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Prevalence Of Diabetes Melltus Among B-Thalassemia Major Patients In Al-Ramadi Teaching Hospital For Maternity And Children

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Abstract

Thalassemia is an inherited (i.e., passed from parents to children through genes) blood disorder caused when the body doesn't make enough of a protein called hemoglobin, an important part of red blood cells. Diabetes mellitus is a prevalent endocrine consequence in patients with β thalassemia major affecting 20-30%. Early detection of glucose dysregulation plays an important role in prevention of DM and is an area of considerable research interest for patients with β thalassemias. ***Aim of study:*** *To survey the prevalence of diabetes mellitus and its some of possible related factors among children diagnosed with β thalassemia major.* ***Methods:*** *A retrospective cross sectional study conducted at Al-Ramadi Teaching Hospital for Maternity and children during a period of six months from 1st of December 2022 to 1st of June 2023. It included 200 patients. All of them were known cases of β-thalassemia major aged < 18 years and attended the hospital for serial follow up and blood transfusion. Patients those who refused to make their children a part of this study were excluded from this study.* ***Results:*** *In this study, 30 patients were diagnosed with diabetes mellitus, with a prevalence of 15%. Diabetes mellitus was significantly higher among those aged more than 14 years and those on irregular chelating therapy. Diabetic patients had significantly higher mean levels of ferritin than the non-diabetic patients. Also, they had been transfused with significantly higher blood volume per year when compared with the non-diabetic patients.* ***Conclusion:*** *The prevalence of diabetes mellitus is 15% in patients with β-thalassemia major . Diabetes occurs more frequently with patients aged 14 years and older , those on irregular chelating therapy, those with high s. ferritin level, and those with high blood transfused per year.*

Keywords:*, Thalassemia major ,Diabetes, prevalence, beta, Iraq, Ramadi.*

Introduction

Thalassemia is derived from the Greek word "Thalassa" meaning sea. Thalassemia is a heterogeneous grouping of genetic disorders that result from a decreased synthesis of alpha or beta chains of hemoglobin (Hb). Hemoglobin serves as the oxygen-carrying component of the red blood cells. It consists of two proteins, alpha, and beta. If the body does not manufacture enough of one or the other of these two proteins, the red blood cells do not form correctly and cannot carry sufficient oxygen; this causes anemia that begins in early childhood and lasts throughout life [1, 2]. Thalassemia is an inherited disease, meaning that at least one of the parents must be a carrier of the disease. It is caused by either a genetic mutation or a deletion of certain key gene fragments. There are two types of thalassemia, α, and β, which are frequently found. This is based on the involvement of the globin chain [2]. Two versions of the Hb α gene (HBA1 and HBA2) encode an α-chain, and the pair genes are

placed on chromosome 16, and Hb β gene encodes the β chain and is located on Chromosome 11 [2]. β-thalassemia intermedia patients may or may not need blood transfusions in the first two years of life; however, the frequency of transfusions may increase in later life. Thalassemia minor patients are present in a carrier state and are usually clinically asymptomatic. The severity of the disease often remains immensely variable [3, 4]. Children with thalassemia suffer from the disease's consequences and treatment complications. The disease also causes a negative impact on family members, who suffer mentally, socially, financially, and even physically [1].

Both α- and β-thalassemia are often inherited in an autosomal recessive manner. both parents must be carriers for a child to be affected. If both parents carry a hemoglobinopathy trait, the risk is 25% for each pregnancy for an affected child [5].

The genes involved in thalassemia control the production of healthy hemoglobin. Hemoglobin binds oxygen in lungs and releases it when the red cells reach peripheral tissues, such as liver [6].

B-Thalassemia is the most common single-gene, autosomal recessive, inherited disease, impacting over 200 million individuals worldwide. It is reported that globally approximately 300-400 thousand children are born yearly with inherited substantial Hb diseases and around 80 million are carriers of β-thalassemia [7]. The beta form of thalassemia is particularly prevalent among Mediterranean peoples, and this geographical association is responsible for its original name. In Europe, the highest concentrations of the disease are found in Greece, coastal regions in Turkey, in southern Spain, in parts of Italy, particularly southern Italy. Other Mediterranean peoples have high rates of thalassemia, including people from North Africa and West Asia. Far from the Mediterranean, South Asians are also affected, with the world's highest concentration of carriers (16–18% of the population) in the Maldives [8] . B-Thalassemias are particularly associated with people of Mediterranean origin, Arabs (especially Palestinians and people of Palestinian descent), and Asians [9]. There are almost 80-90 million carriers of β-thalassemia globally, accounting for 1.5% of the world population. Additionally, it has been reported that around 68,000 infants are born yearly with β-thalassemia, both minor and major [10]. Multiple studies reported that around 23,000 as thalassemia major and 90% of these children are born in low or middle-income countries [11].

Thalassemia presentation varies widely depending on the type and severity. A complete history and physical examination can give several clues that are aid in the diagnosis. The following findings can be noted:skin can show pallor due to anemia and jaundice due to hyperbilirubinemia resulting from intravascular hemolysis. Patients usually report fatigue due to anemia as the first presenting symptom. Extremities examination can show ulcerations. Chronic iron deposition due to multiple transfusions can result in bronze skin [2].Bone deformities: Thalassemia can make the bone marrow expand, which causes bones to widen. This can result in abnormal bone structure, especially in the face and skull. Bone marrow expansion also makes bones thin and brittle, increasing the risk of broken bones [12].Enlarged spleen: The spleen aids in fighting infection and filters unwanted material, such as old or damaged blood cells. Thalassemia is often accompanied by the destruction of many red blood cells and the task of removing these cells causes the spleen to enlarge. plenomegaly can make anemia worse, and it can reduce the life of transfused red blood cells. Severe enlargement of the spleen may necessitate its removal [13].Infection: People with thalassemia have an increased risk of infection. This is especially true if the spleen has been removed [13]. Slowed growth rates: Anemia can inhibit a child's growth rate, and thalassemia can cause a delay in puberty. Particular attention should focus on the child's growth and development according to age [14].

•Cardiac: Iron deposition in cardiac myocytes due to chronic transfusions can disrupt the cardiac rhythm, and the result is various arrhythmias. Due to chronic anemia, overt heart failure can also result [2]. Endocrinopathies: Iron overload can lead to its deposition in various organ systems of the body and resultant decreased functioning of the respective systems. The deposition of iron in the pancreas can lead to diabetes mellitus; in the thyroid or parathyroid glands can lead to hypothyroidism and hypoparathyroidism, respectively [15].

Laboratory tests for diagnosis of thalassemia include: CBC is often the first investigation in a suspected case of thalassemia. It shows low hemoglobin and low MCV is the first indication of thalassemia, after ruling out iron deficiency as the cause of anemia. The calculation of the Mentzer index (the mean corpuscular volume divided by red cell count) is useful. A Mentzer lower than 13 suggests that the patient has thalassemia, and an index of more than 13 suggests that the patient has anemia due to iron deficiency [16]. Peripheral blood film examination reveals marked hypochromasia and microcytosis, hypochromic macrocytes that represent the polychromatophilic cells, nucleated RBCs, basophilic stippling, and occasional immature leukocytes [17]. Iron studies: serum iron, ferritin, unsaturated iron-binding capacity, total iron-binding capacity, and percent saturation of transferrin) are also done to rule out iron deficiency anemia as the underlying cause. Erythrocyte porphyrin levels may be checked to distinguish an unclear beta-thalassemia minor diagnosis from iron deficiency or lead poisoning. Individuals with beta-thalassemia will have normal porphyrin levels, but those with the latter conditions will have elevated porphyrin levels [18].Hb electrophoresis can usually confirm the diagnosis of beta thalassemia, HbH disease, and HbE/β-thalassemia. The electrophoresis usually reveals an elevated HbF fraction, which is distributed heterogeneously in the RBCs of patients with beta thalassemia. HbH is usually found in patients with HbH disease (but it is unstable), while Hb Bart is found in newborns with alpha-thalassemia trait. In β0 thalassemia, no HbA is usually present; only HbA2 and HbF are found [17].DNA analysis: These tests serve to help confirm mutations in the alpha and beta globin-producing genes. DNA testing is not a routine procedure but can be used to help diagnose thalassemia and to determine carrier status if needed. family studies may be necessary to assess carrier status and the types of mutations present in other family members [19]. Genetic testing of amniotic fluid is useful in those rare instances where a fetus has an increased risk for thalassemia. This is particularly important if both parents are likely to carry a mutation because that increases the risk that their child may inherit a combination of abnormal genes, causing a more severe form of thalassemia. Prenatal diagnosis with chorionic villi sampling at 8 to 10 weeks or by amniocentesis at 14 to 20 weeks' gestation can be carried out in high-risk families [18].

Diabetes mellitus in thalassemia Patients with severe form of thalassemia (thalassemia major or transfusion dependent thalassemia) require regular blood transfusions to maintain an appropriate hemoglobin level. Although, life expectancy of patients with thalassemia major has improved substantially by regular blood transfusions, secondary hemosiderosis and organ dysfunctions including cardiomyopathies, endocrinopathies, gonadal insufficiency and osteoporosis are yet among the most debating conundrums in thalassemia major [20].

Two hypotheses have been postulated to explain glycemic dysregulation in thalassemia. The first supports pancreatic β-cell damage and insulin deficiency, associated with insulin resistance (IR) [21]. The progressive and early loss of β-cell mass, leading to pancreatic dysfunction, may be due to iron-mediated oxidative stress that triggers apoptosis, volume loss, and fatty replacement [22].

The second hypothesis suggests that the "primum movens" is IR which results in impaired fasting glucose (IFG); chronic iron overload and progressive damage of β-cell function later induce impaired glucose tolerance

(IGT) or thalassemia related-diabetes (T-RD). The IR has been postulated to be at the level of the liver (due to iron deposition), where it may interfere with insulin's ability to suppress hepatic glucose uptake, and at the level of muscles, where iron deposits may decrease the glucose uptake. This hypothesis is supported by several studies showing higher fasting plasma insulin concentration with increased IR index and normal plasma glucose, preceding the onset of frank GD in patients with thalassemia. Thalassemia associated DM has been reported to be specially more frequent in older patients and has been responsible for high rate of morbidities [22, 23].

The prevalence of diabetes mellitus in thalassemia major patients varies from 9.7% to 29%. The overall prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) is 17.2% and 12.4% respectively in transfusion dependent thalassemia (TDT) patients [24]. The highest prevalence of IFG and IGT has been observed in countries of the Middle East (27.8%) and the Mediterranean coast (15.1%) [25]. Therefore, early detection of glucose dysregulation (GD) plays an important prevention role and is an area of considerable research interest for patients with thalassemias. The current international guidelines recommend annual screening for GD in all patients with TDT from the age of ten years (25). Annual screening becomes even more important in the light of evidence showing that intensive chelation regimen (monotherapy or combined) in the early stages of glucose abnormalities can improve insulin secretion and normalize glucose metabolism [26].

The etiological classification of diabetes and related disorders includes: (a) T1DM, (b) T2DM, (c) those due to specific mechanisms and diseases, and (d) gestational diabetes mellitus. T1DM is characterized by destructive lesions of pancreatic β-cells either by an autoimmune mechanism or an unknown cause. T2DM is characterized by a combination of decreased insulin secretion and decreased insulin sensitivity. Category (c) includes two subgroups: subgroup A is a diabetes in which specific mutations have been identified as cause of genetic susceptibility, while subgroup B is diabetes associated with other pathological conditions or diseases [27, 28].

A typical example of subgroup B is the diabetes of β-TM patients, that recently defined as thalassemia-related diabetes (Th-RD), as it has not yet been clearly classified. It differs from T1DM and T2DM, although it has similarities with both (insulin insufficiency and variable insulin resistance) [29].

The International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) recommend two different screening parameters for abnormalities of glucose homeostasis: (a) a periodic assessment of FPG from the age of 5 years (b) a 2-h OGTT, preferably combined with determination of insulin secretion at 10, 12, 14, and 16 years and annually thereafter [31]. At present, the criteria for the interpretation of OGTT do not support the use of HbA1C for defining prediabetes. The credibility of HbA1c has been questioned because the hemoglobin composition in thalassemia patients is considerably modified due to regular and frequent transfusions. The results may be falsely increased or decreased depending on the proximity to transfusion, shortened erythrocyte lifespan and the assay used [32, 33]. However, HbA1c, in efficiently transfused β-TM patients seems valuable in diagnosis and monitoring treatment of DM. Other glycemic markers such as glycated albumin and fructosamine have the potential for identifying prediabetes. However, these biomarkers have not been incorporated into guidelines, and there is currently no consensus on their use in clinical practice for defining glycemic status [30].

Despite the high prevalence of DM in patients with TDT, there is limited evidence about its management. In this context, considering the lack of high-quality data on the use of oral glucose-lowering agents (oral GLAs) in patients with TDT and DM, a recent survey in 8 thalassemia care centers, including 1,554 patients with TDT

and 687 with NTDT was performed. The records of 117 TDT patients with DM and 9 with NTDT treated with oral GLAs were analyzed. The most frequently used antidiabetic medication was metformin (in 47.6%), followed by acarbose (5.5%), gliptins (4%), and insulin secretagogues (gliclazide and repaglinide in 3.1%) [39]. As many as 40.4% of patients, who were initially treated with oral GLAs for a mean duration of 61 months, later required insulin therapy. This study suggests that oral GLAs are effective and safe for the treatment of DM in patients with thalassemias, achieving adequate glycemic control for a substantial period [22]

Aim of study

To survey the prevalence of diabetes mellitus and its possible related factors among children diagnosed with β thalassemia major.

Patients and Methods

Study design, setting and data collection time

This was a retrospective cross sectional study conducted at Al-Ramadi Teaching Hospital for Maternity and children during a period of six months from 1st of December 2022 to 1st of June 2023.

Study population and sample size

The total number of β - thalassemic patients in thalassemia unit was 234

patient. The study included 200 patients. All of them were known cases of β-thalassemia major and attended the hospital for serial follow up and blood transfusion. The data was collected from the archive files of the patients.

All patients were sent for fasting and 2hr post-prandial glucose to diagnose diabetes mellitus.

Diabetes Mellitus was diagnosed as: (a) a fasting glucose of ≥126 mg/dL (≥ 7.0 mmol/L), or (b) a 2-hour glucose on an OGTT of ≥ 200 mg/dL (≥ 11.1 mmol/L) ([16,17]). In the absence of unequivocal hyperglycemia, the ADA recommends that the result should be confirmed with repeat testing, or (c) a random glucose of ≥ 200 mg/dL (11.1 mmol/L) with classic diabetes symptoms ([40]).

Exclusion criteria

- ✓ Parents who refused to make their children a part of this study.
- ✓ Patients with family history of Diabetes Mellitus.

Data collection tools

The data had been collected through a well-designed questionnaire from the archive files including the following:

- Age and sex.
- Therapeutic strategy (Regular or irregular of taking iron chelating agent and volume of blood transfusion).
- Family history of Diabetes Mellitus type 1 and type 2.
- Investigation done during hospital attendance (S. ferritin, fasting, random blood glucose).

Ethical considerations and official approvals

Verbal permission was obtained from each parent by call phones prior to collecting data, and information were anonymous. Names were removed and replaced by identification codes. All information kept confidential in a password secured laptop and data used exclusively for the research purposes.

Administrative approvals were granted from the following

Scientific Council of Arab Board of Pediatrics. Thalassemia unit in Al-Ramadi Teaching Hospital for Maternity and children.

Statistical analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. The significance of difference of different means (quantitative data) was tested using Student t-test for difference between two independent means. The significance of difference of different percentages (qualitative data) were tested using Pearson Chi-square test (χ^2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. The correlation coefficient value (r) either positive (direct correlation) or negative (inverse correlation) with value <0.3 represent no correlation, 0.3-<0.5 represent weak correlation, 0.5-<0.7 moderate strength, >0.7 strong correlation. A level of P – value less than 0.05

Results

The total number of β - thalassemic patients in thalassemia unit was 234 patient
This study included a total of 200 patients who were diagnosed with β – thalassemia major.

Sociodemographic and clinical characteristics

The age range of studied patients was 1 - 18 years with a mean of 11.08 ± 5.50 years. The highest proportion of patients aged ≥ 14 years, 89 patients (44.5%) (Figure 3.1).

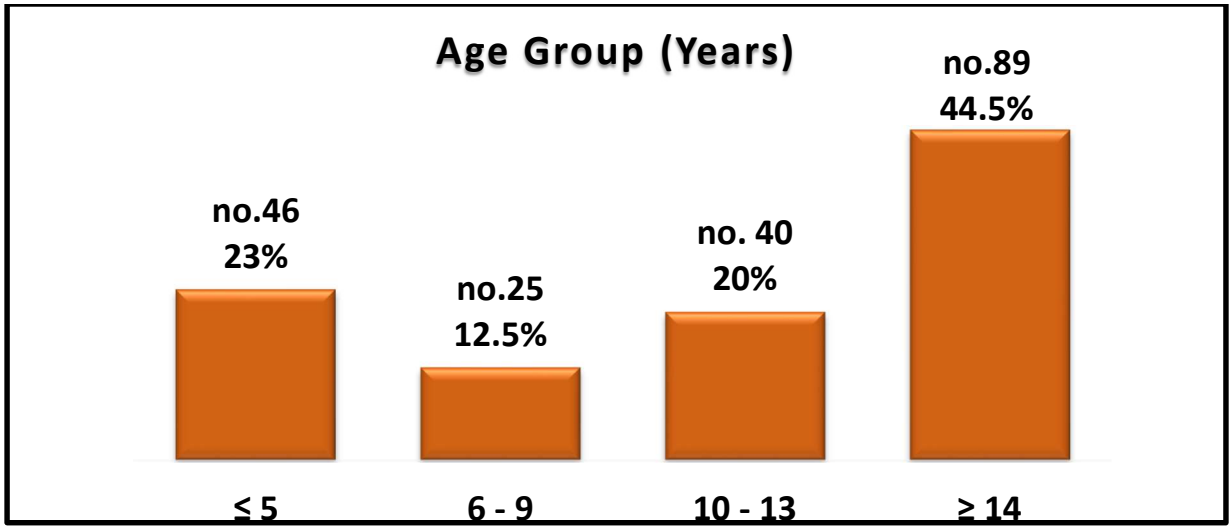

Figure 3.1: Distribution of the studied children according to age group

Regarding gender, there were 110 males (55%) versus 90 females (45%) with a ratio of 1.22:1. More than half of the studied patients 118 (59%) had regular iron chelating therapy and the remaining 82 (41%) were

with irregular iron chelating therapy (Table 3.1).

Table 3.1: Distribution of the study group according to baseline characteristics

Patients' characteristics	No. (n= 200)	Percentage (%)
Gender		
Male	110	55.0
Female	90	45.0
Therapeutic Strategy(iron chelating agent)		
Regular Therapy	118	59.0
Irregular Therapy	82	41.0

Prevalence of diabetes

Of the 200 patients with Beta thalassemia major, 30 patients were diagnosed with Diabetes Mellitus, with a prevalence of 15% (Figure 3.2).

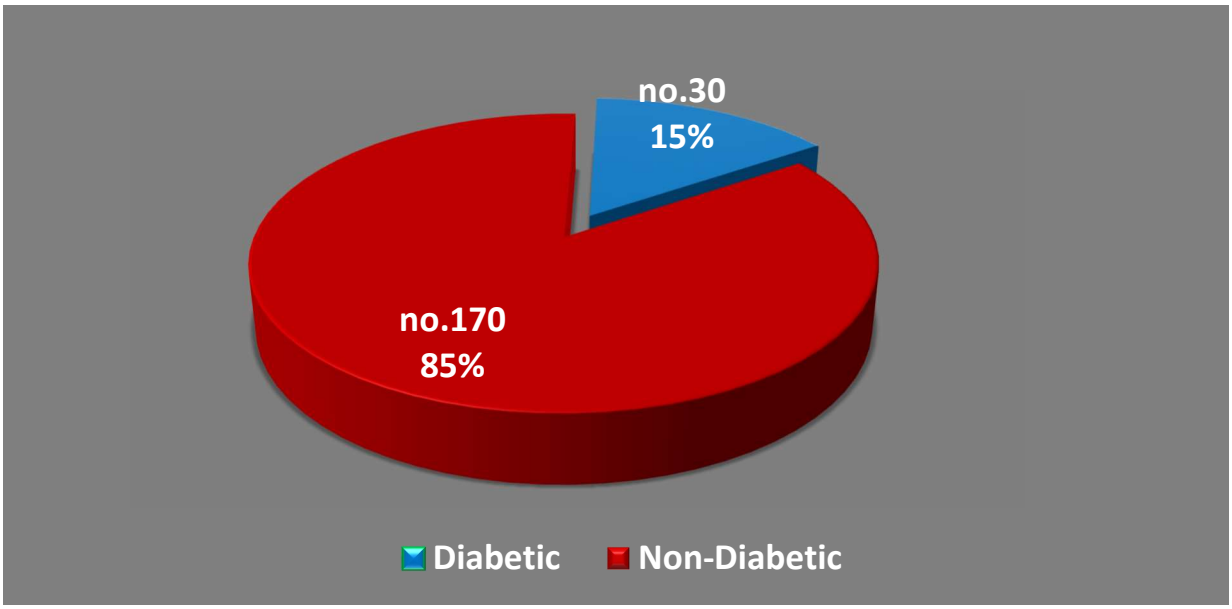

Figure 3.2: Prevalence of diabetes mellitus among B- thalassemia major patients

In this study, we found significant association between diabetes mellitus and patients age group and so as therapeutic strategy. Diabetes mellitus was significantly higher among those with age group ≥ 14 years (23.6%, P= 0.003) and those on irregular chelating therapy (29.3%, P= 0.001). Gender of patients was not significantly associated (P ≥ 0.05) with diabetes mellitus (Table 3.2).

Table 3.2: Distribution of the study group according to sociodemographic characteristics and diabetes mellitus

Patients' characteristics	Diabetes Mellitus		P- Value*
	Yes n= 30 (%)	No n= 170 (%)	
Age (Years)			
6th month-5yr	0 (0)%	46 (100.0)%	**0.003**
6 - 9	3 (12.0)%	22 (88.0)%	
10 - 13	6 (15.0)%	34 (85.0)%	
≥ 14	21 (23.6)%	68 (76.4)%	
Gender			
Male	17 (15.5)%	93 (84.5)%	**0.842**
Female	13 (14.4)%	77 (85.6)%	
Therapeutic Strategy (iron chelating agent)			
Regular Therapy	6 (5.1)%	112 (94.9)%	**0.001**
Irregular Therapy	24 (29.3)%	58 (70.7)%	

* Significant difference between percentages using Pearson Chi-square test at 0.05 level.

It was clear that the mean level of ferritin and mean volume of blood transfusion were significantly different according to the blood glucose levels. Diabetic patients had significantly higher mean levels of ferritin than the non-diabetic patients (7435.2 mg/dl vs 3108 mg/dl, P= 0.001). Also, the diabetic patients had been transfused with significantly higher blood volume per year when compared with the non-diabetic patients (11696.6 ml vs 9149.4 ml, P= 0.001) (Figures 3.3 and 3.4) (Table 3.3).

Table 3.3: Distribution of the study group according to diabetes mellitus

Variable	Diabetes Mellitus		P- Value*
	Yes Mean ± SD	No Mean ± SD	
Ferritin (mg/dl)	7435.2 ± 1736	3108 ± 2171	**0.001**
Blood Volume (ml)	11696 ± 3179	9149 ± 3622	**0.001**

* Significant difference between two independent

Discussion

Prevalence of diabetes Of the 200 patients with Beta thalassemia enrolled in this study, 15% of patients had DM. As compared to Al-Gharbawy et al study in Iraq a different result observed, in which 287 patients with beta thalassemia major were participated, 1.1%were diagnosed with diabetes, while 9.7% were diagnosed as impaired glucose tolerance test [45]. similarly to Ahmed et al study in Pakistan, a different result observed, in which 193 patients with thalassemia major were participated. Based on their results, 5% of patients were observed to be diabetic while DM was not observed in 95% patients of thalassemia [40]. Moreover, and in accordance with the current results, a previous study carried out by Bazi, and other co-authors in Iran published a different result, in which 148 patients with thalassemia major participated. They found that DM was diagnosed

among 13 patients with thalassemia major (8.8%) [35]. Similarly, another study carried out by Azami M et al in Iran reported a comparable result to the current findings. They found that the incidence of DM among Iranian children with thalassemia major was reported to be 9% and estimated rate was 12.6% for males and 10.8% for females [36].

In the same regard, a total of 44 studies with 16605 patient with thalassemia major were included in an analysis conducted by He LN and other co-authors in China. Results published revealed that diabetes mellitus was present in 6.54% of patients presented with β-thalassemia major [42]. In contrary to current results, a study done by Au WY et al, reported high frequency of DM in patients with thalassemia major (29%) [40]. Another study done by Matter and colleagues in Egypt, reported high frequency of DM in those with thalassemia major (25%) [41].

In addition to the different diagnostic criteria for DM and thalassemia major, genetic, geographical, cultural, economic factors, and the quality of blood transfusion and chelation therapy, particularly the onset and the rate of the deferoxamine dosage can be the reason for the difference in prevalence in various countries.

The current study revealed that proportion of patients with DM were significantly higher in those aged ≥ 14 years (P= 0.003). As compared to local study at AlGharbawy et al in Iraq an agreement observed that the prevalence of DM in β-thalassemia patients was increased with patients older than 10 years [50] .similarly, an agreement observed by Liange et al in China, that the prevalence of DM in β-thalassemia group was higher in children aged >10 years (OR 6.5; 95% CI 3.7–11.4; P < 0.001[42]. Similarly, El-Samahy et al study in Egypt found that age of the participants had significantly related to the occurance DM among the participants (P<0.05) [43].In contrary to the current results, Farooq et al study in Pakistan found that age was not related to the prevalence rate of DM in 193 participants diagnosed with β-thalassemia major (P>0.05) [34].

The present work reported that gender was not significantly associated (P≥0.05) factor with DM.As compared to AlGharbawy et al in Iraq, the agreement was observed with our study that gender was not significantly associated with DM[50].Similarly, same result with no significant association between gender and DM were observed by by Liange et al in China (P>0.05) [47] and El-Samahy et al study in Egypt[38].

The current study revealed that proportion of patients with DM were significantly higher in patients with irregular chelating therapy (P= 0.001). As compared to another studies an agreement was observed by El-Samahy et al study in Egypt that found chelating agents used had significantly related to the occurance DM among the participants (P<0.05)[43].similarly an agreement observed by Liange et al in China that children on regular chelating therapy had a significant reduced incidence of glycemic aberrations than those on irregular chelating agents (P < 0.05) [42].

The present work reported that diabetic patients had a significantly higher mean levels of ferritin than the non-diabetic patients (P= 0.001). Also, they were transfused with significantly higher blood volume per year than non-diabetic patients (P= 0.001).As compared to AlGarbawy el al study in Iraq, an agreement was observed that patients with higher mean levels of sr.ferritin was associated with increased incidence of DM[45].In the same concern, Zhang and colleagues in China reported that thalassemic patients with iron deposition or serum ferritin > 4000 μg/L were prone to abnormal glucose metabolism, so chelation therapy should be reinforced. They found a statistically significant differences in age and serum ferritin between the diabetic and non-diabetic groups (P<0.05) [44].

The current results agreed with Liange et al study, in which they found that prevalence of DM in β-thalassemia group was higher in children with higher levels of ferritin >2500 lg/l (P < 0.01) and in those required a frequent blood transfusion (P<0.05) [42].Furthermore, results observed in El-Samahy et al study found that the only significant independent factor for elevated random blood glucose among thalasemic patients participated was serum ferritin. They reported that serum ferritin was significantly higher in thalasemic patients with elevated blood glucose, while no significant relation with amount of blood transfused per year (P=0.4) [38].

Conclusion

He prevalence of diabetes mellitus is 15% in patients with β thalassemia major.Diabetes occurs more frequently with: Patients aged 14 years and older (23.6%).Those on irregular chelating therapy. Those with high s. ferritin level.Those with high blood transfused per year.

Recommendation

There is a need to encourage primary health care physicians Especially those who are working in thalassemia units to give advices to attendants towards early screening of the glycemic indices especially for all patients especially those with irregular chelating therapy and high s. ferritin This can help early detection of DM in thalassemia patients.We recommend starting chelating agents as early as possible when there is high s. ferritin level to decrease endocrine complication mainly DM. Regular screen for DM by FBS and 2hr postprandial glucose and early start of treatment is highly recommended.

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