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Association of Iron Overload with Insulin Resistance in Transfusion-Dependent Beta Thalassemia Major Patients via Homeostatic β-Cell Model (HOMA-Beta) and Homeostatic Insulin Resistance Model (HOMA-IR): Insights from a Thalassemia Center in Karachi, Pakistan

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Abstract

Objective: To determine incidence of diabetes mellitus in transfusion dependent beta-thalassemia major patients, pancreatic beta-cell function by HOMA-beta & insulin resistance by HOMA-IR in beta-thalassemia major patients and the relation of beta-cell function and insulin resistance with iron overload in transfusion dependent beta-thalassemia major patients.

Methodology: This cross-sectional study was conducted in Baqai Medical University Karachi and Muhammadi Thalassemia Center Karachi. A total of 100 patients of both genders; age group between 2 years to 16 years were included in this study. Lab investigations were performed for FBS, Plasma Insulin, HbA1c, and Serum Ferritin on fully automated chemiluminence analyzer. HOMA-IR and HOMA-Beta were calculated.

Results: Prevalence of diabetes mellitus in transfusion dependent beta-thalassemia major patients was 15%. According to HOMA-IR, 48% patients had severe insulin resistance. HOMA-Beta was significantly lower in diabetic than non-diabetic patients. Relationship between HOMA-IR and HOMA-Beta according to iron overload status (≤ 2500 and >2500) was positive but the correlation was strong (r=0.85) between HOMA-IR and HOMA-Beta in patients whose iron overload status was less than and equal to 2500 however correlation of these HOMA-IR and HOMA-Beta was week (r=0.209) in those whose iron overload was >2500.

Conclusion: Iron overload is significantly promoting insulin resistance in transfusion-dependent beta-thalassemia major patients. Beta-thalassemia major patients are developing insulin resistance because of repeated blood transfusions. HOMA-Beta and HOMA-IR are reliable predictors of insulin resistance.

Keywords: Iron overload, insulin resistance, beta-thalassemia, HOMA-IR, HOMA-Beta.

Introduction

All over the world Thalassemia is the most prevalent hereditary hemoglobinopathy of autosomal recessive inheritance, resulting in life threatening hemolytic anemia.[1] Worldwide there are an estimated 15 million people with thalassemia and over the next 20 years, an additional 900,000 cases of clinically severe thalassemia are predicted to be diagnosed. [2] Based on available data, thalassemia is a major health concern in our country as Pakistan is among the countries with the highest incidence of thalassemia globally.[3]

Absent or reduced synthesis of the beta globin chain results in beta-thalassemia, beta-thalassemia major and beta-thalassemia intermedia are two clinically significant forms that require medical attention.[4] Beta-thalassemia major also known as Cooley's anemia is the most severe type of thalassemia, usually diagnosed between the age of 2 months to 2 years and frequent blood transfusions are required for the survival in these patients.[5] The survival rate and life expectancy of thalassemia patients has been significantly increased to reach into 4th and 5th decades of life by blood transfusions and treatment with iron chelation therapy.[6] However, as beta thalassemia major patients live longer and receive multiple blood transfusions, iron tissue toxicity has increased in frequency and has a significant impact on morbidity, thus, because of iron overload, these patients experience various complications throughout their lives, including behavioral and neurotic issues, endocrinopathies,

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cardiovascular issues, liver disease, gonadal dysfunction, growth failure and delayed puberty. [7,8] Approximately 200 mg of iron is present in each unit of packed cell so around 5 grams of iron per year would accumulate in a patient who is receiving 25 units in one year.[2]

Consequently, in beta-thalassemia major patients, iron overload begins in pancreatic beta cells in their early childhood, leading to one of the most common complications diabetes mellitus, according to different cross-sectional studies worldwide. The prevalence of diabetes mellitus ranges from 6.4% to 14.1%.[9,10] Decreased pancreatic beta cell function and increased insulin resistance lead to the pathogenesis of diabetes.[11]

The Homeostatic Model of Assessment (HOMA) is a preferable statistical method for assessing insulin resistance (HOMA-IR) and pancreatic beta-cell function (HOMA-β or HOMA-Beta), both are calculated by using values of fasting glucose and insulin levels; however, the formulas are different. [12] HOMA-IR is calculated by using formula, HOMA-IR = fasting insulin (μU/ml) × fasting plasma glucose (mg/dl)]/405 and HOMA-Beta is calculated by using formula, HOMA-Beta = 20 × fasting insulin (μU/ml)/[fasting plasma glucose (mg/dl) – 63. [13]

Hence, this research aims to determine incidence of diabetes mellitus in transfusion dependent beta-thalassemia major patients, beta-cell function of pancreas by HOMA-beta & insulin resistance by HOMA-IR in beta-thalassemia major patients and the relation of beta-cell function and insulin resistance with iron overload status in transfusion dependent beta-thalassemia major patients. Therefore, in light of the information obtained from this study, the authors hope to contribute in planning an effective management strategy for the prevention of diabetes mellitus and thus reduce its complications in transfusion-dependent beta-thalassemia major patients. The results of this study will also aid in establishing the local data, as there is a paucity of local studies.

Methodology

This cross-sectional study was conducted at Baqai Medical University Karachi and Muhammadi Thalassemia Center Karachi, after approval from Ethics Committee Baqai Medical University and Board of Advanced Studies and Research (BASR), Baqai Medical University. The study population of transfusion dependent beta thalassemia major patients was included from the city of Karachi, the duration of study was 6 months from December 2021 to May 2022. A total of 100 transfusion dependent beta-thalassemia major patients with more than 20 units of RBC transfusion, of both genders of age 2 years and above, were selected after taking written and informed consent from their parents and guardians.

Samples for fasting blood sugar levels, insulin levels, ferritin levels, and HbA1c were collected. The Roche Cobas e411 analyzer was used for samples of serum ferritin and fasting blood insulin and for samples of HbA1c and fasting blood glucose, the Roche Cobas c111 analyzer was used. For determining insulin resistance and pancreatic beta cell functions, HOMA-IR and HOMA-Beta were calculated.

Data was analyzed on SPSS Version 22. Quantitative variables were estimated either mean ±SD and median with IQR. Normality of data was checked by Kolmogorov–Smirnov test and histogram. For the qualitative variables frequencies and percentages were calculated. Independent sample t test and Mann-Whitney U test was used for mean or median comparison between two categories. Chi-square test and Fisher exact test were used for proportion comparison between categories. Spearman and Pearson correlation was also computed between HOMA-IR and HOMA-Beta and with hematological and biochemical variables. Linear regression analysis was performed for multivariable analysis. $p<0.05$ was considered as significant.

Results

The average age of the patients was 7.91±2.92 years. There were 49% male and 51% females. Out of 100 patients 10% were pre-diabetic and the prevalence of diabetes mellitus in transfusion dependent beta-thalassemia major patients was 15% In accordance with HOMA-IR, 13% of patients had optimal (mild) insulin resistance, 15% had early (moderate) IR, 48% had severe IR, and 24% had normal insulin. Mean insulin resistance was significantly high in diabetic as compare to non-diabetic cases. [5.54±1.35 vs. 2.72±1.74; $p=0.0005$. Median HOMA-beta cell function was significantly lower in diabetic patients than non-diabetic patients ($p=0.023$). Similar median Serum ferritin was significantly high in diabetic patients than non-diabetic patients ($p<0.01$) (Table I; Figues1-5).

Table I: Diabetic and Non-Diabetic Status.	
Diabetic and Non-diabetic status	Percentage
Normal	75%
Diabetic	15%
Pre-Diabetic	10%

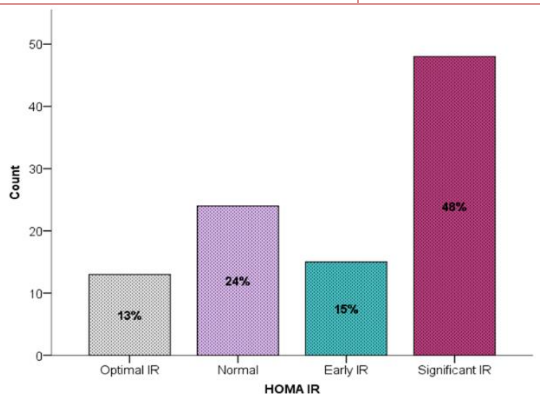

Figure 1. Insulin Resistance According to HOMA-IR in Transfusion-Dependent β-Thalassemia Major Patients (n = 100)

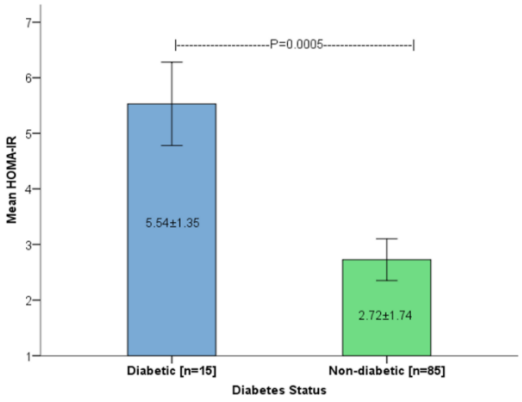

Figure 2. Comparison of Mean HOMA-IR Between Diabetic and Non-Diabetic Transfusion-Dependent β-Thalassemia Major Patients (n = 100)

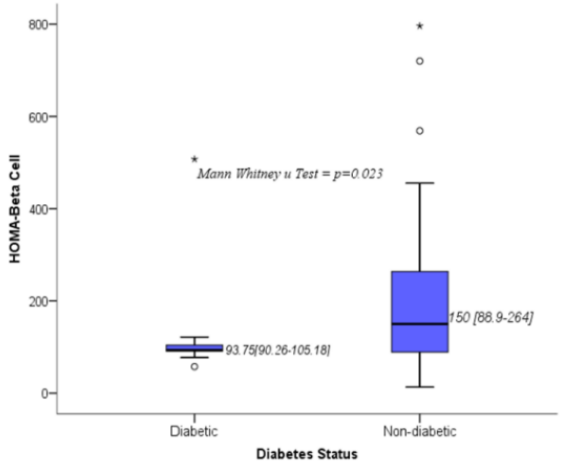

Figure 3. Comparison of Median HOMA-Beta Cell Function Index Between Diabetic and Non-Diabetic Transfusion-Dependent β-Thalassemia Major Patients. (n = 100)

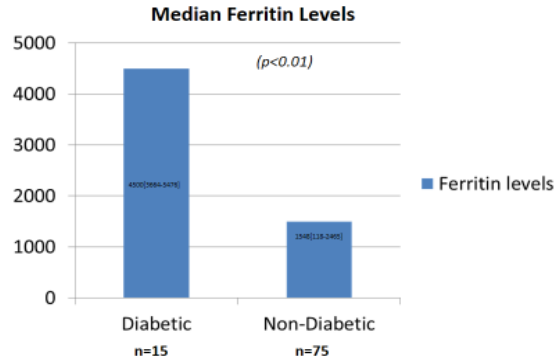

Figure 4. Comparison of Median Ferritin Levels in Diabetic and Non-Diabetic Transfusion-Dependent β-Thalassemia Major Patients.

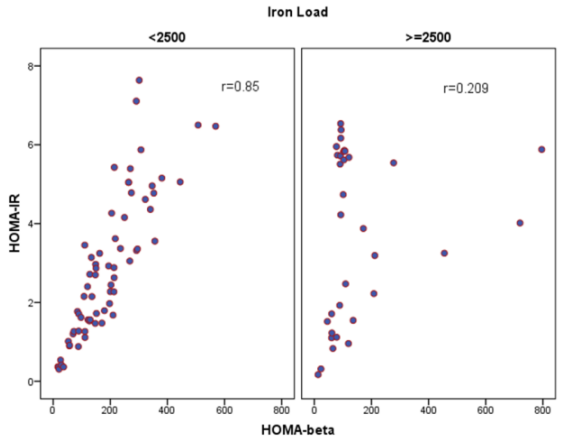

Figure 5. Relationship Between HOMA-IR and HOMA-Beta According to Iron Overload in Transfusion-Dependent β-Thalassemia Major Patients.

Discussion

Blood transfusions have significantly increased life expectancy in beta-thalassemia major patients by decreasing the risk of anemia, but because of the deposition of iron in different body tissues, specifically in vital organs, iron overload and complications related to it are still a major concern. [14]

In our study relationship between HOMA-IR and HOMA-Beta according to iron overload status (≤ 2500 and >2500) was positive but the correlation was strong (r=0.85) between HOMA-IR and HOMA-Beta in patients whose iron over load status was less than and equal to 2500 however correlation of these HOMA-IR and HOMA-Beta was weak (r=0.209) in those whose iron overload status was >2500 as shown in scatter plot (figure 5). Correlation between HOMA-IR and FBS, HbA1c, serum ferritin was positive and statistically significant however

correlation between HOMA-Beta and FBS, serum ferritin was negative and statistically significant.

Our study revealed that excessive iron levels are greatly exacerbating insulin resistance there is an association of iron overload with insulin resistance in transfusion dependent beta-thalassemia major patients and despite having iron chelation therapy the transfusion dependent beta-thalassemia major patients developed insulin resistance because of increased frequency of blood transfusions and HOMA-Beta & HOMA-IR are useful predictors of insulin resistance.

Shah S et al. reported 5% of patients with diabetes mellitus, by considering random blood glucose levels (RBS) of ≥200 mg/dl as diabetes mellitus.[15] This might be due to the reason that they only use RBS level and no other parameters like FBS, HbA1c and HOMA-IR & HOMA-Beta. Compared to our study, Zafar U et al. found 13% of the patients with impaired fasting blood glucose, 5.6% patients with impaired 2-hour postprandial levels and 2 patients had their levels in diabetic range. These results are almost similar to our study and emphasize the value of routine follow-up for individuals with beta-thalassemia major for the early identification of complications and treatment of related problems HOMA-IR and HOMA-beta were not employed in this investigation to predict pre-diabetic status.[16]

Results of various international studies are also similar to the findings of our study, and they used more or less the same parameters. Liang LY et al. reported 7% patients with diabetes mellitus and 24% with impaired fasting glucose, concluded that iron overload was the key factor that was closely associated to the high prevalence of impaired glucose metabolism in beta-thalassemia major patients, in addition, T2* for the liver and heart were estimated in 36 patient.[17] In our study because of limited budget and financial resources we were not able to analyze iron load in cardiac and liver tissues. Sadullah RK et al. identified 3.3% patients with diabetes mellitus as a complication associated with iron overload, considered patients already on treatment for diabetes or on the FBS level, HbA1c, HOMA-IR, HOMA-Beta were not evaluated.[18]

Studies of Tangvarasittichai S et al, and Setoodeh S et al. concluded an association between iron overload and insulin resistance in thalassemia major patients by using HOMA-IR as a predictor of insulin resistance. [19,20] Our study agrees with Ghergherehchi R et al. findings that repeated blood transfusions are contributing to impaired beta cells functions of pancreas and increased insulin resistance, which are attributable to abnormal glucose metabolism in beta-thalassemia major patients. [21] In agreement to our study Matar BM et al. found high incidence rate of glycemic disorders as a result of increased iron overload in beta-thalassemia major patients, by analyzing serum ferritin, serum iron, fasting glucose and insulin levels, though HOMA-IR and HOMA-Beta were not evaluated.[22] Wankanit S et al. also reported association between iron overload and insulin resistance in transfusion dependent beta-thalassemia patients by evaluating serum ferritin, HOMA-IR and HOM-Beta, in addition oral glucose tolerance test was also performed.[23] Similarly, Zhang L et al. reported 14.41% of patients with diabetes, whereas 40.68% had both impaired fasting glucose and impaired glucose tolerance by analyzing Serum ferritin, HOMA-IR and HbA1c, also oral glucose tolerance test and cardiac T2 were performed.[24] Aligning with our study, by investigating serum iron, serum ferritin, fasting serum glucose, fasting serum insulin, HOMA-IR and HOMA-Beta, AbdElkawy MM et al. determined that despite iron chelating therapies, transfusion dependent beta-thalassemia major children are at high risk of developing insulin resistance, which will lead to abnormalities in glucose metabolism; therefore, effective management and continuous follow-up are essential for early diagnosis and to prevent miserable complications.[25] De Sanctis V et al. concluded, transfusion dependent beta-thalassemia major on effective iron chelation therapy are still at high risk of developing disorders of glucose metabolism, iron chelation therapy did not completely prevent individuals of experiencing these complications.[26]

STUDY LIMITATIONS: Along with the COVID-19 delay and time limitations, constrained financial resources were the main issue experienced during this research work. Since the majority of parents and guardians were illiterate and had inadequate medical knowledge, it was difficult to guide them to keep patient NPO (nil per orally) as it was required to obtain the samples. Also, it was challenging for parents and guardians to keep patient NPO as patients were too young with various complications and starving is problematic in such scenarios. Cardiac T2* MRI is considered as a gold standard technique to assess iron over load in heart but because of limited budget and resources we were not able to analyze iron load in cardiac tissues.

Conclusion

There is an association of iron over load with insulin resistance in transfusion dependent beta-thalassemia patients & despite having iron chelation therapy the transfusion dependent beta thalassemia major patients developed insulin resistance because of increased frequency of blood transfusions. For the prediction of insulin resistance HOMA-Beta and HOMA-IR can be used as reliable predictors of insulin resistance.

References

1. Shafique F, Ali S, Almansouri T, Van Eeden F, Shafi N, Khalid M, et al. Thalassemia, a human blood disorder. Braz J Biol. 2021 Sep 3;83. https://doi.org/10.1590/1519-6984.246062
2. Ullah W, Anjum P, Sultana A, Khan M, Amin R. Assessment of serum ferritin in beta thalassemia major patients: Insights from a thalassemia centre in Pakistan. J Popul Ther Clin Pharmacol. 2024;31(1):579-86.
3. Bibi A, Hassan M, Khan SU, Naeem MO, Asnath L. Assessment of the quality of life of children with beta thalassemia in Peshawar district: A cross-sectional study. Pak J Med Res. 2021;60(3):121-5.
4. Origa R. Beta-thalassemia. Genet Med. 2017;19(6):609-19. https://doi.org/10.1038/gim.2016.173
5. Ali S, Mumtaz S, Shakir HA, Khan M, Tahir HM, Mumtaz S, et al. Current status of beta-thalassemia and its treatment strategies. Mol Genet Genomic Med. 2021;9(12):e1788. https://doi.org/10.1002/mgg3.1788
6. Farmakis D, Porter J, Taher A, Cappellini MD, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-Dependent Thalassemia. Hemasphere. 2022 Aug 1;6(8):e732. https://doi.org/10.1097/HS9.0000000000000732
7. Yadav PK, Singh AK. A review of iron overload in beta-thalassemia major, and a discussion on alternative potent iron chelation targets. Plasmatology. 2022;16:26348535221103560. https://doi.org/10.1177/26348535221103560
8. Jahir SJ, Anwar S, Khasru AKMAM, Islam A, Islam K, Khan MKA. Advantages of Deferiprone with Deferasirox over Deferiprone alone in iron chelation therapy of thalassemic children. Insight. 2019;3(1). https://doi.org/10.3329/bjch.v43i3.49571
9. El-Samahy MH, Tantawy AA, Adly AA, Abdelmaksoud AA, Ismail EA, Salah NY. Evaluation of continuous glucose monitoring system for detection of alterations in glucose homeostasis in pediatric patients with β-thalassemia major. Pediatr Diabetes. 2019;20(1):65-72. https://doi.org/10.1111/pedi.12793
10. Erdem R, Erdem NŞ, Kurtoğlu E. Restless leg syndrome in adult patients with β-thalassemia major. Clin Neurosci. 2021 Jul 30;74-81. https://doi.org/10.18071/isz.74.0266
11. Lee SH, Park SY, Choi CS. Insulin resistance: from mechanisms to therapeutic strategies. Diabetes Metab J. 2022 Jan;46(1):15-21. https://doi.org/10.4093/dmj.2021.0280
12. MJ A. Diagnostic usefulness of HOMA-β and HOMA-IR in diabetes mellitus: A review. Int J Pharm Res Allied Sci. 2019;8(1).
13. Yoon H, Jeon DJ, Park CE, You HS, Moon AE. Relationship between homeostasis model assessment of insulin resistance and beta cell function and serum 25-hydroxyvitamin D in non-diabetic Korean adults. J Clin Biochem Nutr. 2016;59(2):139-44. https://doi.org/10.3164/jcbn.15-143
14. Zarghamian P, Azarkeivan A, Arabkhazaeli A, Mardani A, Shahabi M. Hepcidin gene polymorphisms and iron overload in β-thalassemia major patients refractory to iron chelating therapy. BMC Med Genet. 2020;21(1):1-5. https://doi.org/10.1186/s12881-020-01011-3
15. Shah S, Farooq N, Basharat A, Shah M, Mukhtiar S, Farhad S. Frequency of iron overload complications in beta thalassemia major patients. J Postgrad Med Inst. 2019;33(1):1132-7.
16. Zafar U, Khan AA, Uppal R, Asif N, Hassan K. Effect of iron overload on glucose regulation in transfusion-dependent beta thalassemia major patients. Int J Pathol. 2019;112-6.
17. Liang LY, Lao WQ, Meng Z, Zhang LN, Hou LL, Ou H, et al. Analysis of the influence of iron overload in glucose metabolism in thalassemia major patients. Chin J Pediatr. 2017;55(6):419-22.
18. Sadullah RK, Atroshi SD, Al-Allawi NA. Complications and challenges in the management of Iraqi patients with β-thalassemia major: a single-center experience. Oman Med J. 2020;35(4):e152. https://doi.org/10.5001/omj.2020.72
19. Tangvarasittichai S, Pimanprom A, Choowet A, Tangvarasittichai O. Association of iron overload and oxidative stress with insulin resistance in transfusion-dependent beta-thalassemia major and beta-thalassemia/HbE patients. Clin Lab. 2013;59(7-8):861-8. https://doi.org/10.7754/Clin.Lab.2012.120906
20. Setoodeh S, Khorsand M, Takhshid MA. The effects of iron overload, insulin resistance and oxidative stress on metabolic disorders in patients with β-thalassemia major. J Diabetes Metab Disord. 2020;19:767-74. https://doi.org/10.1007/s40200-020-00560-x
21. Ghergherehchi R, Habibzadeh A. Insulin resistance and β cell function in patients with β-thalassemia major. Hemoglobin. 2015;39(1):69-73. https://doi.org/10.3109/03630269.2014.999081
22. Matar BM, Sakr MMA, Alsehaimy LA, Al-samee A, Samir H. Evaluation of serum insulin, glucose and liver function in β-thalassemia major and their correlation with iron overload. Int J Med Arts. 2021;3(1):1088-96.
23. Wankanit S, Chuansumrit A, Poomthavorn P, Khlairit P, Pongratanakul S, Mahachoklertwattana P. Acute effects of blood transfusion on insulin sensitivity and pancreatic β-cell function in children with β-thalassemia/hemoglobin E disease. J Clin Res Pediatr Endocrinol. 2018;10(1):1-6. https://doi.org/10.4274/jcrpe.4774
24. Zhang L, Meng Z, Jiang Z, Liu Z, Hou L, Cai G, et al. Indicators of glucose dysregulation and the relationship with iron overload in Chinese children with beta thalassemia major. Pediatr Diabetes. 2022;23(5):562-8. https://doi.org/10.1111/pedi.13260
25. AbdElkawy MMN, Elrifaey SM, Mabrok MM, Badraia EM. Study of insulin hormone level and β-cell function in children with β-thalassemia major. J Adv Med Med Res. 2022;34(21):214-23. https://doi.org/10.9734/jammr/2022/v34i2131541
26. De Sanctis V, Soliman A, Daar S, Tzoulis P, Di Maio S, Kattamis C. Glucose homeostasis and assessment of beta-cell function by 3 hours oral glucose tolerance (OGTT) in patients with beta-thalassemia major with serum ferritin below 1,000 ng/dl. Mediterr J Hematol Infect Dis. 2023;15(1):e2023006. https://doi.org/10.4084/MJHID.2023.006