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ORIGINAL: Prevalence and Risk Factors of Diabetes Mellitus in β-thalassemia Major Patients in the North of Iran: Mazandaran β-thalassemia Registry - 2017 to 2019

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ABSTRACT

Introduction: Thalassemia is a hereditary hemolytic disease spread throughout India, Arabian Peninsula, Iran, Turkey, and Southeast Asia. Diabetes mellitus (DM) is a common complication of patients with β-thalassemia major (β-TM) due to iron sediment in the pancreas. The purpose of this study was to survey the prevalence of DM in patients with β-TM.

Material and Methods: Demographic, clinical information, and some biological tests in conjunction with the proportion of T2DM were retrieved from the Mazandaran Thalassemia Registry (MTR) affiliated to the Mazandaran University of Medical Science. The data belong to December 2017 until December 2019.

Results: The results are as follows: Use of iron chelators like deferiprone should be with caution and with respect to the patients' metabolic state to avoid complications like diabetes. 2024 β-TM patients have registered in MTR (Mazandaran Thalassemia Registration). Data were completed for 597 cases including 72 patients (12.1%) diabetic and 525 patients (87.9%) non-diabetic. Beta-thalassemia patients with DM were significantly older than non-diabetic patients. Also, the percentage of β -TM cases dependent on red cell transfusion and patients with a history of spleen surgery in the diabetic group was significantly higher than in the non-diabetic group. Also, (42.7%) of diabetic patients (34 patients) were treated with insulin.

Conclusion: We concluded that the history of splenectomy and the number of blood transfusions was higher in the diabetic group and associated with it. Future therapeutic approaches need to focus on reducing splenectomy and a high number of blood injections to avoid diabetes, and its complications in TM patients need to be investigated in future researches.

Introduction

Beta-thalassemia major is an inherited hemolytic disease and a severe form of β-thalassemia, caused by abnormal production of the globin gene and reduces

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globin in hemoglobin. It also reduces the production of β-globin chains and causes severe anemia. Thalassemia spreads over the Mediterranean coast and throughout the Arabian Peninsula, Turkey, Iran, India, and Southeast Asia. This disease has different categories, and beta-thalassemia form (minor, moderate, and major) is one of the most common hemoglobinopathies in the world, especially in Iran (1-3). Approximately 1.5% of the world's population have a thalassemia gene (4). This disease is prevalent in Iran, especially near the Caspian Sea, the Persian Gulf, and the Oman Sea. It is also estimated that 11% of the population of Mazandaran has the thalassemia gene (5-7). β-Thalassemia Various symptoms and complications The most effective way to increase life expectancy in these patients is regular blood transfusions, but side effects of this method include excessive iron, which causes oxidative stress and thus causes damage to organs such as the endocrine system (8). Besides, frequent blood transfusions, high intestinal absorption of iron due to chronic anemia, and ineffective red blood cells due to excessive destruction of red blood cells are factors that contribute to excessive iron accumulation (9-11). This disease's most common complications are cell death and organ failure, liver disorders, hypothyroidism, and diabetes (1-8, 12). One of the dangerous diseases that can be considered the most common and crucial metabolic disease in humans is diabetes. The most important and common complications of diabetes can be mentioned: cardiovascular diseases, kidney failure, neuropathy, eye lesions, male impotence, and infection. According to studies, the prevalence of diabetes in these patients is between 9.7 to 29%, which leads to problems such as bleeding in beta cells, cell destruction, and insulin resistance. Also, its duration and age of patients play an essential role in the incidence. Has impaired glucose uptake in β-TM patients (1-8, 10-12).

This study aimed to study the prevalence and risk factors of diabetes in β_thalassemia major patients in northern Iran: Registration of β-thalassemia in Mazandaran-2017 to 2019.

Methods

Study design

This cross-sectional study was based on the recorded data and census methods of patients from the Mazandaran thalassemia registry (MTR) admitted to the thalassemia center of BO-ALI SINA hospital.

Patients and Data collection

Based on a study conducted on patients with β-TM and based on the American Diabetes Association (ADA) and World Health Organization (WHO) diagnostic criteria and based on the results of electrophoresis, diagnosis of a specialist, and determination of mutations by genetic testing have entered into our study. Fasting blood glucose (FBG) level >126 mg/dl, Glycated hemoglobin (HbA1C)> 6.5% and Glucose Tolerance Test (GTT) level >200 mg/dl, was considered as diabetic (13, 14). The patient's information was extracted from the registry of the thalassemia research center (TRC) with ethical points using a checklist. The checklist contains variables, including demographic and clinical features, information about iron chelation therapy, history of splenectomy, and hepatomegaly. Also, we used medical history and clinical examination of patients, such as fasting blood glucose (FBG), AST (aspartate aminotransferase), ALT (alanine aminotransferase), ferritin, urea, and hyperuricemia.

Statistical analysis

At first, Microsoft excel 2016 was used to categorize the extracted data. Statistical Package for the Social Sciences 16.0 (SPSS Inc., Chicago, Illinois, USA) used for data analysis. Data are reported as a number (percentage) for qualitative data and mean ± standard deviation (SD) or median [range] for continuous variables. The normal distribution of the data was assessed by Histograms and Kolmogorov–Smirnov test. Comparison of two groups (diabetics and non-diabetics) was performed by Student's t-test for parametric data and the Mann-Whitney U test for nonparametric data. Pearson or Spearman

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correlation coefficient was used to testing the association between two quantitative variables based on data distribution. We also estimated crude odds ratio (OR) to identify risk or protective factors of DM in our study. Cohen's d as a standardized mean difference calculated to compare significant quantitative values between diabetic and non-diabetic groups. The significance level for *P*-value was set at 0.05.

Ethical considerations

In this study, considering that the patients' consent had been obtained before and the confidentiality of the information was assured, it was finally approved by the Ethics Review Committee of Mazandaran University of Medical Sciences due to ethical code "IR.MAZUMS.REC.1398.5385".

Results

There were 2,024 β-Thalassemia Major (β-TM) patients who have been registered at the MTR (Mazandaran Thalassemia Registry). The data was completed for 597 cases, including 72 (12.1%) diabetic and 525 (87.9%) non-diabetic patients. Demographic and clinical characteristics of β-TM patients have been shown in ***Table 1***.

Beta-thalassemic patients with DM were significantly older than non-diabetic patients (3.89 ± 0.38 year; P = 0.001). Spearman correlation coefficient between age and fasting blood sugar (FBS) was 0.03 (P = 0.49). Also, NBTP and patients with history of splenectomy were significantly greater in the diabetic group compared to non-diabetic group (75% versus 60%, OR 2.29 [95% CI 1.09 to 4.77]; P = 0.03 and 62.5% versus 44.8%, OR 3.06 [95% CI, 1.58 to 5.96]; P = 0.001, respectively). The iron chelation status in both groups of thalassemia patients is shown in the ***table 2***.

The percentage of cases under treatment with deferoxamine in diabetic patients was 68.1% (n=49) versus 51.8% (n=272) in non- diabetic patients, OR 1.98 [95% CI 1.14 to 3.51; P = 0.01. The use of deferiprone in diabetic

Table 1. Demographic and Clinical characteristics of β-TM

	Diabetics (%) (n=72)	Non-diabetics (%) (n=525)	P-value
Age, year*	37.21±9.14	33.32 ± 8.76	0.001 ⌂
Male	31 (43.1)	248 (47.2)	0.53
Weight, kg*	55.48 ± 11.62	58.35 ± 9.31	0.08 ⌂
PWICT	11 (15.3)	137 (26.1)	0.06
NBTP	54 (75)	315 (60)	0.03
History of splenectomy	45 (62.5)	235 (44.8)	0.001
History of hepatomegaly	7 (9.7)	99 (18.9)	0.07

Abbreviations: NBTP: The number of blood transfusions to the patients, PWICT: Patients without iron chelation therapy, β-TM: β-thalassemia major

*: Data are presented as mean ± standard deviation or number (percent).

⌂: p-value was obtained by Student's t-test

P-value < 0.05 was considered as significant level.

Table 2. Iron chelators used in β-TM patients

	Diabetics (n=72)	Non-diabetics (n=525)	P-value
Deferoxamine	49 (68.1)	272 (51.8)	0.01 ⌂
No of deferoxamine injections, per week (20-40 mg/kg/day subcutaneously)	4.94 ± 1.14	5.08 ± 1.14	0.43
Deferasirox	13 (18.1)	139 (26.5)	0.14
Dose of deferasirox, mg/kg)	23.34 ± 13/43	22.91 ± 7.75	0.85 ⌂
Deferiprone	36 (50)	146 (27.8)	0.001
Dose of deferiprone, mg/kg	50.11 ± 13.43	31.45 ± 15.42	0.11 ⌂

β-TM: β-thalassemia major

Data are presented as mean ± standard deviation or number (percent).

⌂ p-value was obtained by Student's t-test

P-value < 0.05 was considered as significant level.

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Table 3. Laboratory tests information in β-TM patients with diabetes and non-diabetic

	Diabetics (n=72)	Non-diabetics (n=525)	P-value
FBS (mg/dl)	184.75 ± 97.89	93.57 ± 19.23	<0.001 ⌂
AST (units/liter)	32.63 ± 18.99 26.5 [11 – 91]	30.79 ± 25.98 24 [3 – 263]	0.17 ∞
ALT (units/liter)	33.67 ± 22.13 25 [11 – 108]	33.57 ± 41.83 22 [4 – 405]	0.06 ∞
Ferritin (ng/mL)	2397± 1902 2140 [181 – 9800]	1891± 1887 1265 [49 – 11750]	0.02 ∞
Hb (gr/dl)	8.80 ± 0.80	8.92 ± 0.93	0.31 ⌂
Urea (mg/dl)	33.16 ± 15.97 31 [17 – 124]	28.39 ± 8.11 27 [1 – 62]	0.02 ∞
Hyperuricemia	38 (52.8)	269 (51.2)	0.91

Abbreviations: β-TM: β-thalassemia major, *FBS: fasting blood sugar, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Hb: hemoglobin*
Data are presented as mean ± standard deviation or median [range] or number (percent).
P-value < 0.05 was considered as significant level.
∞ p-value was obtained by Mann-Whitney U test
⌂ p-value was obtained by Student's t-test

patients was significantly higher compared to non-diabetic cases (50% versus 27.8, OR 2.59 [95% CI 1.52 to 4.41]; P = 0.001).
In the diabetic group, the levels of ferritin and blood urea were significantly more than non-diabetic group (Cohen's d 0.27 [95% CI 0.02 to 0.51]; P = 0.02 and Cohen's d 0.51 [95% CI 0.26 to 0.75]; P = 0.02, respectively. Spearman correlation coefficient between ferritin level and FBS was 0.22 (p<0.001) and for blood urea and FBS was 0.16 (P = 0.001). A comparison of the information of laboratory tests in Beta-thalassemia patients is shown in ***Table 3***.

Discussion

This study aimed to investigate the clinical and demographic variables of beta-thalassemia patients and their relationship with the prevalence and incidence of diabetes. The relationship between these variables and the prevalence of diabetes was examined using statistical tests.
According to our study and in a clinical study, it was observed that increasing age is the prevalence factor for diabetes in beta-thalassemia patients. With increasing age and more blood transfusions, iron accumulates in body tissues and causes the possibility of developing diabetes despite the use of iron cheaters (15-21). Our study showed that patients who needed regular blood transfusions were 1.29 times more likely to develop diabetes, which, as noted, was more likely to cause iron deposition in sensitive tissues, including the pancreas.
Patients with beta-thalassemia with splenectomy are 2.06 times more likely to develop diabetes than those without splenectomy. Our study and other studies showed that the spleen plays a vital role in supporting the endocrine gland (22, 23). Lack of spleen can increase glucose and ultimately increase the risk of death in patients. Other studies have shown a significant association between splenic trauma and hyperglycemia, although 82 months are needed to follow this issue (22). However, in our study, the association between the incidence of diabetes and splenectomy in beta-thalassemia patients is evident also; one of the possible reasons is the higher prevalence of endocrine disorders for wrong detoxification (24).
Some studies have confirmed an association between a non-significant increase in urea and beta-thalassemia (25). However, it has been scientifically proven that the proportion of normal urea levels in diabetic individuals is significantly higher than that of healthy individuals (26). In our study, it was found that

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patients with diabetes had significantly higher plasma urea levels than patients in the control group. It seems that these significant changes are due to metabolic changes and damage caused by diabetes in patients (27, 28).

Iron is a transition metal that is easily oxidized and therefore acts as an oxidizer. The general effect of catalytic iron is to convert weakly reactive free radicals such as H2O2 to highly reactive radicals such as hydroxyl radicals. Increased iron accumulation affects insulin synthesis and secretion in the pancreas (29, 30). It interferes with the liver's ability to extract insulin (30, 31). Iron deposition in muscle reduces glucose uptake due to muscle damage (32).

Conversely, insulin stimulates cellular iron uptake by increasing the transferrin receptor externally (33). Thus, insulin and iron can potentiate their interactions, leading to insulin resistance and diabetes after a vicious cycle. The results of our studies, in line with recent epidemiological studies, showed that there is a direct connection between elevated serum ferritin levels and type 2 diabetes (34-36).

Prolonged use of deferoxamine and repeated effusions have been reported to reduce all of the body's immune response and cause glomerular damage (26). Administration of deferoxamine reduces cardiovascular complications due to iron deposition in tissues and hospitalization duration in patients with thalassemia. In beta-thalassemia patients with diabetes, iron accumulation is higher, which is a risk factor for these patients' death (19, 37). For preventing this position, patients should use chelating agents to remove excess use (37).

Deferiprone was first developed in 1987 and has been around since 1987 (38). In comparison with deferoxamine, Deferiprone can improve to the level of serum ferritin, which takes iron in the liver and heart and increases urinary iron excretion (37). One of the most common side effects of deferiprone is neutropenia, which can cause infections in the body and organs (39). Many infections in the liver and pancreas can cause diabetes. However, various studies have evaluated the benefits of using deferiprone (due to iron-chelating effects) and decreasing the likelihood of iron deposition more than reducing the strength of the immune system (40, 41).

Limitations

Duration of blood transfusion, type of insulin, oral medication received, dosage, duration of use, and the period of using iron-chelating agents, were not recorded in the patient registration system.

Conclusion

We concluded that the history of splenectomy and NBTP was higher in the diabetic group and associated with it. Future therapeutic approaches need to focus on reducing splenectomy and a high number of blood injections to avoid diabetes, and its complications in TM patients need to be investigated in future research.

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Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

All authors have intellectually committed to the study design and process. The final manuscript was revised and accepted by all authors.

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