Review Article

The key complications of beta thalassemia major: a review and update

Jia Ying Chiew, Jeevitha Thiruchelvam, Mohd Azlan Bin Rahmat, Stephanie Priscilla William, Zikril Iman Bin Shafien, Kishore Gopal Banerjee*

Department of Pathology, International Medical School, Management and Science University, Selangor, Malaysia

Received: 13 May 2021
Accepted: 28 May 2021

*Correspondence:
Dr. Kishore Gopal Banerjee,
E-mail: kishore.patho@gmail.com

Abstract: Thalassemia is a heterogeneous group of genetic disorder with the defective synthesis of one or more globin chains. β-thalassemia is a global disease with high prevalence in Africa, Southeast Asia and Mediterranean countries. In Malaysia, the α and β-thalassemia are the commonest. In the articles that we reviewed, transfusion-dependent β-thalassemia is highly associated with complications related to thalassemia such as cardiovascular disease, endocrine disorders, skeletal deformities and others. Following advancements in β-thalassemia major treatment, cardiovascular disease remains the leading cause of mortality in β-thalassemia major patients. Thalassemia-associate cardiac pathology includes several conditions, such as myocardial dysfunction, arrhythmias and atrial fibrillation. Endocrine disorders, caused by iron deposition in the gland, resulting in impaired endocrine function. The commonest presentation is short stature followed by impaired puberty, abnormal thyroid function and diabetes mellitus. Moreover, skeletal complications remain a challenge. The most prevalent complications are malocclusion of the teeth, frontal bossing and chipmunk facies whilst osteoporosis, osteopenia and fracture are seen in a minority of the patient. Although comprehensive care has resulted in long-term survival and good quality of life, poor management will lead to complications that increase the treatment cost. However, genetic study (DNA analysis) examines the deletions and mutations in the α and β-globin-producing genes that help to correct diagnosis and improve management in thalassemia patients.

Keywords: β-thalassemia major, Hemosiderosis, Cardiomyopathy, Endocrinopathy, Skeletal complications

INTRODUCTION

β-thalassemia major is an inherited hemoglobinopathy which is passed to an individual following mutation within the genes coding the β-globin chain. It’s an autosomal recessive genetic disorder characterised by a reduced or absent β-globin chain synthesis. β-thalassemia is profoundly common in Africa, Mediterranean nations and Southeast Asia, including Malaysia. The latest study done in June 2020 showed 6.8% of Malaysian are thalassemia carriers and likely to have various degrees of anemia. Meanwhile in Malaysia, an expected total of thalassemia patients was 4541 as reported by Malaysian Thalassemia Registry. The number of heterozygous carriers of β-thalassemia patients in Malaysia has reach 4.5% of its population. This may cause increase in the total number of patients in the country. There are two key types of thalassemia which are α-thalassemia and β-thalassemia. They are named because of the defects in α-globin and β-globin chain. In β-thalassemia patients, β-globin chain is either reduced (β0) or absent (β-). This will lead to an excessive amount of α-globin chain in the red blood cells which precipitate in the red blood cell precursors within the bone marrow. This will cause mechanical and oxidative damage to the red blood cell precursors in the bone marrow leading to ineffective erythropoiesis. Shortening of the life span of the red blood cells is seen due to associated haemolysis.
β-thalassemia is divided into thalassemia minor, intermedia and major. The red blood cells are generally smaller in size and survival rate of the cells change from 15 to 20 days compared to normal red blood cells which last up to 120 days. The clinical features of thalassemia major are usually seen a few months after birth. Affected infants failed to thrive and become progressively pale. The individuals who are untreated or poorly treated are probably going to encounter growth retardation, paleness and skeletal changes resulting from the expansion of the bone marrow. These skeletal deformities include typical craniofacial changes, long-bone deformities of the legs and osteoporosis. Thalassemia is also further classified into transfusion-dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT). Individuals that develop severe anaemia due to β-thalassemia need regular blood transfusions for survival and optimal growth. Over time, regular blood transfusions will result in iron overload. Such iron accumulation over a prolonged period may result in iron-toxicity and prompt complications such as heart failure, malocclusion of the teeth, infections and endocrine abnormalities.

Objective and methodology

The objective of the study was to determine the association between β-thalassemia major and its key complications. We had reviewed published articles in indexed journals from the year 2010 to the year 2020 about the key complications associated with β- thalassemia major. The search-engines used to find the articles were pubmed, sciedirect, research gate, google scholar, clinical key and others. The keywords used to search the articles were β-thalassemia major, hemosiderosis, cardiomyopathy, endocrinopathy, skeletal complications.

DISCUSSION

Cardiovascular complications

Management protocol of transfusion-dependent thalassemia consists of repeated transfusions of red blood cells along with iron chelation to get rid of excess iron introduced with transfusions. The toxic effects of excess accumulation of iron are mediated by free-radicals (‘Fenton reactions’) that cause cardiac muscle injury and ion-channel dysfunction especially when non-transferrin-bound iron (NTBI) is oxidatively-active and can enter the heart through non-specific, poorly regulated channels of cation, leading to an overload of cardiac iron. Once labile iron within myocyte is increased, it causes impairment of the mitochondrial, sarcoplasmic and lysosomal membranes further increasing oxidative stress to the myocyte. Sodium, calcium and potassium ions are disrupted causing conduction/repolarization disturbances and diastolic and systolic dysfunction.

Thalassemic cardiomyopathy and arrhythmias caused by myocardial siderosis are the most severe side effect of iron overload in patients with β-thalassemia contributing to mortality and morbidity; and they account for 71% of global deaths related to β-thalassemia major. The clinical presentation of cardiac failure varies from affecting ventricular pathology to pulmonary hypertension, to symptomatic supraventricular arrhythmias which will cause sudden death.

Arrhythmia

Cardiac pathologies such as an increase in left atrial diameter, interventricular septum diameter, and left ventricular posterior wall diameter seem to contribute in the pathogenesis of arrhythmias, particularly supraventricular arrhythmias. In addition to atrial fibrillation and flutter, the most common thalassemia-related arrhythmias were premature atrial contractions, premature ventricular contractions, ventricular hypertrophy and atrioventricular, ventricular tachycardia and cardiac arrhythmia. In terms of electrocardiographic and echocardiographic parameters, thalassemia major patients displayed increase of the length of P wave, and increased length of QRS relative to normal controls. Additionally, prolonged P wave and dispersion of P wave are seen in patients with thalassemia major, and that they were related to increased risk of episodes of atrial fibrillation. It has been shown that increased length of QRS, even among normal limits, predicts mortality within the general population.

Heart failure

Until chelation was introduced till late 1960s, heart failure used to be the most common cause of death in thalassemia major patients undergoing daily transfusions. Magnetic resonance imaging assessment of iron overload using T2* imaging is used to measure iron loading in all organ systems, including the heart, prior to clinical manifestations. A cardiac T2* below 20 ms is indicative of cardiac iron and a T2* below 10 ms carries substantial prospective risk of cardiac dysfunction. Latest autopsy data showed that iron deposition in the myocardium in thalassemia major patients occurs preferentially in the subepicardium and iron is highly representative of total cardiac iron in the interventricular septum.

Changes in the heart that occurs in addition to ventricular systolic impairment include the following: (a) decreased left atrial activity due to ventricular stiffening or direct atrial toxicity; (b) impaired right ventricular function that may result from increased sensitivity of the right ventricular to the consequences of iron deposition due to its thin wall; (c) impaired endothelial function in iron overload; (d) impaired diastolic function by tissue of the cardiac iron overload in Doppler imagery.
Pericarditis and myocarditis

Pericarditis appears to be another common cardiac complication of the disease, along with the presence of cardiomyopathy. Thus, in a cohort of 202 well-treated patients, only 5% of the individuals had a history of acute pericarditis. Myocarditis additionally tends to play a role within the pathological process of cardiomyopathy in thalassemia patients. Thus, in an exceedingly giant cohort of 1048 patients with thalassemia, 4.5% of cases developed clinical features of acute myocarditis and histopathology supported in the designation of more than half of cases.12

Pulmonary hypertension

It is well known that thalassemia, in particular non-transfusion-dependent thalassemia (NTDT), is associated with an elevated risk of developing pulmonary hypertension. The key downside of the studies available in the literature is that they are focused on echocardiographic data, which could overestimate the important existence of pulmonary hypertension due to high cardiac activity.15 The main risk factors for developing pulmonary hypertension among β-thalassemia major patients were with hypertension, older age, history of splenectomy and failure of iron chelation therapy. Increased age, low body mass index (BMI) and increasing size of splenomegaly and hepatomegaly were factors linked to pulmonary hypertension severity.16 Symptoms for clinical evaluation of pulmonary hypertension can be counteracted into two categories, those reflecting elevated pulmonary vascular resistance and symptoms of right cardiac dysfunction and failure.3

Infection

Blood transfusions are important for the management of severe thalassemia major; a safe blood transfusion procedure is significant to prevent the risk of transfusion transmitted infections. Frequent blood transfusions in these patients increase their chance of transmitting transfusion transmissible infections relative to the general population.

This disparity is due to lack of properly and organised equipped transfusion services, resulting in increased risk of transfusion transmissible infections, hepatotoxicity, iron overload, and cardiac complications. Hepatitis C virus (HCV) infection is the most prevalent transfusion transmissible infections in thalassemia following infection with hepatitis B virus (HBV) and an increased risk of contracting the human immunodeficiency virus (HIV).17

Endocrine complications

Endocrine dysfunction is a common complication seen in transfusion-dependent thalassemia major patient. Transferrin is fully saturated due to excessive iron absorption in β-thalassemia patients. Non-transferrin-bound iron will increase in the blood and enters non-hematopoietic cells which may cause cell damage.18 88.4% of β-thalassemia major patients will have at least one endocrine complication which mostly develops in the second decade of life.19

Common endocrine complications include growth disturbance, impaired thyroid function, impaired gonadal dysfunction and diabetes mellitus.20 Iron deposition in the endocrine glands lead to low production of hormones especially growth hormone (GH) and gonadotropin (LH and FSH).21 A study done among 35 thalassemia major patients in India showed 87.5% of girls presented with primary amenorrhea and low FSH and LH level while 89.47% of boys had low free testosterone.22

Short stature

The commonest presentation of endocrine complication is short stature.23 It is mainly due to high serum ferritin levels during puberty.24 This leads to dysregulation of the GH-IGF-1 axis and causes deficiency of growth hormone (GH). It can also be caused by anemia, hypoxia and chronic liver disease.25 A study was conducted among thalassemia patients with a mean age of 9.94 which concluded that 57% of them had short stature. The mean height was 115.77 cm from the range of 72 cm to 148 cm.26 β-Thalassemia patients who were on oral iron chelation therapy with deferasirox for six years or more before reaching puberty had improvement in their final height.27 Research was done in a hospital in New Delhi also stated that the combination of deferoxamine and deferiprone can prevent growth failure.28

Delayed puberty

β-Thalassemia major patients who had delayed puberty and hypogonadism were caused by iron deposition mainly in the pituitary gland (hypogonadotropic hypogonadism) followed by gonads or both in both pituitary gland and gonads.29 To ensure normal reproductive lives of patients, MRI for detection of iron overload in pituitary gland is needed. Spontaneous fertility is possible for well-chelation and well-transfused hypogonadism patients. Exogenous gonadotropin therapy can induce ovulation or spermatogenesis in hypogonadotropic hypogonadism patients.18 Combined chelation therapy (use of deferiprone and deferoxamine), gonadotrophins and sex steroid can be used as treatment for induction of puberty and fertility.30

Thyroid dysfunction

Thalassemic patients in the second decade of life have a higher prevalence of hypothyroidism.31 This is due to thyroid gland infiltration, chronic tissue hypoxia, organ siderosis (deposition of excess iron in organ tissue) and free radical injury. All patients with impaired thyroid function have high serum ferritin levels. Severe thyroid hemosiderosis leads to disruption of regulatory hormone secretions.32 In patients presenting with short stature,
regular screening for evaluation of endocrine function is needed.\textsuperscript{33}

\textit{Diabetes mellitus}

A study showed high prevalence of abnormal glucose metabolism in \(\beta\)-thalassemia major patients.\textsuperscript{34} Diabetes mellitus is commonly seen in transfusion-dependent thalassemia patient due to excessive iron overload and leading to the \(\beta\)-cell destruction, insulin resistance secondary to liver disease and immunity.\textsuperscript{35} Among 30 \(\beta\)-thalassemia major patients who needed blood transfusion, reduce in insulin-resistant, fasting insulin and \(\beta\)-cell function was seen as age increases and the number of units transfused reached maximum level.\textsuperscript{36} Risk factors of impaired fasting glucose and diabetes mellitus include higher age, mean five-years ferritin, the volume of blood transfusion and splenectomy.\textsuperscript{37} Patients with \(\beta\)-thalassemia major need to go for regular follow up and screening test for early detection, because diabetes develop gradually and may not present the early symptoms.\textsuperscript{38} For severely symptomatic patients, insulin should be prescribed while for patients with milder hyperglycaemia, antidiabetic drugs should be used as treatment.\textsuperscript{39}

\textit{Skeletal complication}

Another common complication of \(\beta\)-thalassemia major is the skeletal complication. This complication is further divided into 3 main categories which are orofacial changes, craniofacial changes, and bone diseases that compromise osteopenia, osteoporosis and fracture of the bone.

\textit{Orofacial changes}

The orofacial change seen in \(\beta\)-thalassemia major patients is the malocclusion of the teeth. The main cause of this change is due to the overexpansion of bone marrow spaces which leads to such changes in the orofacial bones.\textsuperscript{39} Malocclusion of the teeth is characterized as an unpredictable impediment where the teeth are in an irregular position comparative with the neighboring teeth inside a similar jaw while the jaw is closed. The most common type seen is Class 2 malocclusion. It is said that this complication occurs due to both marrow hyperplasia because of chronic anemia that prompts maxillary strength and also due to mandibular retraction caused by growth development by various researchers.\textsuperscript{40}

\textit{Craniofacial changes}

Moreover, the craniofacial changes seen in \(\beta\)-thalassemia major patient are frontal bossing, depressed nasal bridge, protrusion of the cheekbones and canting of the eyes which are collectively known as “chipmunk face” occurs because of different factors, for example, the age of the patient, the severity of \(\beta\)-thalassemia major, the duration of their manifestations and the age of initiation of their blood transfusion treatment.\textsuperscript{41} However, the most prevalent craniofacial changes seen are frontal bossing, enlargement of maxilla and prominent molar teeth.\textsuperscript{42}

\textit{Bone disease}

Furthermore, osteoporosis and osteopenia are also widely seen in \(\beta\)-thalassemia major patient and it is detected by a decline in both the bone mineral density (BMD) and bone turnover. Besides that, it is also known as the significant complication that leads to morbidity in \(\beta\)-thalassemia major patients.\textsuperscript{43} The cause of this bone ailment is multifactorial; both genetic and acquired factors lead to demineralization of bone. With respect to the genetic factors, the collagen type la 1 gene which is the COLIA 1 gene that encodes the type 1 collagen which is the significant protein of the bone is affected. Whereas, with respect to the acquired factors, the expansion of the bone marrow caused by inadequate erythropoiesis, also certain endocrine dysfunctions, impacts of iron overload and chelation treatment causes this bone disease.\textsuperscript{44} According to a study done in Italy, it stated that the highest prevalence of osteoporosis is seen in males compared to females.\textsuperscript{45}

Last but not the least, pathologic fractures among \(\beta\)-thalassemia major patient are not commonly seen but it’s one of the remarkable skeletal complications. This is supported by a study which was done in Thailand states that 35.3% of the Thalassemia patients suffer from fracture and most of them are having \(\beta\)-thalassemia (44.1%) as compared to those who are having alpha thalassemia (16.9%).\textsuperscript{46} The root cause of fracture (usually seen in the upper limbs whilst the pelvis, spine and hips are least affected) in \(\beta\)-thalassemia major patient is unclear however there is a possibility that anemia is responsible for it because there is a reduction in the hemoglobin level which in turn impairs the oxygen delivery to the skeletal muscles and bone thus, overtime, it decreases the bone mineral density and influence the muscle power making it susceptible to fracture.\textsuperscript{45,47} However, other studies have referred to various causes including inadequate erythropoiesis with medullary expansion, numerous endocrine dysfunctions, deposition of iron directly to the bone, deferoxamine-initiated bone dysplasia, and diminished physical movement.\textsuperscript{48}

CONCLUSION

Beta thalassemia major, especially in the transfusion-dependent population, is commonly known to cause numerous complications. \(\beta\)-thalassemia complications include infections, iron overload, splenomegaly, delayed puberty, skeletal deformities and cardiac complications. Short stature is the commonest complication seen in a child affected by \(\beta\)-thalassemia. Excess of iron can result in damage primarily to the cardiac, liver and endocrine system. People with thalassemia have an increased risk of infection which typically occurred when splenectomy was performed. Expansion of the bone marrow makes the bones weak and brittle, which raises the likelihood of pathologic fractures. Among cardiovascular problems,
congestive heart failure and arrhythmias are associated with severe Thalassemia. The most common causes of mortality among thalassemia patients in Malaysia were cardiac failures (41.78%) and infections (38.16%).

Till today the bone marrow transplant (BMT), allogeneic hematopoietic stem cell transplantation (HSCT) remains the only definitive cure available for patients with thalassemia. The current management available for β-thalassemia major patient in most of the countries is regular transfusion of packed red cells, effective chelating therapy and management of complications of iron overload. Clinical manifestations of iron overload among regular transfusion-dependent patients progressively develop into hypogonadism (35-55% of the patients), hypothyroidism (9-11%), hypoparathyroidism (4%), diabetes (6-10%), liver fibrosis, and heart dysfunction (33%). Malaysia government nowadays started in MRI T2* sequence investing, to evaluate and monitor myocardial iron concentration specifically. This will help to optimise chelation therapy for thalassemia patients. Most of the chelation drugs available in the market are deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX). Prevention β-thalassemia major can be done by premarital screening, carrier detection and prenatal testing. Patients survival rate prolonged by transfusion and chelation therapy into the second decade. Genetic studies mainly on DNA analysis need to be explored further especially in investigations of deletions and mutations in the α and β-globin-producing gene. Current advancements in the field of medicine and genetics are expected to provide a better outcome of the β-thalassemia major patients in the days ahead.

ACKNOWLEDGEMENTS

Authors would like to thank International Medical School (IMS), Management and Science University (MSU) for giving us the opportunity to conduct this research work.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Arian M, Mirmohammadkhani M, Ghorbani R, Soleimani M. Health-related quality of life (HRQoL) in beta-thalassemia major (β-TM) patients assessed by 36-item short form health survey (SF-36): a meta-analysis. Qual Life Res. 2019;28(2):321-34.
2. Mohd IH, Muda Z, Othman IS, Mohamed UMN, Teh KH, Thevarajah A, et al. Observational study on the current status of thalassaemia in Malaysia: a report from the Malaysian Thalassaemia Registry. BMJ Open. 2020;10(6):37974.
3. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis. 2010;5:11.
4. Kohne E. Hemoglobinopathies: clinical manifestations, diagnosis, and treatment. Dtsch Arztebl Int. 2011;108(31):532-40.
5. Meng CY, Esa E, Yacob AM, Ramachandran S, Zakaria Z. Screening for Hemoglobinopathies among Patients in a Government Hospital and Health Clinic in Perlis, Malaysia. J Med Sci Technol. 2014;3(2):82-6.
6. Shah FT, Sayani F, Trompeter S, Drasar E, Piga A. Challenges of blood transfusions in β-thalassemia. Blood Rev. 2019;37:100588.
7. Verma M. Genetic disorder Thalassemia: Causes and Prevention. Sociology. 2019;3085(1):2078-80.
8. Origa R. β-Thalassemia. Genet Med. 2017;19(6):609-19.
9. Kolios M, Korantzopoulos P, Vlahos AP, Kapsali E, Briasoulis E, Goudevenos JA. Electrocardiographic abnormalities and arrhythmic risk markers in adult patients with beta thalassemia major. Int J Cardiol. 2016;221:932-6.
10. Russo V, Rago A, Papa AA, Nigro G. Electrocardiographic Presentation, Cardiac Arrhythmias, and Their Management in β-Thalassemia Major Patients. Ann Noninvasive Electrocardiol. 2016;21(4):335-42.
11. Borgna PC, Gamberini MR. Complications of thalassemia major and their treatment. Expert Rev Hematol. 2011;4(3):353-66.
12. Kremastinos DT, Farmakis D, Aessopos A, Halalis G, Hamodraka E, Tsiapras D, et al. Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. Circ Heart Fail. 2010;3(3):451-8.
13. Hamed AA, Elguindy W, Elhenawy YI, Ibrahim RH. Early Cardiac Involvement and Risk Factors for the Development of Arrhythmia in Patients With β-Thalassemia Major. J Pediatr Hematol Oncol. 2016;38(1):5-11.
14. Pennell DJ, Udelson JE, Arai AE, Cohen AR, Galanello R, et al. Cardiovascular function and treatment in β-thalassemia major: a consensus statement from the American Heart Association. Circulation. 2013;128(3):281-308.
15. Motta I, Mancarella M, Marcon A, Vicenzi M, Cappellini MD. Management of age-associated medical complications in patients with β-thalassemia. Expert Rev Hematol. 2020;13(1):85-94.
16. Muhamedamin HK, Mohammad ZM. Prevalence of Pulmonary Hypertension among Patients with β-thalassemia Major in Erbil Province -Iraq. Diyala J Med. 2019;16(2):17-30.
17. Ehsan H, Wahab A, Anwer F, Itikhar R, Yousaf MN. Prevalence of Transfusion Transmissible Infections in Beta-Thalassemia Major Patients in Pakistan: A Systematic Review. Cureus. 2020;12(8):10070.
18. Srisukh S, Onghiphiphadhanakul B, Bunmag P. Hypogonadism in thalassemia major patients. J Clin Transl Endocrinol. 2016;5:42-5.
19. Sanctis V, Elsedfy H, Soliman AT, Elhakim IZ, Soliman NA, Elalaily R, Kattamis C. Endocrine
profile of β-thalassemia major patients followed from childhood to advanced adulthood in a tertiary care center. Indian J Endocrinol Metab. 2016;20(4):451-9.

20. Wong SH, Omar J, Ismail TST. Multiple Endocrinologic Complications in Thalassemia Major. The Korean J Clinical Lab Sci. 2017;49(4): 495-7.

21. Abdulzahra MS, Al-Hakeim HK, Ridha MM. Study of the effect of iron overload on the function of endocrine glands in male thalassemia patients. Asian J Transfus Sci. 2011;5(2):127-31.

22. Merchant RH, Shirodkar A, Ahmed J. Evaluation of growth, puberty and endocrine dysfunctions in relation to iron overload in multi transfused Indian thalassemia patients. Indian J Pediatri. 2011;78(6):679-83.

23. Tan KA, Lum SH, Yahya A, Krishnan S, Jalaludin MY, Lee WS. Prevalence of growth and endocrine disorders in Malaysian children with transfusion-dependent thalassemia. Singapore Med J. 2019;60(6):303-8.

24. Hashemi A, Ghilian R, Golestan M, Akhavan Ghalibaf M, Zare Z, Dehnhani MA. The study of growth in thalassemia patients and its correlation with serum ferritin level. Iranian J Paediatrics Hematol Oncol. 2011;1(4):147-51.

25. Shamaoon M, Nawaz J, Ahsan M. B-Thalassemia Major; Frequency of Short Stature in Children With B-Thalassemia Major Receiving Multiple Blood Transfusion Original Prot-4721. The Professional Med J Professional Med J. 2018;25(6):823-7.

26. Aslam MS, Roshan E, Iqbal A, Shahid M. Frequency of Short Stature in -Thalassemia Major Patients. Pak Armed Forces Med J. 2013;63(4): 503-7.

27. Soliman AT, Yassin MA, Sanctis V. Final adult height and endocrine complications in young adults with β-thalassemia major (TM) who received oral iron chelation (OIC) in comparison with those who did not use OIC. Acta Biomed. 2018;89(2):27-32.

28. Sharma R, Seth A, Chandra J, Gohain S, Kapoor S, Singh P, Pemde H. Endocrinopathies in adolescents with thalassemia major receiving oral iron chelation therapy. Paediatr Int Child Health. 2016;36(1):22-7.

29. Sinharay M, Mitra S, Dasgupta A. Effect of Iron Overload on Gonadotrophins and Organ Sex Steroids in Pubertal Thalassemia Patients. Int J Current Res Rev. 2011;9(23):15-21.

30. Sanctis V, Soliman AT, Yassin MA, Maio S, Daar S, Elsedy H, et al. Hypogonadism in male thalassemia major patients: pathophysiology, diagnosis and treatment. Acta Biomed. 2018;89(2):6-15.

31. Soliman AT, Al Yafei F, Al-Naimi L, Almarri N, Sabt A, Yassin M, De Sanctis V. Longitudinal study on thyroid function in patients with thalassemia major: High incidence of central hypothyroidism by 18 years. Indian J Endocrinol Metab. 2013;17(6):1090-5.

32. Upadya SH, Rukmini MS, Sundararajan S, Baliga BS, Kamath N. Thyroid Function in Chronically Transfused Children with Beta Thalassemia Major: A Cross-Sectional Hospital Based Study. Int J Pediatr. 2018;9071213.

33. Eshragi P, Tamaddoni A, Zarifi K, Mohammadhasani A, Aminzadeh M. Thyroid function in major thalassemia patients: Is it related to height and chelation therapy? Caspian J Intern Med. 2011;2(1):189-93.

34. He LN, Chen W, Yang Y, Xie YJ, Xiong ZY, Chen DY, et al. Elevated Prevalence of Abnormal Glucose Metabolism and Other Endocrine Disorders in Patients with β-Thalassemia Major: A Meta-Analysis. Biomed Res Int. 2019;6573497.

35. Barnard M, Tzoulis P. Diabetes and thalassaemia. Thalassemia Reports. 2013;3(1):18.

36. Bhat KG, Periasamy PK. Effect of long-term transfusion therapy on the glycometabolic status and pancreatic Beta cell function in patients with Beta thalassemia major. J Family Med Prim Care. 2014;3(2):119-23.

37. Bazi A, Sharifi RJ, Rostami D, Sargazi AO, Safa A. Diabetes Mellitus in Thalassaemia Major Patients: A Report from the Southeast of Iran. J Clin Diagn Res. 2017;11(5):1-4.

38. Karuppiah D. Evaluation and management of diabetes in patients with thalassaemia major. J Ceylon College of Physicians. 2016;46(1):39.

39. Karakas S, Tellioglu AM, Bilgin M, Omurlu IK, Caliskan S, Coskun S. Craniofacial Characteristics of Thalassemia Major Patients. Eurasian J Med. 2016;48(3):204-8.

40. Gupta DK, Singh SP, Utreja A, Verma S. Prevalence of malocclusion and assessment of treatment needs in β-thalassemia major children. Prog Orthod. 2016;17:7.

41. Toman HA, Hassan R, Hassran R, Nasir A. Craniofacial deformities in transfusion-dependent thalassemia patients in Malaysia: prevalence and effect of treatment. Southeast Asian J Trop Med Public Health. 2011;42(5):1233-40.

42. Venkatesh BN, Amitha H. Radiological study of Oral and Craniofacial Findings in β Thalassaemic Children Undergoing Blood Transfusion. Int J Scientific Study. 2014;2(1):11-5.

43. Saki A, Abroun S, Salari F, Rahim F, Shahjahan M, Javad MA. Molecular Aspects of Bone Resorption in Thalassemia. Anemia. 2016;39.

44. Yigitoglu PH, Guzel R. Osteoporosis in Thalassaemia Major. Turk Ostekporoz Dergisi. 2012;18(3):89-91.

45. Perisano C, Marzetti E, Spinelli MS, Calla CA, Graci C, Maccaruto G. Physiopathology of Bone Modifications in β-Thalassemia. Anemia. 2012;320737.

46. Sutipornpalangkul W, Janechetsadatham Y, Siriratanakul N, Haroonrojog T. Prevalence of fractures among Thais with Thalassaemia syndromes. Singapore Med J. 2010;51(10):817-21.

47. Chen YG, Lu CS, Lin TY, Lin CL, Tzeng HE, Tsai CH. Risk of fracture in transfusion-naïve thalassemia
population: A nationwide population-based retrospective cohort study. Bone. 2018;106:121-5.

48. Pellegrino F, Zatelli MC, Bondanelli M, Carnevale A, Cittanti C, Fortini M, et al. Dual-energy X-ray absorptiometry pitfalls in Thalassemia Major. Endocrine. 2019;65(3):469-82.

Cite this article as: Chiew JY, Thiruchelvam J, Rahmat MAB, William SP, Shafien ZIB, Banerjee KG. The key complications of beta thalassemia major: a review and update. Int J Res Med Sci 2021;9:1846-52.