematic in patients who are inadequately transfused and results in leucopenia, thrombocytopenia, and exacerbation of anemia[39]. Splenectomy is indicated for patients with: increased blood requirement (200-220 ml/kg/year) which prevents adequate control with ICTs, symptoms of upper quadrant pain or feel of early satiety and/or massive splenomegaly with a danger of rupturing[9,40]. Although splenectomy relieves anemia and decreases the frequency of blood transfusion; It is associated with risks such as infections because the spleen is a major site of antibodies production, and thrombotic risk due to increased thrombin generation and decreased proteins C and S[40,41]

Liver disease

The primary site of iron storage is in the liver. Furthermore, it is the only site of transferrin and ferritin synthesis[42]. Liver disease is one of the major complications affecting patients with β-TM.Liver damage is multifactorial with iron overload is considered the main causative factor, as well as hepatitis C (HCV) and hepatitis B (HBV) infections which are acquired on recurrent blood transfusions[43]. Normally iron is stored protein-bound in the liver; which in cases of iron overload free iron is very toxic and catalyzes the production of free radical with a resultant lipid peroxidation causing hepatotoxicity[42]. Iron overload provokes malignant transformation in the liver by accelerating fibrosis and ultimate cirrhosis formation. This ccurs by activating stellate cells and by the profibrogenic effect of lipid peroxidation. Hepatocellular carcinoma (HCC) is caused by iron overload and chronic viral hepatitis; which was not a common complication of β-TM in the past since patients were used to die at a younger age because of heart failure[44]. Acute or chronic injury to the liver would result in elevated concentrations of Alanine transaminase (ALT) and Aspartate transaminase (AST)[45]. ALT serum level is considered an indicator of the necroinflammatory process of the liver[46]. To assess the extension of liver cell damage a sensitive indicator of liver function is used namely serum bilirubin; hyperbilirubinemia in β-TM could be pre-hepatic (hemolytic), hepatic or post-hepatic (obstructive)[47]. The incidence of gallbladder stones (cholelithiasis) and hepatic duct stones (choledocholithiasis) is 30-80% in patients with β-

TM. Approximately two-thirds of β-TM patients have multiple calcified-bilirubin stones by age 15. Thalassemia patients have gallbladder dysmotility with delayed small bowel transit and autonomic dysfunction; resulting in gallstone formation. 30% of gallstones are due to hemolysis, and about 30% due to cholestasis, chronic liver disease, ileac disease or resection, and 40% of cases are idiopathic[48]. Patients who undergo splenectomy should have their gallbladder evaluated for gallstones before surgery, especially if the patients have symptoms suggestive of biliary tract disease; at which time concomitant cholecystectomy should be performed[9].

Cardiac disease

Cardiomyopathy and arrhythmia in β-TM are the most important complications caused by iron overload accounting for 71% of deaths globally[49]. Patients with β-TM undergo chronic hemolysis that causes anemia; if left untreated leads to increased cardiac output, which ultimately results in left ventricular (LV) dilatation and hypertrophy ending with high rate heart failure (HF). On the other hand in iron overload, excess iron (NTBI) after saturation of reticulocyte system, deposits in cardiomyocytes through T and L-type calcium channels. The free radicals of deposited iron overcome the cellular antioxidant mechanisms resulting in peroxidative cellular injury. As a result, iron overload is the leading cause of LV cardiomyopathy development. Arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, and ventricular arrhythmia; is increased in parallel with increased cardiac siderosis[50,51]. Neither serum ferritin nor liver iron concentration (LIC) gives a reliable measure of cardiac iron concentrations, even modern measures such as tissue Doppler imaging has a poor correlation with cardiac iron. Endomyocardial biopsy is an invasive and unreliable as well for measuring cardiac iron due to the small samples which cause sampling error[52]. An alternative non-invasive technique for measuring cardiac siderosis is by using MRI-T2*[52]. MRI-T2* also detects early ventricular dysfunction and can be used to monitor cardiac iron during ICT. In β-TM normal myocardial T2* (T2*> 20 ms) is associated with normal LV and RV ejection fraction (EF). On the other hand, lower myocardial T2* (T2*<20) is associated with LV and RV dysfunction, and an improvement in T2* results indicate improvement in LV and RF ejection fraction[49,52,53].

Complications associated with iron chelation therapy (ICT)

Deferoxamine (DFO) has a negative impact on thalassemia patients' quality of life (QOL) as the infusions can be very troublesome, painful and time consuming with restrictive activity[54,55]. Compliance with DFO and its rigorous requirements of daily subcutaneous infusion still a limiting factor for treatment success. DFO chelates iron only during the time infused, hence, Poor compliance with DFO results in gaps in chelation coverage, leading to an increase in LPI levels which cause further tissue damage[56]. Many side effects are associated with DFO treatment including Local skin reaction,growth retardation,visual disturbances and hearing loss, and infections are negatively impact thalassemia patients. Although the oral deferasirox (DFX) iron chelation is more favorable, it is associated with nausea, vomiting, abdominal pain,rash, and acute renal failure, in addition to its high cost that may complicate the disease[9,57].

Conclusion

The iron-loading rate from the blood transfusion in transfusion-dependent thalassemias (TDT) is about ten times the rate in non-transfusion-dependent thalassemias (NTDT). Iron overload causes multiple organs damage including; liver, endocrine glands, bones, and heart.Better managing of iron overload and prevention of complications should be considered to prevent morbidity and mortality in those patients.

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