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Glycemic Abnormalities Assessment on Children and Adolescents with Beta-Thalassemia Major

Siska Mayasari Lubis[1]*, Bidasari Lubis[2], Nadhira Anindita Ralena[3]

[1]Division of Pediatric Endocrinology, Department of Child Health, Faculty of Medicine, Universitas Sumatera Utara, Medan, Sumatera Utara, Indonesia; [2]Division of Pediatric Hematology-Oncology, Department of Child Health, Faculty of Medicine, Universitas Sumatera Utara, Medan, Sumatera Utara, Indonesia; [3]General Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

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***Correspondence:** Siska Mayasari Lubis, Child Health Department, Faculty of Medicine, Universitas Sumatera Utara, Jl. Dr. Mansur No.5, Kampus USU, Medan, Sumatera Utara, 20155, Indonesia. E-mail: siskamayasarilubis@gmail.com
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Abstract

BACKGROUND: Iron overload in persons with beta-thalassemia major can result in organ damage. Excessive iron can result in endocrine disorders, including diabetes. Diabetes mellitus is a significant problem in individuals with beta-thalassemia major, particularly in children and adolescents.

AIM: To determine, if children and adolescents with beta-thalassemia major have glycemic problems.

METHODS: This cross-sectional research enrolled beta-thalassemia major patients who did not have a history of diabetes mellitus and had routine blood transfusions. Fasting insulin and blood glucose levels and 2 h postprandial plasma glucose, fasting insulin, and serum ferritin levels were determined in the laboratory. Insulin resistance was quantified using the homeostatic model assessment of insulin resistance (HOMA-IR). The correlation was considered statistically significant when $p < 0.05$.

RESULTS: This study enrolled 56 children with significant beta-thalassemia. The subjects' mean age was 9.46 (2−18) years. The mean age was 40 (3−180) months at the time of diagnosis. We discovered a strong association between serum ferritin levels and the participants' ages, body weight, body height, age of diagnosis, and blood volume per transfusion. Nonetheless, no significant link between serum ferritin and glycemic indicators was observed with $p > 0.05$, including fasting blood glucose, 2 h postprandial plasma glucose, fasting insulin levels, and HOMA-IR.

CONCLUSIONS: There was a strong association between serum ferritin levels and age at diagnosis and blood transfusions volume. However, no association between serum ferritin levels and glycemic status was seen.

Introduction

Beta-thalassemia is a heterogeneous autosomal recessive anemia that is inherited genetically. This condition is defined by a decreased or complete lack of beta-globin chain production. When iron accumulates in the spleen, liver, pancreas, heart, kidney, skin, pituitary, and other organs due to iron overload, it can cause various organ damage. Iron excess can result in myocardiopathy, congestive heart failure, cirrhosis, rheumatoid arthritis, and endocrine problems such as diabetes mellitus [1], [2].

Diabetes mellitus has been identified as a common complication of beta-thalassemia major. Diabetes mellitus is a critical endocrine condition that can develop due to iron overload. Insulin insufficiency, insulin resistance, and liver dysfunction are three pathways that are likely to develop [3]. Nonetheless, one study concluded that the most significant factor in the etiology of the disease's consequences is oxidative stress caused by iron buildup. Insulin resistance and insulin secretion disturbances result in poor glucose tolerance and type 2 diabetes mellitus [4].

The probable processes behind illness development have been examined and are diverse. Iron deficiency in patients with thalassemia and the oxidative stress associated with it may induce islet cell death in the pancreas, resulting in a decrease in insulin secretory ability [5]. Oxidative stress associated with iron overload may potentially cause harm, as islet cells release glucose-induced insulin nearly completely through mitochondrial glucose metabolism [4].

Nonetheless, the incidence of impaired glucose metabolism in individuals with beta-thalassemia major, particularly in children and adolescents, has been debated. As a result, we undertook this study to evaluate the glycemic aberrations associated with beta-thalassemia in children and adolescents.

Methods

Subjects

This is a cross-sectional research conducted in Medan, Sumatera Utara, Indonesia, at H. Adam Malik General Hospital and Universitas Sumatera Utara Hospital. The research enrolled 56 children and adolescents under 18 who had significant beta-thalassemia and had routine blood transfusions. Electrophoresis of hemoglobin (Hb) was used to confirm the diagnosis in the included participants. The study excluded patients diagnosed with diabetes mellitus before being diagnosed with thalassemia and children with other blood disorders. Consecutive sampling was used to get the samples.

Collection of samples

All individuals were requested to provide a thorough history, including their blood transfusion history and family history of thalassemia. Following that, a clinical examination was conducted, which included the determination of weight (kg), height (m), and body mass index (BMI) (kg/m^2). Weighing scales with a sensitivity of 0.1 kg were used to determine the child's weight (kg); height was determined using the SECA brand standing height meter (sensitivity 0.1 cm).

The serum ferritin concentration was determined using the immunochemiluminescent technique. The fasting blood glucose level (after an 8-h fast) was determined using the hexokinase technique, GOG-PAP. Fasting blood glucose is considered normal when it is less than 100 mg/dL, intolerance when it is between 100 and 125 mg/dL, and diabetes mellitus when greater than 100 mg/dL. Insulin secretion during a 12-h fast was determined using a chemiluminescent microparticle immunoassay (CMIA).

The fasting insulin and blood glucose levels (after 8 h of fasting), as well as the 2 h postprandial plasma glucose, fasting insulin, and serum ferritin levels, were determined in the laboratory. Insulin resistance was quantified using the homeostatic model assessment of insulin resistance (HOMA-IR). The HOMA-IR score was calculated using the following formula: Fasting insulin (U/mL) × fasting glucose (mg/dL)/405 [6]. The commonly used normal reference range for HOMA-IR is 0.7−2, [7] and any value more than this indicates insulin resistance.

Statistical techniques

SPSS version 16 was used to analyze the gathered data. Spearman's correlation and Mann–Whitney U-test were used to analyze the data; p = 0.05 was considered statistically significant.

Results

The participants included 56 beta-thalassemia major children with a mean age of 9.46 ± 4.44 years; 48.2% (27 patients) of the patients were boys, and 51.8% (27 patients) were girls (29 patients). There was a significant age difference (p = 0.001) (Table 1).

Table 1: Association between variables and levels of ferritin

Variables	Mean ± SD	p
Ferritin (ng/ml)	4503.65 ± 5081.41	-
Age (years)	9.46 ± 4.44	0.001
Sex, *n* (%)		
Male	27 (48.2)	0.616†
Female	29 (51.8)	
Body weight (kg)	23.63 ± 8.77	0.004
Body height (cm)	121.41 ± 19.06	0.003
BMI (kg/m^2)	15.5 ± 2.16	0.592
Age at diagnosis (months)	40 ± 33.61	0.016
Family history of thalassemia, *n* (%)		
Yes	12 (21.4)	0.143†
No	44 (78.6)	
Blood volume per transfusion	187.23 ± 89.83	0.001
Blood transfusion frequency (times per year)	17.27 ± 8.67	0.208
Family history of diabetes mellitus, *n* (%)		
Yes	49 (87.5)	0.88†
No	7 (12.5)	
Iron chelating agent consumption, *n* (%)		
Yes	39 (69.6)	0.221†
No	17 (30.4)	
Fasting plasma glucose (mg/dl)	78.96 ± 9.05	0.118
2 h postprandial plasma glucose (mg/dl)	130.71 ± 6.93	0.643
Fasting insulin (mIU/L)	3.56 ± 2.62	0.424
HOMA-IR	0.73 ± 0.6	0.481

**Spearman correlation test, †Mann–Whitney test. SD: Standard deviation, BMI: Confidence interval, HOMA-IR: Homeostatic model assessment for-insulin resistance.

The patients' mean body weight was 23.63 ± 8.77 kg, and the mean body height was 121.41 ± 19.06 cm. With p = 0.05, body weight and height demonstrated a significant connection with ferritin levels. Ferritin levels were also substantially associated with the subjects' age of diagnosis, which was on average 40 months (Table 1). The association between body weight and height and ferritin levels was positive, but the correlation between age at diagnosis and ferritin levels was negative (Table 2).

A total of 21.4% (12 patients) of the participants had a family history of thalassemia, whereas 78.6% (44 patients) did not. A total of 87.5% (49 patients) of the patients had a family history of diabetes mellitus, while 12.5% (7 patients) did not. Both factors were unrelated to ferritin levels (Table 1).

There was a significant positive connection between blood volume per transfusion and ferritin levels (Figures 1 and 2). Nonetheless, there was no significant

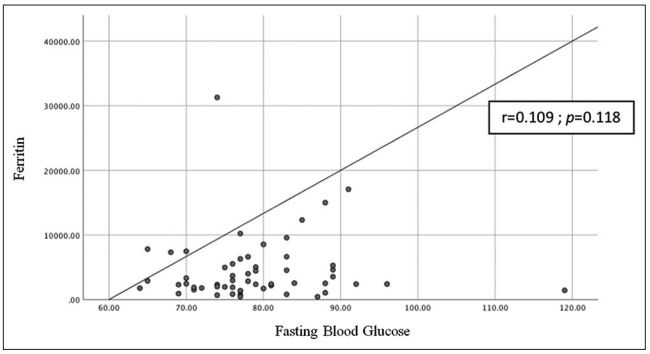

Figure 1: Scatter diagram between ferritin with fasting blood glucose

Table 2: Correlations between all variables

Variables	Age	Body weight	Body height	BMI	Age at diagnosis	Blood volume per transfusion	Blood transfusion frequency	Fasting plasma glucose	2 h postprandial plasma glucose	Fasting insulin	HOMA-IR	Ferritin
Age	1											
Body weight	0.881	1										
Body height	0.894	0.943	1									
BMI	0.282	0.499	0.227	1								
Age at diagnosis	0.214	0.174	0.147	0.071	1							
Blood volume per transfusion	0.563	0.553	0.562	0.116	−0.063	1						
Blood transfusion frequency	−0.099	−0.12	−0.132	0.036	−0.143	−0.418	1					
Fasting plasma glucose	0.298	0.227	0.273	−0.017	0.01	0.191	−0.161	1				
2 h postprandial plasma glucose	0.075	0.003	0.013	0.72	0.197	−0.013	0.012	0.105	1			
Fasting insulin	0.472	0.447	0.46	0.203	−0.02	0.252	−0.074	0.565	0.00	1		
HOMA-IR	0.472	0.448	0.47	0.188	−0.013	0.245	−0.082	0.614	0.023	0.995	1	
Ferritin	0.438	0.377	0.385	0.73	−0.321	0.465	0.208	0.109	0.063	0.109	0.096	1

BMI: Body mass index, HOMA-IR: Homeostatic model assessment for-insulin resistance.

association between blood transfusion frequency (in times per year) and ferritin levels (Table 1).

A total of 69.6% of patients received iron chelating therapy (18 received Exjade and 21 received Ferriprox), whereas 30.4% did not get iron-chelating therapy. There was no significant association between this variable and ferritin levels (Table 1).

All glycemic measurements, including fasting plasma glucose, 2 h postprandial plasma glucose, fasting insulin, and HOMA-IR, did not demonstrate a significant connection with ferritin levels with p-value greater than 0.05 (0.118, 0.643, 0.424, and 0.481, respectively) (Table 1, Figures 3 and 4).

Discussion

Regular and frequent blood transfusions may have prolonged and improved the quality of life of people with beta-thalassemia. Nonetheless, it may lead to chronic iron excess, occasionally resulting in endocrine dysfunction, most notably diabetes mellitus. In our study, the frequency of blood transfusions had no significant link with ferritin levels; however, the volume of blood transfused had a substantial positive correlation with ferritin levels. This finding is consistent with prior research that revealed a link between the blood volume required for transfusion and ferritin levels in patients with thalassemia [8].

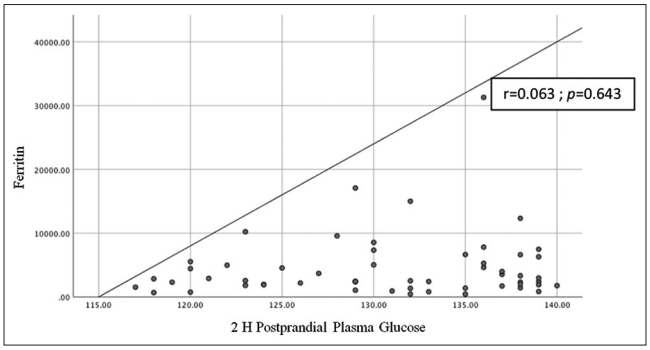

Figure 2: Scatter diagram between ferritin with 2 h postprandial plasma glucose

This study discovered a substantial positive connection between ferritin levels and body weight and height. No patient in our research had obesity. One study showed Iranian girls' ferritin level to be negatively related to BMI. This is consistent with a study conducted by Shattnawi *et al*. (2019), which established a favorable correlation between obesity and plasma ferritin, particularly among obese adolescents [9]. Huang *et al*. (2015) found that BMI was favorably linked with plasma ferritin but negatively associated with serum iron when overweight adolescents were compared to normal weight or underweight adolescents. Thus, their findings indicated that ferritin levels in the blood did not suggest an iron shortage in overweight teenagers. The current and prior findings indicated that alternative ferritin reference levels should be considered when diagnosing iron insufficiency in adolescents with obesity [10].

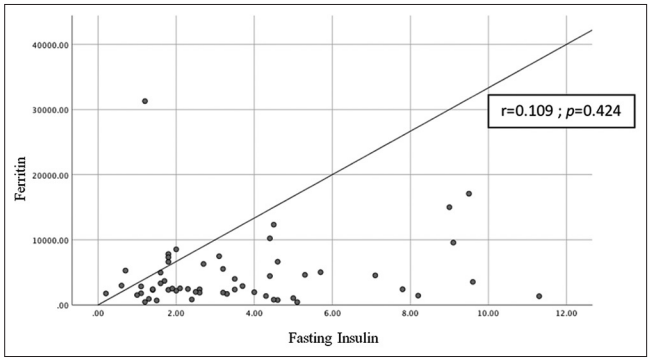

Figure 3: Scatter diagram between ferritin with fasting insulin

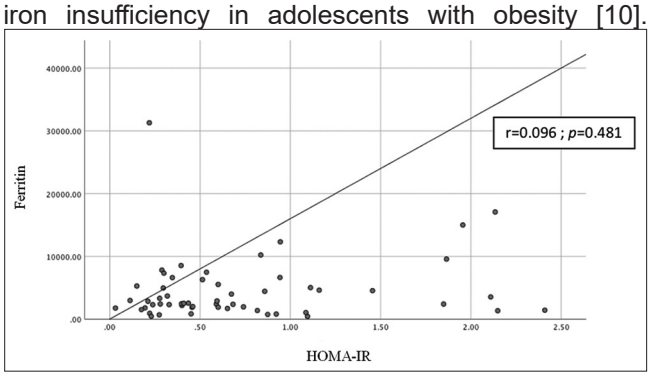

Figure 4: Scatter diagram between ferritin with HOMA-IR

Obesity may activate specific inflammatory pathways and enhance adipose tissue cytokine release, raising CRP hepatic secretion. Iron concentration and transferrin saturation decrease as BMI increases, but ferritin and CRP concentrations double. Iron deficiency may be exacerbated in people with obesity by inflammatory processes that trap iron in the reticuloendothelial system and promote the release

of specific cytokines. Simultaneous elevations in ferritin and CRP levels in the presence of an abnormally high body fat content may cause ferritin to serve as an acute phase reactant [11].

Our research discovered a strong negative connection between ferritin levels and age at diagnosis. This might be taken as the younger the patient was at the diagnosis, the greater the ferritin levels. Suriapperuma *et al*. (2018) previously reported that the mean serum ferritin level progressively increased until five and then plateaued. Although optimal body iron management was favorably linked with older age at thalassemia diagnosis and higher family wealth, it was not connected with transfusion length [12].

There was no significant association between family history of thalassemia and diabetes mellitus and blood ferritin levels in this investigation. Both thalassemia and diabetes are hereditary disorders. Serum ferritin levels may be hereditary, as evidenced by various iron overload illnesses handed on from parents to children through gene abnormalities. Nonetheless, no other study has established a link between familial thalassemia, diabetes mellitus and iron buildup [13].

In addition, our research found no significant link between the use of iron-chelating drugs and serum ferritin levels. Ferriprox, which contains Deferiprone, and Exjade, which contains Deferasirox, were utilized as iron-chelating agents in this study. Deferasirox (DFX) was created as a once-daily oral monotherapy to treat iron excess caused by transfusions. Deferasirox was initially dosed at a rate of 20 mg/kg/day in patients getting 2−4 packed red blood cell units per month, and at a rate of 10 or 30 mg/kg/day in patients receiving fewer or more frequent transfusions, respectively. A significant slight overall decrease in ferritin was seen at one year. Meanwhile, Deferiprone (DFP) is a bidentate iron chelator that is also orally absorbed. Numerous non-randomized cohort studies have demonstrated that taking 75 mg/kg/day in three doses reduced serum ferritin. At this dosage, the impact on serum ferritin appeared to be larger at higher baseline ferritin levels [14]. Our investigation may not demonstrate a significant link between iron-chelating agent intake and serum ferritin levels in respect to the dose and duration of the drugs. In addition, not all individuals in our research got iron-chelating drugs due to budgetary constraints.

Diabetes mellitus was diagnosed using the WHO criteria 2019 when a fasting plasma glucose of 126 mg/dL (7.0 mmol/L) or a 2-h plasma glucose of 200 mg/dL (11.1 mmol/L) during OGTT or an A1C of 6.5% (48 mmol/mol) or a patient with classic symptoms of hyperglycemia or hyperglycemic crisis had random plasma glucose of 200 mg/dL (11.1 mmol [15] In our investigation, patients had a mean fasting blood glucose level of 78.96 mg/dl, a mean 2 h postprandial plasma glucose level of 130.71 mg/dl, and a mean fasting insulin level of 3.56 mIU/L. These are sometimes referred to as standard measures. The average of the collected HOMA IR values was 0.73, indicating the lack of insulin resistance (A range between 0.7 and 2.0 means insulin sensitive). According to Wu *et al*. (2020), elevated ferritin levels in obese children may be associated with poor glucose tolerance and other metabolic problems [16].

Iron excess exacerbated the endothelial cell dysfunction induced by elevated glucose levels at the cellular level. In a study by Diab *et al*. (2021) and Swaminathan *et al*. (2007), they discussed the role of iron in diabetes complications, establishing a common etiologic link between hepatic iron, hepatic dysfunction, and insulin resistance associated with beta-cell oxidative stress caused by catalytic iron. Their study demonstrated a significant positive correlation between serum ferritin and fasting plasma insulin, fasting plasma glucose, and 2 h post [17], [18]. Similarly, Liang *et al*. (2017) found a substantial positive connection between HOMA-IR, the gold standard measure of insulin resistance, and age, serum ferritin, and ALT levels, suggesting that the degree of iron overload and hepatic dysfunction contributed to insulin resistance [19]. Meanwhile, our investigation discovered a non-significant link between ferritin levels and normal glycemic outcomes.

We did not analyze HbA1c levels in our participants, because hemolytic anemia, particularly thalassemia, has been shown to lower HbA1c levels due to increased erythropoiesis and shortened erythrocyte life span. Thus, if a clinician diagnoses diabetes mellitus only based on HbA1c levels in patients with hemolytic anemia, a mistaken diagnosis or management may result [20].

Our study is the first to correlate glycemic indices with ferritin levels in children patients with thalassemia in North Sumatera. We were able to assess each subject's fasting blood glucose, 2-h postprandial plasma glucose, fasting insulin, and HOMA-IR. However, most patients in our study hailed from low-income families, making iron-chelating agents unavailable to them. In addition, due to financial constraints, several patients who resided a great distance from the hospital were unable to acquire transfusions on a routine basis, resulting in the stated negligible correlations.

Conclusions

There was a strong association between serum ferritin levels and age at diagnosis and blood transfusions volume. Serum ferritin levels have no significant connection with the glycemic state. Nonetheless, adolescents and children with beta-thalassemia receiving long-term transfusions should have their glycemic indices and serum ferritin levels evaluated regularly to detect diabetes mellitus early. In transfusion-dependent individuals with thalassemia,

therapeutic methods to alleviate insulin resistance should be examined.

References

1. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis. 2010;5(1):11. https://doi.org/10.1186/1750-1172-5-11
   PMid:20492708
2. Agouzal M, Arfaoui A, Quyou A, Khattab M. Beta thalassemia major: The Moroccan experience. JPHE. 2010;2(2):25-8.
3. Bazi A, Sharifi-Rad J, Rostami D, Sargazi-Aval O, Safa A. Diabetes mellitus in thalassaemia major patients: A report from the southeast of Iran. J Clin Diagn Res. 2017;11(5):1-4. https://doi.org/10.7860/JCDR/2017/24762.9806
   PMid:28658748
4. Barnard M, Tzoulis P. Diabetes and thalassaemia. Thalassemia Rep. 2013;3(11):49-53.
5. Simcox JA, McClain DA. Iron and diabetes risk. Cell Metab. 2013;17(3):329-41. https://doi.org/10.1016/j.cmet.2013.02.007
   PMid:23473030
6. Majid H, Masood Q, Khan AH. Homeostatic model assessment for insulin resistance (HOMA-IR): A better marker for evaluating insulin resistance than fasting insulin in women with polycystic ovarian syndrome. J Coll Physicians Surg Pak. 2017;27(3):123-6.
   PMid:28406767
7. Salgado AL, Carvalho LD, Oliveira AC, Santos VN, Vieira JG, Parise ER. Insulin resistance index (HOMA-IR) in the differentiation of patients with non-alcoholic fatty liver disease and healthy individuals. Arq Gastroenterol. 2010;47(2):165-9. https://doi.org/10.1590/s0004-28032010000200009
   PMid:20721461
8. Mishra AK, Tiwari A. Iron overload in beta thalassaemia major and intermedia patients. Medica (Bucur). 2013;8(4):328-32. PMid:24790662
9. Shattnawi KK, Alomari MA, Al-Sheyab N, Bani Salameh A. The relationship between plasma ferritin levels and body mass index among adolescents. Sci Rep. 2019;9(1):692. https://doi.org/10.1038/s41598-018-37077-6
   PMid:30679763
10. Huang YF, Tok TS, Lu CL, Ko HC, Chen MY, Chen SC. Relationship between being overweight and iron deficiency in adolescents. Pediatr Neonatol. 2015;56(6):386-92. https://doi.org/10.1016/j.pedneo.2015.02.003
    PMid:25987352
11. Alam F, Memon AS, Fatima SS. Increased body mass index may lead to hyperferritinemia irrespective of body iron stores. Pak J Med Sci. 2015;31(6):1521-6. https://doi.org/10.12669/pjms.316.7724
    PMid:26870128
12. Suriapperuma T, Peiris R, Mettananda C, Premawardhena A, Mettananda S. Body iron status of children and adolescents with transfusion-dependent β-thalassaemia: Trends of serum ferritin and associations of optimal body iron control. BMC Res Notes. 2018;11(1):547. https://doi.org/10.1186/s13104-018-3634-9
    PMid:30071883
13. Taher AT, Saliba AN. Iron overload in thalassemia: Different organs at different rates. Hematology Am Soc Hematol Educ Program. 2017;2017(1):265-271. https://doi.org/10.1182/asheducation-2017.1.265
    PMid:29222265
14. Cappellini M, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the Management of Transfusion-Dependent Thalassaemia (TDT). 3rd ed. Nicosia: Thalassaemia International Federation; 2014.
15. American Diabetes Association. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2019. Diabetes Care. 2018;42 Suppl 1:13-28. https://doi.org/10.2337/dc19-S002
    PMid:30559228
16. Wu W, Yuan J, Shen Y. Iron overload is related to elevated blood glucose levels in obese children and aggravates high glucose-induced endothelial cell dysfunction *in vitro*. BMJ Open Diabetes Res Care. 2020;8(1):e001426. https://doi.org/10.1136/bmjdrc-2020-001426
    PMid:32675293
17. Diab AM, Abdelmotaleb GS, Abdel-Azim Eid K, Sebaey S. Mostafa E, Sabry Ahmed E. Evaluation of glycemic abnormalities in children and adolescents with β- thalassemia major. Egypt Pediatr Assoc Gazette. 2021;69(1):1-7.
18. Swaminathan S, Fonseca VV, Alam MG, Shah SV. The role of iron in diabetes and its complications. Diabetes Care. 2007;30(7):1926-33. https://doi.org/10.2337/dc06-2625
    PMid:17429063
19. Liang Y, Bajoria R, Jiang Y, Su H, Pan H, Xia N, *et al*. Prevalence of diabetes mellitus in Chinese children with thalassaemia major. Trop Med Int Health. 2017;22(6):716-24. https://doi.org/10.1111/tmi.12876
    PMid:28544032
20. Son JI, Rhee SY, Woo JT, Hwang JK, Chin SO, Chon S, *et al*. Hemoglobin a1c may be an inadequate diagnostic tool for diabetes mellitus in anemic subjects. Diabetes Metab J. 2013;37(5):343-8. https://doi.org/10.4093/dmj.2013.37.5.343
    PMid:24199163