International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at http://www.ijmscrr.in Volume 6|Issue 01 (January-February)|2023 Page: 316-321

Original Research Paper

Diabetes Mellitus in Polytransfused Beta-thalassemia Patients.

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Article Received: 01-01-2023 Revised: 20-01-2023 Accepted: 10-02-2023

ABSTRACT:
Introduction: B-Thalassemia is a chronic hereditary hemolytic anemia characterized by a defect of synthesis of beta-globin chains, particularly common in the Mediterranean region, southern Asia, and the Middle East (1). Chelation therapy significantly prolonged the life expectancy of patients (2). This has led to an increase in the prevalence of cardiac, hepatic and endocrine complications, in particular the development of diabetes linked to iron overload (3). **Objectives:** Describe the frequency of glucose homeostasis abnormalities in patients with polytransfused β-thalassemia and to study the relationship between abnormalities in glycoregulation and : serum ferritin level , duration of transfusion treatment, splenectomy and Compliance with chelation treatment. **Method:** It is a descriptive, analytical and mono-centric cross-sectional study which was carried out in the department of pediatrics of Mustapha Pacha University hospital and which involved 87 patients (46 Girls and 41 Boys), followed for several years on a regular basis and treated by a transfusion regimen (more than 10 transfusions) combined with a chelating treatment. All patients were assessed by a clinical history, physical examination, fasting blood glucose and Oral Glucose Tolerance Test (OGTT) combined with a test of HOMA-IR (Homeostasis Model Accessment of insulin resistance). **Results:** Twenty eight (32.2%) patients presented glycoregulation disorders ,with 17 (60.7%) girls and 11 (39.3%) boys, there is no statistically significant relationship between the two genders (p = 0.31). The average age of patients with glycoregulation disorders is 13.4 ± 6.58 years, 16 (18.4%) patients had moderate fasting hyperglycemia , 8 (9.2%) patients had glucose intolerance (GI), and 4 (4.6%) patients had diabetes (3 patients diagnosed before the start of the study). 10 (12%) patients presented a positive HOMA test. There is no statistically significant relationship between ferritinemia and glycoregulation disorders (p = 0.65). **Conclusion**: Our results suggest that children with β-thalassemia have a high incidence of glycoregulation disorder in the second decade of life or later.

KEY WORDS: Diabetes, polytransfused β-thalassemia

INTRODUCTION:

B-Thalassemia is a hereditary chronic haemolytic anemia characterized by a defect in the synthesis of beta-globin chains, particularly common in the Mediterranean region, southern Asia, and the Middle East (1).Transfusion programs and the chelation therapy have considerably prolonged the life expectancy of patients (2). This has led to an increase in the prevalence of cardiac, hepatic and endocrine complications, in particular the development of diabetes, related to iron overload (3). The prevalence of diabetes and glucose intolerance (GI) in adolescents and young adults with thalassemia treated conventionally varies between series, from 0 to 10.5% (4) and from 17 to 24%, respectively (5). The mechanism of impaired glucose homeostasis in β-thalassemia is complex and multifactorial (6). The key factors responsible for the development of diabetes in thalassemia are iron overload, chronic liver disease, viral liver infections (transfusion-associated infections such as hepatitis C) and the individual's genotype (7). The objective of our study is to describe the frequency of glucose homeostasis abnormalities in patients with polytransfused β-thalassemia and to study the relationship between glycoregulation abnormalities and serum ferritin level, duration of transfusion treatment, splenectomy and compliance with chelation therapy.

MATERIAL AND METHODS:

This is a cross-sectional, analytical and monocentric study which was carried out in the department of

Pediatrics at Mustapha pacha university hospital and which involved 87 patients with beta thalassemia major (46 girls and 41 boys), followed up on a regular basis, and treated by a transfusion regimen (more than 10 transfusions) combined with chelation therapy. All patients were on a transfusion program, with the objective of maintaining the hemoglobin level above 9g/dl associated with chelation therapy. In our department before 2008, deferoxamine (DFO) was the only chelator available, used intravenously at a dose of 40 mg/kg/day, then replaced between 2008 and 2011 by deferiprone (DFP) orally, and since 2011, we use deferisirox (DFX) orally. DFX has been prescribed when serum ferritin exceeds 1000 ug/l at a dose of 20 mg/kg/day; this dose was maintained as long as serum ferritin was controlled (<2500 ug/l). In patients, whose serum ferritin exceeds 2500 ug/l, an increase in the dose of DFX to 40 mg/kg/day is recommended. After 3 months of treatment, if serum ferritin remains above 2500 ug/l, DFO is added at a dose of 40 mg/kg/day subcutaneously 5 days a week until the serum ferritin values drop below of 2500 µg/l. Patients were assessed by clinical history, physical examination, fasting blood glucose and oral glucose tolerance test (OGTT) associated with a test measurement of HOMA-IR (Homeostasis Model Accessment of insulin resistance). Diagnosis of diabetes mellitus and glucose intolerance were established according to the criteria of the American Diabetes Association (ADA) (Table 1) (8).

Table 1: Criteria for increased risk for diabetes (prediabetes)

Moderate fasting hyperglycemia: fasting blood glucose ≥1g/l and <1.26 g/l (5.6-7mmol/l) and < 1.4g/l (7.8mmol/l) two hours after glucose loading.
Glucose intolerance (GI): fasting blood glucose <1.26 g/l (7 mmol/l) and blood glucose ≥ 1.40 and <2 g/l (7.8-11.1 mmol/l) two hours after glucose loading.
Diabetes: fasting blood glucose ≥ 1.26 g/l (mmol/l) twice or ≥2g/l (11mmol/l) two hours after glucose loading.

The HOMA-IR index (the HOMA of insulin resistance) was the product of fasting plasma insulin (FPI) times fasting blood glucose (FPG), then dividing by the constant 22.5, (HOMA-IR = (FPI × FPG) /22.5) (9). A serum ferritin value > 2500 ug/l has been considered as an indicator of severe iron overload, poor compliance with chelation treatment is defined by repeated forgetfulness of treatment, and / or interruption of treatment for more than a week. Statistical analysis was performed using R software. A descriptive analysis was performed (mean ± standard deviations and/or medians, for quantitative variables and percentages for qualitative variables). The statistical tests of chi2, Fisher, Student, Wilcoxon-Mann-whitney, ANOVA were used for comparisons of two or more variables, and the analysis was completed by carrying out a logistic regression. The statistical significance level was set at 0.05.The bibliography was automatically generated by Zotéro, according to the Vancouver style.

RESULTS:

Our study included eighty-seven cases of β-thalassemia, all the patients were enrolled at the department of Pediatrics at Mustapha pacha university hospital. The average age was 11.2 ± 5.8 years with a range of 2 to 25.7 years, 25% of patients are over 15 years old. Both sexes were equally represented in our series with 46 girls, 41 boys, and a sex ratio of 0.9. The average duration of blood transfusion in our population (which reflects the duration of follow-up of these patients) was 10 years with extremes of 6 months to 24.7 years. Splenectomy was performed in 40% of our patients. Mean serum ferritin was 1653.16±1272 ug/l, 38% of patients had mild iron overload (<1000 µg/l), 41.3% had moderate iron overload (1000-2500 µg/l), and 20.7 % of patients presented with severe iron overload (serum ferritin > 2500 ug/l). Compliance with chelation treatment was considered poor in 15% of our patients. OGTT was performed in 84 patients, and not performed in 3 patients, who had diabetes before the start of the study; twenty eight (32.2%) patients presented with glycoregulation disorders 16 (18.4%) patients presented with moderate fasting hyperglycaemia , 8 (9.2%) patients with GI, 4(4, 6%) patients with diabetes. Among patients with abnormal results, 17 (60.7%) were girls and 11 (39.3%) boys, there is no statistically significant relationship between the two sexes (p=0.31). The average age of patients who presented with glycoregulation disorders was 13.4 ± 6.58 years, compared to unaffected patients 10.2 ± 5.2 years; there was a statistically significant correlation between the two groups (p=0.01). The HOMA test was found positive in 10 (12%) patients; among them, 4 (4.7%) patients had Glucose Intolerance (GI), 2 (2.5%) patients had moderate fasting hyperglycemia, and 4 (4.7%) patients had normal OGTT; there is a significant correlation between the HOMA test and glycoregulation disorders (p=0.02), (OR=4.3). Among the 28 patients with glycoregulation disorders, 5 (27.8%) presented with

severe iron overload (serum ferritin > 2500 µg/l), the other patients presented with moderate to slight iron overload; there is no statistically significant relationship between serum ferritin and glycoregulation disorders (p=0.65). Among the patients with glycoregulation disorders, 15 (53.6%) presented a splenectomy, compared to 13 (46.4%) patients without splenectomy, there is a statistically significant correlation between dysglycemia and splenectomy (OR=2.6), (p=0.03). Sixteen patients had a duration of transfusion greater than 10 years, compared to 12 patients with a duration of transfusion less than 10 years, there is a significant correlation between the duration of transfusion and the glycoregulation disorders (p=0.01, OR=3).

Table 2: Specimen Characteristics by Glycoregulatory Disorder Status

		Glycoregulation disorder		P	OR
		Yes n=28	No n=59		
Mean age		13,4 ans	10,2 ans	0,01	
Sex	Male	11(39,3)	30(50,8)	0,31	
	Female	17(60,7)	29(49,2)		
Ferritinemia (ug/l)	>2500	5(17,9)	13(22)	0,49	
	< 2500	23(82,1)	46(78)		
HOMA	Positive	6(24)	4(6,8)	0,02	4,3
	Negative	19(76)	55(93,2)		
Splénectomy	Yes	15(53,6)	18(30,5)	0,03	2,6
	No	13(46,4)	41(69,5)		
traitment Compliance	No	25(89,3)	49(83,1)	O,44	
	Yes	3(10,7)	10(16,9)		

DISCUSSION:

In our study, glycoregulation disorder, which includes moderate fasting hyperglycemia, Glucose Intolerance (GI), and diabetes, was found with a frequency of 32%. Moderate fasting hyperglycemia was present in 18.4%, GI in 9.2% and diabetes in 4.6% of cases. Najafipour (10) found a higher frequency of moderate fasting hyperglycemia at 28.6% for an average age of 15.5 years. The worldwide prevalence of Diabetes and GI in thalassemia patients treated conventionally with Deferoxamine (DFO) varies in the different series from 0 to 10.5% for diabetes and from 17 to 24% for IG (5), which is similar to our study that finds a prevalence of 4.6% and 9.2% respectively. The frequency of diabetes and GI in our series is higher than in the cohort of De Sanctis (TIF) (11) (2004), (average age of 13 years) that found respectively 3.2% and 6.5% of cases. It is similar to Sharma's study (12), (average age of 13.6 years), at 3.6% and 9.7% of cases (2014), and less frequent than the Khalifa cohort (13), (average age of 16) at 12.1 and 14%.

The considerable variation in the frequency of glycemic abnormalities can be explained by the marked differences in the age of the cohorts, their genetic origin, the transfusion regimens, the degree of chelation and the method of screening used (7). In our study, patients with glycemic abnormalities were significantly older (mean age: 13.4±6.58) compared to patients without glycemic abnormalities (10.2±5.2), (p= 0.01). Khalifa (13) found a higher average age of 17 years, Najafipoor found a similar average age to our study of 14 years (10); the same results are found in several studies where glycoregulation disorder are present in β-thalassemic children from the age of 10 years (14,15). In our study, the condition is more frequent in girls than in boys, but there is no significant difference between the two sexes (p=0.31); This is similar to the Tunisian study by Guirat (16), and does not correspond to the study by De Sanctis and Eslam, where male sex was identified as a risk factor (7,17). Insulin resistance and insulin deficiency, alone or in combination, lead to impaired glucose tolerance and then progress to diabetes in polytransfused β-thalassemia patients, secondary to severe iron overload (6, 18). Tangvarasittichai in 2013 and several other works showed a significant association between glycoregulation disorder and serum ferritin (19–20), whereas this association was absent in our series (p=0.65). Khalifa and Sharma showed the lack of correlation (13, 21), suggesting that other factors are responsible for glycoregulation disorder namely chronic liver disease, viral liver infections (hepatitis C), genetic and autoimmune factors, and family history of diabetes mellitus, (22). HOMA-IR was used for estimation of insulin resistance; it is calculated by multiplying fasting plasma insulin (FPI) by fasting blood glucose FPG, then dividing by the constant 22.5, (HOMA-IR = (FPI × FPG) /22.5) (23). In our

population, HOMA-IR was calculated using OGTT data; the test did not concern the three diabetic patients already treated with insulin who were diagnosed before the start of the study. In our series, 10 (11.9%) patients presented with insulin resistance with a HOMA-IR > 2.5; among these patients, 6 (7.2%) have glycoregulation disorder (4 HGM patients and 2 IG patients) and four (4.7%) patients have normal blood sugar levels. The relationship was statistically significant between disorders of glycoregulation and HOMA-IR (p=0.02), (OR=4.3). Our results confirm the results of Cario and Suvarna, which showed that β-thalassemia patients show an increase in HOMA-IR test compared to the healthy population (24, 25); this confirms the initial concept of diabetes in thalassemia and insulin resistance induced by iron overload (26). Pancreatic beta-cell injury and insulin deficiency caused by the direct toxic damage of the iron not bound to transferrin explain the development of diabetes. (27). Our study shows that splenectomy and the duration of transfusion treatment significantly increase the risk of glycoregulation disorder (p=0.03), (OR=2.6); (0.01), (OR=3) respectively, which corresponds perfectly to the studies of Eslam and De Sanctis which found that splenectomy and long duration of transfusion treatment constitute an important risk factor for glycoregulation disorder (17,28). After logistic regression, only age was retained as a prognostic factor for glycoregulation disorder (ORa = 2. P = 0.02).

CONCLUSION:

Our results suggest that children with β-thalassemia have a high incidence of impaired glycoregulation, usually developing in the second decade of life or later. Detection of the pre-diabetes stage is essential, and can be reversed by intensification of chelation therapy.

Conflict of interests:

The authors report no conflict of interests.

REFERENCES:

1. Cunningham MJ. Update on Thalassemia: Clinical Care and Complications. Pediatr Clin North Am. avr 2008;55(2):447-60. DOI : 10.1016/j.pcl.2008.02.002.
2. Brittenham GM. Iron-Chelating Therapy for Transfusional Iron Overload. N Engl J Med. 13 janv 2011;364(2):146-56. DOI : 10.1056/NEJMct1004810.
3. Vantyghem M-C, Dobbelaere D, Mention K, Wemeau J-L, Saudubray J-M, Douillard C. Endocrine manifestations related to inherited metabolic diseases in adults. Orphanet J Rare Dis. 2012;7(1):11. DOI : 10.1186/1750-1172-7-11.
4. Hafez M, Youssry I, El-Hamed FA, Ibrahim A. Abnormal Glucose Tolerance in β-Thalassemia: Assessment of Risk Factors. Hemoglobin. janv 2009;33(2):101-8. DOI : 10.1080/03630260902817131.
5. Gamberini MR, Fortini M, Sanctis VD, Gilli G, Testa MR. Diabetes Mellitus and Impaired Glucose Tolerance in Thalassaemia Major: Incidence, Prevalence, Risk Factors and Survival in Patients Followed in the Ferrara Center. 2004;2(sup2):8
6. Angelopoulos NG, Zervas A, Livadas S, Adamopoulos I, Giannopoulos D, Goula A, et al. Reduced insulin secretion in normoglycaemic patients with ?-thalassaemia major. Diabet Med. déc 2006;23(12):1327-31. DOI : 10.1111/j.1464-5491.2006.01988.x.
7. De Sanctis V. The Icet-Recommendations for the Diagnosis and Management of Disturbances of Glucose Homeostasis in Thalassemia Major Patients. Mediterr J Hematol Infect Dis. 25 oct 2016;8:14. DOI : 10.4084/MJHID.2016.058.
8. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care. janv 2017;40(Supplement 1):S11-24. DOI : 10.2337/dc17-S005.
9. Gutt M, Davis CL, Spitzer SB, Llabre MM, Kumar M, Czarnecki EM, et al. Validation of the insulin sensitivity index (ISI0,120): comparison with other measures. Diabetes Res Clin Pract. mars 2000;47(3):177-84. DOI : 10.1016/s0168-8227(99)00116-3.
10. Najafipour F. Evaluation of Endocrine Disorders in Patients with Thalassemia Major. Int J Endocrinol Metab. 2008;2:104-13.
11. De Sanctis V, Eleftheriou A, Malaventura C, Thalassaemia International Federation Study Group on Growth and Endocrine Complications in Thalassaemia. Prevalence of endocrine complications and short stature in patients with thalassaemia major: a multicenter study by the Thalassaemia International Federation (TIF). Pediatr Endocrinol Rev PER. déc 2004;2 Suppl 2:249—255.

12. Sharma R, Seth A, Chandra J, Gohain S, Kapoor S, Singh P, et al. Endocrinopathies in adolescents with thalassaemia major receiving oral iron chelation therapy. Paediatr Int Child Health. 2 janv 2016; 36(1):22-7. DOI : 10.1179/2046905514Y.0000000160.
13. Khalifa AS, Salem M, Mounir E, El-Tawil MM, El-Sawy M, Abd Al-Aziz MM. Abnormal glucose tolerance in Egyptian beta-thalassemic patients: possible association with genotyping. Pediatr Diabetes. sept 2004;5(3):126-32. DOI : 10.1111/j.1399-543X.2004.00051.x.
14. Soliman A, Yasin M, El-Awwa A, De Sanctis V. Detection of glycemic abnormalities in adolescents with beta thalassemia using continuous glucose monitoring and oral glucose tolerance in adolescents and young adults with β-thalassemia major: Pilot study. Indian J Endocrinol Metab. 2013; 17(3):490. DOI : 10.4103/2230-8210.111647.
15. Tzoulis P, Shah F, Jones R, Prescott E, Barnard M. Joint Diabetes Thalassaemia Clinic: An Effective New Model of Care. Hemoglobin. avr 2014;38(2):104-10. DOI : 10.3109/03630269.2013.862541.
16. Guirat N. Growth and Endocrine Function in Tunisian Thalassemia Major Patients. Mediterr J Hematol Infect Dis. 1 mai 2018; 10(1): 9. DOI : 10.4084/MJHID.2018.031.
17. Eslam M, Kawaguchi T, Del Campo JA, Sata M, Abo-Elneen Khattab M, Romero-Gomez M. Use of HOMA-IR in hepatitis C: Use of HOMA-IR in hepatitis C. J Viral Hepat. oct 2011;18(10):675-84. DOI: 10.1111/j.1365-2893.2011.01474.x.
18. Zamani F. T2* magnetic resonance imaging of the liver in thalassemic patients in Iran. World J Gastroenterol. 2011;17(4):522. DOI : 10.3748/wjg.v17.i4.522.
19. Tangvarasittichai S, Pimanprom A, Choowet A, Tangvarasittichai O. Association of Iron Overload and Oxidative Stress with Insulin Resistance in Transfusion-Dependent β-Thalassemia Major and β-Thalassemia/HbE Patients. Clin Lab. 2013 ; 59(07+08/2013) :861-8. DOI : 10.7754/clin.lab.2012.120906.
20. McClain DA, Abraham D, Rogers J, Brady R, Gault P, Ajioka R, et al. High prevalence of abnormal glucose homeostasis secondary to decreased insulin secretion in individuals with hereditary haemochromatosis. Diabetologia. juill 2006;49(7):1661-9. DOI: 10.1007/s00125-006-0200-0. Epub 2006 Mar 15.
21. Sharma S, Dutt N, Sidhu M, Digra S, Meenia R. Prevalence of hypothyroidism, diabetes mellitus and delayed puberty in patients of thalassemia major in a tertiary care center of Jammu province, Jammu Kashmir, India. Int J Adv Med. 23 mai 2017;4(3):673.
22. Chatterjee R, Bajoria R. New Concept in Natural History and Management of Diabetes Mellitus in Thalassemia Major. Hemoglobin. janv 2009;33(sup1):S127-30. doi: 10.3109/09553000903347880
23. Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, Gude F, García F, De Francisco A, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. BMC Endocr Disord. déc 2013;13(1):10. DOI : 10.1186/1472-6823-13-47.
24. Cario H, Holl RW, Debatin K-M, Kohne E. Insulin sensitivity and β-cell secretion in thalassaemia major with secondary haemochromatosis: assessment by oral glucose tolerance test. Eur J Pediatr. mars 2003;162(3):139-46. DOI : 10.1007/s00431-002-1121-7. Epub 2003 Jan 15.
25. Suvarna J, Ingle H, Deshmukh CT. Insulin Resistance and Beta Cell Function in Chronically Transfused Patients of Thalassemia Major. INDIAN Pediatr. 2006;43:8.
26. De Sanctis V, Soliman A, Yassin M. Iron overload and glucose metabolism in subjects with β-thalassaemia major: an overview. Curr Diabetes Rev. juill 2013;9(4):332—341. DOI : 10.2174/1573399811309040005.
27. Chern JPS, Lin K-H, Lu M-Y, Lin D-T, Lin K-S, Chen J-D, et al. Abnormal Glucose

Tolerance in Transfusion-Dependent - Thalassemic Patients. Diabetes Care. 1 mai 2001;24(5):850-4. DOI : 10.2337/diacare.24.5.850.

28. De Sanctis V, Soliman AT, Elsedfy H, Pepe A, Kattamis C, El Kholy M, et al. Diabetes and Glucose Metabolism in Thalassemia Major: An Update. Expert Rev Hematol. 2 avr 2016;9(4):401-8. DOI : 10.1586/17474086.2016.1136209.