Current Science International
Volume: 12 | Issue: 01| Jan. - March| 2023

EISSN:2706-7920 ISSN: 2077-4435
DOI: 10.36632/csi/2023.12.1.1
Journal homepage: www.curresweb.com
Pages: 1-6

Assessment of the Pattern of Alternation of Glucose Homeostasis in Adult Patients with Beta Thalassemia

Nadia S. Eltahan[1], Noha E. Esheba[1], Amira A. Yousef[2] and Abd Elmoteleb T. Eissa[1]

[1]Department of Internal Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt
[2]Department of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt

Received: 10 Nov. 2022 **Accepted:** 11 Dec. 2022 **Published:** 10 Jan. 2023

ABSTRACT

Glucose homeostasis is the process of maintaining of blood glucose at steady-state. One significant disease that can affect glucose homeostasis is thalassemia. Iron over load in thalassemic patients affects insulin resistance and aggravates glucose disturbances leading to glucose intolerance and DM. **Methods**: This study was carried on 50 Patients with beta thalassemia, Also 20 healthy volunteers were enrolled as a control group to assess the pattern of alternation of glucose heamostasis in adult patients of beta thalasse mia. **Results**: Insulinogenic index was significaly reduced in thalassemic patients, whole body insulin sensetivity index was significaly reduced in thalassemic patients and Roc curve analysis of the studied parameters to assess glucose homeostasis revealed that, IG I had the highest sensitivity and specificity among the studied parameters. **Conclusion:** The incidence of diabetes mellities in 50 patients of thalassemia major was (10**%**), only 5 patients are diabetic, ferretin level was higher in thalassemic patient, so it could to attribute the pathogenesis of impairment of β-cell function, level of oral glucose tolerance test (0 minute) was higher in β-thalassemia major patients, two hour post prandial glucose was higher in thalassemic patients, whole body insulin sensetivity index was significaly reduced in thalassemic patients, insulinogenic index was significaly reduced in thalassemic patients and Roc curve analysis of the studied parameters to assess glucose homeostasis revealed that, IG I had the highest sensitivity and specificity among the studied parameters.

Keywords: glucose homeostasis, thalassemia

1. Introduction

Glucose homeostasis is the process of maintaining of blood glucose at steady-state. Therefore, blood glucose concentration needs to be maintained within narrow limits. Long-lasting disturbances in blood glucose concentrations can cause diseases and death (Alonge *et al.,* 2021). Most tissues as brain need glucose constantly, as an important source of energy. The low blood concentration of glucose can cause seizures, loss of consciousness, and death. On the other hand, long lasting elevation of blood glucose concentration, can result in blindness, renal failure, vascular disease, and neuropathy (Wilson *et al.,* 2019). The body can adjust glucose levels by secreting two hormones which are insulin and glucagon that work in opposition to each other (Espinoza-Hernández *et al.,* 2021).

Normally, the body maintains the levels of sugar in the blood within a range of about 70 to 110 mg/dL, depending on when a person last ate. In the fasting state, blood sugar can occasionally fall below 60 mg/dL and even to below 50 mg/dL and not indicate a serious abnormality or disease. This can be seen in healthy women, particularly after prolonged fasting (Zhang *et al.,* 2019). The Pathological changes in glucose homeostasis may by hypoglycemia or diabetes mellitus (Padhi *et al.,* 2020).

One significant disease that can affect glucose homeostasis is thalassemia which is a group of frequent genetic disorders resulting in the synthesis of little or no β-globin chains (Mahmoud *et al.,*

Corresponding Author: Nadia Salah Eltahan, Department of Internal Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt. E-mail: nadiaeltahan44@gmail .com

2021). It is a common cause of hypochromic microcytic anemia which arises from the reduced or absent synthesis of the globin chain of hemoglobin (Alli *et al.,* 2021).

Patients of thalassemia need continuous blood transfusion to survive, the most important problem in this patient include iron overload, cardiac arrhythmia, hepatitis, osteoporosis and endocrine disorder (Demosthenous *et al.,* 2020). Iron overload in thalassemic patients affects insulin resistance and leads to reduction in insulin sensitivity as a result of direct toxic damage to pancreatic ß-cells, aggravates glucose disturbances leading to glucose intolerance and DM (Lytrivi *et al.,* 2020).

The objective of this study was to assess the pattern of alternation of glucose heamostasis in adult patients of beta thalassemia.

2. Patients and Methods

I. Study Design: This is a prospective controlled study.

II. Study Population and study settings

The study was carried out on 50 Patients with beta thalassemia. The patients were recruited from the clinic and wards of the Hematology Unit, Internal Medicine Department, Tanta University Hospital. The study duration started from May 2020 to Novamber 2020. Also 20 healthy volunteers were enrolled as a control group.

The participants were divided into 2 groups:

- Group I: 50 adult patients with beta thalassemia.
- Group II: 20 apparently healthy individuals as a control group.

III. Inclusion criteria: Patients ≥ 18 years diagnosed to have beta thalassemia by high performance liquid chromatography (HPLC).

V. Exclusion criteria: Other hemoglobinopathies as alpha thalassemia or sickle thalassemia. Family history of DM. Patients with other endocrine abnormalities such as hyper- or hypothyroidism. Patients with other systemic illness, such as chronic liver disease, chronic renal disease, cardiomyopathy.

2.1. Methods

2.1.1. Glucose homeostasis abnormalities in thalassemic patients was diagnosed based on:

All the participants were subjected to full history taking with special emphasis on age, sex, consanguinity, age of diagnosis of thalassemia, disease duration, transfusion history, investigation (CBC, reticulocytic count, serum ferritin,triglyceride, low density lipoprotein (LDL), cholesterol, high density lipoprotein (HDL), complete liver function, renal function. fasting and 2 hours post prandial blood glucose, oral glucose tolerance test (OGTT). fasting insulin by immune-enzymometric assay. assessment of insulin resistance using the following parameters (Homeostatic model assessment (HOMA) of insulin resistance) HOMA-IR= glucose in mmol/L x insulin in mIU/mL)/22. Whole body insulin sensitivity index (WBISI) = 10.000/ (fasting insulin × fasting glucose) × (mean glucose × mean insulin). Assessment of beta cell function using the following parameters (Homeostatic model assessment (HOMA) of β-cell functionHOMA-B= (20 × insulin (mU/l))/ (glucose (mmol/l–3.5). Insulinogenic index (IGI) = ($Insulin_{30}$ – $Insulin_{0}$) / ($Glucose_{30}$ – $Glucose_{0}$) and Disposition index (DI) = WBISI x IGI.

2.2. Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 **(**Armonk, NY: IBM Corp**)**. Qualitative data were described using number and percent. The Kolmogorov-Smirnov test and Shapiro-Wilk test were used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were Chi-square test for categorical variables, to compare between different group**.** Fisher's Exact or Monte Carlo correction for chi-square when more than 20% of the cells have expected count less than 5**.** Student t-test for normally distributed quantitative variables, to compare between two studied groups. Pearson coefficien to correlate between two normally distributed quantitative variable. Mann Whitney test for abnormally distributed quantitative variables, to compare

between two studied groups**.** Wilcoxon signed ranks test for abnormally distributed quantitative variables, to compare between two periods Spearman coefficien to correlate between two distributed abnormally quantitative variable. Receiver operating characteristic curve (ROC), It is generated by plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test. The ROC curve allows also a comparison of performance between two tests.

3. Results

There was significant difference (increase) between patients with beta thalassemia and our normal control subjects in Platelets, Retic, Ferritin, TG, SGPT, SGOT and OGTT (0 minute). While there was significant difference (decrease) between patients with beta thalassemia and our normal control subjects in hemoglobin level. On the other hand, there was insignificant difference between patients with beta thalassemia and our normal control subjects in Age, Sex, Cholesterol, HDL, LDL, Urea, Creatinine and OGTT (After 2 hrs) (Table 1).

Table 1: Comparison between the two studied groups according to CBC, retic, ferritin, age, sex and lipid profile, liver enzymes, renal function and oral glucose tolerance test.

Parameter	Mean /median	Group I	Group II	Test of sig.	P
Age (years)	Mean ± SD.	27.44 ± 8.70	29.35 ± 4.92	t=1.157	0.252
Sex	Male	30 60	10 50	χ^2 = 0.583	0.445
	Female	20 40	10 50		
TLCx10^3 (cell/cmm)	Min. – Max.	3.40 – 15.0	4.09 – 11.0	U= 494.50	0.943
	Median (IQR)	6.93 (5.10 – 9.60)	6.80 (5.65 – 9.60)		
Plateletsx10^3 (cell/cmm)	Min. – Max.	150.0 – 700.0	150.0 – 450.0	U =77.0*	<0.001*
	Median (IQR)	527.50 (440 – 606)	295.(190- 380)		
Hemoglobin (g/dl)	Mean ± SD.	7.60 ± 1.20	11.99 ± 0.62	t=20.039*	<0.001*
Retic* (%)	Min. – Max	0.30 – 3.30	0.50 – 2.00	U= 52.50*	<0.001*
	Median (IQR)	2.15 (1.50 – 2.60)	0.90 (0.70 – 1.0)		
Ferritin (ng/ml)	Mean ± SD.	27.44 ± 8.70	29.35 ± 4.92	t=20.039*	<0.001*
TG (mg/dL)	Mean ± SD.	154.64 ± 71.28	118.60 ± 40.85	t=2.237*	0.029*
Cholesterol (mg/dL)	Min. – Max	42.0 – 360.0	93.0 – 300.0	U=453.50	0.545
	Median (IQR)	143.0 (103 - 199)	168.0(108 – 201.5)		
HDL (mg/dL)	Mean ± SD.	69.0 ± 17.25	68.35 ± 13.14	t=0.152	0.880
LDL (mg/dL)	Mean ± SD.	84.46 ± 23.02	94.35 ± 24.14	t=1.602	0.114
SGPT(u/liter)	Mean ± SD	51.76 ± 9.36	26.05 ± 8.69	10.590*	<0.001*
SGOT (u/liter)	Mean ± SD	43.28 ± 5.57	26.85 ± 8.19	8.241*	<0.001*
Urea (mg/dL)	Min. – Max.	15.0 – 63.0	16.0 – 45.0	372.0	0.096
	Median (IQR)	29.0 (22.0 – 38.0)	38.0(29.50– 42.50)		
Creatinine (mg/dL)	Min. – Max.	0.50 – 2.30	0.50 – 1.30	375.0	0.102
	Median (IQR)	1.0 (0.80 – 1.30)	0.90 (0.75 – 1.05)		
OGTT(0 minute)	Min. – Max.	73.0 – 170.0	71.0 – 95.0	U =285.50*	0.005*
	Median (IQR)	95.0 (85 - 101)	88.50(79.5– 91.50)		
OGTT (After 2 hr	Min. – Max.	95.0 – 240.0	100.0 – 136.0	U =432.0	0.380
	Median (IQR)	126.0 (111 - 140)	124.0 (112.5 - 130)		

CBC**:** Complete blood picture**.** TLC: Total leucocytic count**.** Retic: reticulocytic percentage. TG: Triglycerides HDL: High density lipoprotein LDL: Low density lipoprotein SGPT: Serum Glutamic-tranaminase, SGOT: serum glutamic-oxaloacetic Tranaminase. OGTT: Oral glucose tolerance test. 2HPP: Two hours post prandial.

There was significant difference between patients with beta thalassemia and our normal control subjects in IG I. Insulinogenic index was significantly higher in group II in comparison to group I (P= <0.001). While no significant difference was found in parameters as F INS, WBISI, HOMA-B, DI and HOMA-IR between the two groups (Table 2).

Table 2: Comparison between the two studied groups according to different parameters

	Group I (n = 50)	Group II (n = 20)	Test of sig.	P
F INS (mIU/L)				
Min. – Max.	4.0 – 23.0	5.0 – 13.0	U= 482.5	0.819
Median (IQR)	9.0 (6 - 14)	8.50 (6.5 – 11.0)		
WBISI				
Min. – Max.	0.27 – 0.45	0.29 – 0.45	t=2.289*	0.027*
Mean ± SD.	0.37 ± 0.06	0.40 ± 0.04		
HOMA-B				
Min. – Max.	0.20 – 6.0	0.90 – 6.0	U= 395.50	0.173
Median (IQR)	4.0 (1.50 – 5.0)	4.50 (3.85 – 5.20)		
DI				
Min. – Max.	57.0 – 95.0	74.0 – 92.0	t=0.969	0.336
Mean ± SD.	79.22 ± 9.17	81.35 ± 5.50		
HOMA-IR				
Min. – Max.	0.50 – 6.30	0.60 – 2.0	U=472.50	0.719
Median (IQR)	1.10 (0.80 – 2.20)	1.10 (1.0 – 1.30)		
IG I				
Min. – Max.	0.30 – 1.60	1.0 – 2.30	t=4.913	<0.001*
Mean ± SD.	1.0 ± 0.39	1.52 ± 0.43		

DI: Disposition index. INSI: Insulinogenic index. FINS: Fasting insulin WBISI: Whole body insulin sensitivity index. HOMA-IR: Homeostatic model assessment of insulin resistance HOMA-B: Homeostatic model assessment of B -cell function.

Roc curve analysis of the studied parameters to assess glucose homeostasis revealed that, IG I had the highest area under the curve among them (AUC=0.793) at a cut-off value for IG I about≤1.3g/dl achieving 76.0% sensitivity and 55.0% specificity (Table 3).

Table 3: Receiver Operating characteristics curve (ROC curve) for different parameters to discriminate patients with beta thalassemia (n = 50) from control (n = 20)

	AUC	P	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
WBISI	0.643	0.063	0.510 – 0.776	≤0.4	66.0	50.0	76.7	37.0
HOMA-B	0.605	0.174	0.465 – 0.744	≤4.9	70.0	45.0	76.1	37.5
DI	0.546	0.554	0.405 – 0.686	≤80	56.0	55.0	75.7	33.3
HOMA-IR	0.528	0.721	0.394 – 0.661	>1	52.0	40.0	68.4	25.0
IG I	0.793	<0.001*	0.679 – 0.906	≤1.3	76.0	55.0	80.9	55.6

Positive PPV: predictive value. CI: Confidence Intervals AUC: Area Under a Curve p value: Probability value NPV: Negative predictive value

4. Discussion

Glucose homeostasis is the balance between insulin and glucagon to maintain blood glucose within normal range which are necessary for survival (Alonge *et al.,* 2021). Insulin lower blood glucose by increase glucose uptake in the muscle and adipose tissue by promoting glycolysis and glycogenesis (Folli *et al.,* 2018).

A fall in blood glucose increase the release of glucagon from the pancrease to promote glucose production by activating liver glycogenolysis and glycogeonesis which result in release of glucogen to the blood streame (Zhang *et al.,* 2019).

Thalassemia is a group of frequent genetic disorders resulting in the synthesis of little or no β-globin chains (Mahmoud *et al.,* 2021). It is a common cause of hypochromic microcytic anemia which arises from the reduced or absent synthesis of the globin chain of hemoglobin (Alli *et al.,* 2021).

The objective of this study was to assess the pattern of alternation of glucose heamostasis in adult patient of beta thalassemia.

In the current study, regarding to OGTT (0minute) it was significantly higher in thalassemic patients when compared with normal controls (p= 0.005) because abnormal glucose tolerance is common in multi-transfused β-thalasemia major patients and could be attributed to early impaired β-cell function with increasing IR.

In the current study, regarding to OGTT (After 2 hrs) there was no statistically significant difference in thalassemic patients when compared with normal controls (p=0.380).

In the current study, fasting insulin was higher in thalasemic patients when compared to the controls, but the difference did not reach statistical significance (p=0.819) (De Sanctis *et al.,* 2022). On the other hand, Other study showed that insulin and β-cell function decreased significantly in serum of β thalassemia patients when compared with that of the control group, this due to iron excess and its related oxidative stress can mediate apoptosis of pancreatic islet cells resulting in decreased insulin secretory capacity (De Sanctis *et al.,* 2021).

In the current study, regarding to (WBISI) it was significantly lower in thalassemic patients when compared with normal controls (p=0.027). This could be explained by the earliest manifestations of glucose dysmetabolism in patients with β-thalassaemia major is a decrease in insulin sensitivity, followed by the appearance of glucose intolerance (Gao *et al.,* 2021).

In the current study, regarding to homeostatic model assessment of B –cell (HOMA-B) there was no statistically significant difference in thalassemic patients when compared with normal controls (p= 0.173). Other study reported statistical significant reduction in beta cell function in cases when compared to controls. Beta cell function is observed to deteriorate with age and recurrent blood transfusion (De Sanctis *et al.,* 2021).

In the current study, regarding to desposition index (DI) there was no statistically significant difference in thalassemic patients when compared with normal controls (p= 0.336). Other study reported statistical significant reduction in beta cell function in cases when compared to controls. Beta cell function is observed to deteriorate with age and recurrent blood transfusion (De Sanctis *et al.,* 2021).

In the current study, regarding to Homeostatic model assessment of insulin resistance (HOMA-IR), there was no statistically significant difference in thalassemic patients when compared with normal controls (p= 0.719). other study showed that the insulin resistance index was higher in cases compared to controls and the difference was highly significant. This could explained by the increase in fasting serum glucose and insulin resistance index accompanied with normoinsulinemia suggests some degree of insulin resistance and relative pancreatic failure, because normally the islet cells should produce more insulin to overcome hyperglycemia. It is likely that an elevated level of iron and ferritin cause iron toxicity in the liver and pancreas and insulin dysregulation, due to hepatic and pancreatic dysfunction, which is most likely the cause of impaired glucose metabolism in our patients (Gao *et al.,* 2021; De Sanctis *et al.,* 2021).

In the current study, regarding to insulinogenic index (INSI), it was significantly lower in thalassemic patients when compared with normal controls (p= <0.001). This due to iron excess and its related oxidative stress can mediate apoptosis of pancreatic islet cells resulting in decreased insulin secretory capacity (Falcone *et al.,* 2021; De Sanctis *et al.,* 2021).

On performing ROC curve for the studied parameters of glucose homeostasis, we found that INS I had the largest AUC and the highest sensitivity (76%), so it could serve as the best parameter to study glucose homeostasis in thalasemic patients (El samahy *et al.,* 2019).

Based on the results of our study, it could be included that: Out of the four studied parameters of glucose homeostasis, IG I had the highest sensitivity and specificity among them. It can be used for early detection of disturbance of glucose homeostasis.

Reference

Alli, N., M. Patel, J. Pool, *et al.,* 2021. Thalassaemia (part1). South African Medical Journal; 111 (6):529-534.

Alonge, K.M., D.A. D'Alessio, and M.W. Schwartz, 2021. Brain control of blood glucose levels: implications for the pathogenesis of type 2 diabetes. Diabetologia, 64 (1): 5-14.

De Sanctis, V., A. Soliman, P. Tzoulis, *et al.,* 2021. A study of isolated hyperglycemia (blood glucose≥ 155 mg/dL) at 1-hour of oral glucose tolerance test (OGTT) in patients with β-transfusion dependent thalassemia (β-TDT) followed for 12 years. Acta Bio Medica: Atenei Parmensis, 92 (4).

De Sanctis, V., A.T. Soliman, P. Tzoulis, *et al.,* 2021. Glucose metabolism and insulin response to oral glucose tolerance test (OGTT) in prepubertal patients with transfusion-dependent β-thalassemia (TDT): A long-term retrospective analysis.Mediterranean Journal of Hematology and Infectious Diseases, 13 (1):1-8.

De Sanctis, V., S. Daar, A.T. Soliman, *et al.,* 2022. Screening for glucose dysregulation in β-thalassemia major (β-TM): An update of current evidences and personal experience. Acta Bio Medica: Atenei Parmensis, 93 (1): 158.

Demosthenous, C., E. Vlachaki, C. Apostolou, *et al.,* 2019. Beta-thalassemia: renal complications and mechanisms: a narrative review. Hematology, 24 (1): 426-438.

El samahy, M., A. Tantawy, and A. Adly, 2019. Evaluation of continious glucose monitoring system for decection of alternation in glucose homeostasis in pediatric patients with Beta-Thalassemia major pediatric diabetes, 20(1):65-72.

Espinoza-Hernández, F., A. Andrade-Cetto, S. Escandón-Rivera, *et al.,* 2021. Contribution of fasting and postprandial glucose-lowering mechanisms to the acute hypoglycemic effect of traditionally used Eryngium cymosum F. Delaroche. Journal of Ethnopharmacology, 279, 114339.

Falcone, V., F. Heinzl, B.K. Itariu, *et al.,* 2022. Gestational Diabetes Mellitus in Pregnant Women with Beta-Thalassemia Minor: A Matched Case-Control Study. Journal of Clinical Medicine, 11 (7):2-8.

Folli, F., S. La Rosa, G. Finzi, *et al.,* 2018. Pancreatic islet of Langerhans' cytoarchitecture and ultrastructure in normal glucose tolerance and in type 2 diabetes mellitus. Diabetes, Obesity and Metabolism, 20: 137-144.

Gao, W., Y. Jin, M. Wang, *et al.,* 2022. Case Report: Abnormally Low Glycosylated Hemoglobin A1c Caused by Clinically Silent Rare β-Thalassemia in a Tujia Chinese Woman. Frontiers in Endocrinology, 13:1-5.

Lytrivi, M., A.L. Castell, V. Poitout, *et al.,* 2020. Recent insights into mechanisms of β-cell lipo-and glucolipotoxicity in type 2 diabetes. Journal of molecular biology-1514 (5) 432 .1534.

Mahmoud, H., N. Nasef, D. Eldewi, *et al.,* 2021. Role of Complement Regulatory Proteins (CD55, CD59, and CD35) on Red Blood Cells of β-Thalassaemia Patients. Open Journal of Blood Diseases; 11 (4): 89-104.

Padhi, S., A.K. Nayak, and A. Behera, 2020. Type II diabetes mellitus: A review on recent drug based therapeutics. Biomedicine and Pharmacotherapy, 131, 110708.

Wilson, D.F. and F.M. Matschinsky, 2019. Hyperbaric oxygen toxicity in brain: A case of hyperoxia induced hypoglycemic brain syndrome. Medical Hypotheses, 132, 109375.

Zhang, C., L. Zhang, S. Ding, *et al.,* 2018. Postprandial insulin and glucagon secretions during a mixed-meal tolerance test in dietary induced metabolic syndrome cynomolgus monkeys. J. Vet. Sci. Technol., 9 (550), 2.