

# Prevalence of Diabetes Mellitus, Impaired Fasting Glucose, and Impaired Glucose Tolerance in Thalassemia Major in Tabriz

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## Abstract

**Background and Aim:** Thalassemia major is an inherited blood disorder, and multiple blood transfusions are critical for survival in these patients. Over the last two or three decades, transfusion therapy in these patients has led to a significant improvement in life expectancy and quality of life. Iron overload is an uncommon complication of transfusion that occurs in patients after long periods. Endocrine abnormalities, which were not common in the past, are now among the most common complications in these patients. This study aimed to assess the prevalence of diabetes and glucose tolerance test in patients with thalassemia major, with 10–27 years of age in Tabriz. **Methods:** This descriptive study was performed on 56 patients between 10 and 27 years of age with thalassemia major in Tabriz. The demographic information, therapeutic regimen, the age of first transfusion, the level of blood transfusion, the history and dosage of familial history of diabetes, Fe, total iron-binding capacity, and ferritin levels were assessed and recorded. For each patient, fasting blood sugar and oral glucose tolerance tests were performed to diagnose of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes. **Results:** According to the results, the prevalence of diabetes mellitus (DM), impaired fasting glucose, and impaired glucose tolerance test were found in 8.9%, 28.6%, and 7.1% of patients, respectively. **Conclusion:** This study showed that despite recent therapy with desferal in the management of beta-thalassemia major, the risk of secondary endocrine dysfunction remains high. Prevalence of DM, IFG, and IGT is greater than the general population. Endocrine evaluation in patients with thalassemia major must be carried out regularly, especially in those patients over the age of 10 years.

**Key words:** Diabetes mellitus, impaired fasting glucose, impaired glucose tolerance, thalassemia major

## INTRODUCTION

Hereditary disorders are the most common diseases in Iran.<sup>[1]</sup> Thalassemia represents a major group of inherited disorders of hemoglobin synthesis inherited in an autosomal-recessive mode. Beta-thalassemia is the common form of thalassemia in Iran<sup>[2]</sup> and is classified as thalassemia major, thalassemia intermediate, or thalassemia minor. Patients with  $\beta$ -thalassemia major are reliant on regular red blood cell transfusions for survival resulting in iron overload in their various organs. Excess iron is deposited in body organs including liver, heart, pancreas, pituitary, parathyroid, and other organs. This can ultimately lead to cell injury and fibrosis disrupting the functioning of different organs. The dysfunction can manifest itself with liver disorders, heart failure, hypogonadism,

growth disorders, hypothyroidism, hypoparathyroidism, and diabetes.<sup>[3]</sup>

Due to humans lack a mechanism for controlled iron excretion, thus, the prevention of complications hinges on the iron chelation therapy of excess iron. Today, iron chelation therapy is able to prevent the accumulation of iron by deferoxamine (desferal). However, endocrine disorders are frequently observed in these individuals, and even some complications are more common due to increasing the

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lifespan of these patients. Diabetes is one of the endocrine abnormalities in thalassemic patients, which can lead to severe fibrosis due to iron deposition in pancreatic intercellular cells and abnormalities in the pancreatic beta cells functions and consequently diabetes development.<sup>[4]</sup> This study aimed to assess the prevalence of diabetes, impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) among the thalassemic patients between 10 and 27 years of age in Tabriz. Diagnosis of thalassemia major was primarily based on the hemoglobin electrophoresis, and all patients received blood transfusion approximately every 2–3 weeks and treated by desferal administration. Due to the lack of information on the desferal dose and lack of accurate information from patients over the past years, the last desferal dosage was the baseline for the current study. For previously undiagnosed patients, fasting blood glucose and glucose tolerance testing (75 g oral glucose in subjects above 30 Kg or 1.75 g/kg body weight in subjects <30 kg) were evaluated. Patients were classified into one of three categories: Diabetes, IFG, and IGT. Statistical analyzes were performed using SPSS-21 software. The data were expressed as a mean and standard deviation. The level of statistical differences between the ratios was determined using Chi-square test.

## Findings

Of the 56 patients, 20 were female and 36 were male with an age range of 10–27 years (mean, 15.6 years). The patient information has been presented in Table 1.

Among these patients, forty-eight patients were between the ages of 10 and 19 years and eight patients over 20 years of age. Nine patients had a family history of diabetes. Among these, total iron-binding capacity (TIBC) and iron levels were within the normal range in 3 and 10 patients, respectively. The prevalence of diabetes in this study was 8.9%, of which 7.1% was detected by glucose tolerance test and 1.8% had previously diagnosed diabetes. Sixteen patients (12 males and 4 females) had IFG, aged between 10 and 25 years

(mean 16.2 years). Among these, four patients had a positive family history of diabetes and four patients (1.7%) had IGT (1 male and 3 female) and aged between 15 and 23 years (mean 18.5 years). Two patients had a positive family history of diabetes. Age and duration of blood transfusion were shown as risk factors for diabetes and the amount of blood transfusion per month was also recognized as a risk factor for IFG ( $P < 0.05$ ).

## DISCUSSION

Of the 56 patients with thalassemia, 5 (8.9%) had diabetes with a median age of 19.8 years. In this study, none of the newly diagnosed diabetic patients had normal fasting blood glucose level, and their rate of diabetes was measured by glucose tolerance test, indicating that blood glucose measurements cannot be the only criterion for follow-up and close monitoring in these patients. According to the findings of a study in Taiwan (2001), out of 89 patients with thalassemia major, diabetes was reported in 19.5% of patients.<sup>[5]</sup> In another study by Khalifa in Egypt on 56 patients with thalassemia major, 10.4% were known to have diabetes.<sup>[6]</sup> In addition, the results of the study by some Italian researchers (1995) on 1861 patients with thalassemia major in 25 Italian hematology centers revealed that 4.9% of patients had diabetes.<sup>[7]</sup> The findings of another study by Karimi-Fard at Endocrinology and Metabolism Research Center - Shiraz University of Medical Science on 150 patients with thalassemia major aged 10–22 years suggested that 7.3% of patients had diabetes.<sup>[8]</sup> Furthermore, in the study by Gulati on 84 patients with thalassemia major, diabetes was present in 7.9% of patients.<sup>[9,10]</sup> In Germany, Cario found in his study that out of 36 patients with major thalassemia, 19% were diagnosed with diabetes. In addition, based on the study by Mustafavi, of 44 patients with thalassemia major, diabetes was discovered in 11.3% of all patients.<sup>[11]</sup> In this study, the prevalence of diabetes was lower than that of studies conducted in Taiwan,<sup>[5]</sup> Egypt,<sup>[6]</sup> and Tehran<sup>[2]</sup> and higher in

**Table 1: Variables of parameters in thalassemia major**

Variables	Normal 31 persons	DM 5 persons	IFG 16 persons	IGT 4 persons
Age (year)	14.4±4.4	*19.8±4.3	16.2±3.3	18.5±3.4
Blood transfusing (u/m)	1.8±0.54	1.7±0.81	*2.4±0.76	2.3±1.06
Desferal (u/m)	53±25	65±42	63±13	54±12
Iron (µg/dL)	198±83	175±21	210±56	210±11.1
TIBC (µg/dL)	235±68	210±55.5	230±50	226±12.8
Ferritin (µg/dL)	2780±989	2927±943	2985±882	3526±1186
FBS (mg/dL)	85±7	124±18	109±7.4	109±13.1
OGTT (mg/dL)	106±12	266±16	130±42.5	159±19.6
Duration of blood transfusing (year)	12.2±4.6	*17±4.2	13.4±3.4	15.8±5
Duration of desferal (year)	10.2±3.9	14.7±2.5	12.1±3.2	11.1±2.17

\* $P < 0.05$ , data are reported as mean±standard deviation. TIBC: Total iron-binding capacity, DM: Diabetes mellitus, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, FBS: Fasting blood sugar, OGTT: Oral glucose tolerance

Italy<sup>[7]</sup> and Shiraz.<sup>[2,8]</sup> This discrepancy in the prevalence rate of diabetes in different countries (from 4.9% in Italy to 19.5% in Taiwan) can be attributed to the treatment procedures, especially in the onset and dosage of desferal. Furthermore, the different prevalence rate of diabetes in other studies may be due to the age variable of the samples. For example, in the study of 25 hematology centers in Italy, the prevalence rate of diabetes was found to be lower because the subjects were 2 years older, and the clinical manifestation of endocrine complications in thalassemic patients is usually evident more than 10 years later. Our findings suggested that of 56 patients with thalassemia major, 7.1% were diagnosed with glucose tolerance test. In the study in Taiwan, out of 89 patients with thalassemia major, 8.5% of patients had IGT.<sup>[5]</sup> In another study by Khalifa, 14.6% of patients were known to have IGT.<sup>[6]</sup> In the Cairo<sup>7</sup> study, the prevalence of IGT was 16%.<sup>[10]</sup> In the current study, of 56 patients with thalassemia major, 28.6% of patients had IFG. However, these studies did not evaluate the prevalence of IFG among the patients with thalassemia major. IGT, IFG, and diabetes are among the most common complications in patients with thalassemia major receiving regular blood transfusions. The prevalence of these disorders in the Mediterranean countries varies from 5% to 25%. Furthermore, no significant difference was found between the sexes in terms of complications. For most people, diabetes typically begins after age 10.<sup>[12]</sup> Many factors play a crucial role in the development of glucose metabolism disorders in thalassemic patients, including the destruction of secondary beta cells due to iron overload, chronic liver disease, viral infections, and genetic factors.<sup>[4]</sup> Age, amount of blood transfusion per month, and duration of blood transfusion over lifetime were identified as risk factors for diabetes in our study. In the study by Chern, although the variables of age, amount of blood transfusion per month, and duration of blood transfusion over lifetime were not detected as a risk factor, researchers believed that they play a determining role for overload over the lifetime and can be effective in the development of glucose metabolism disorders.<sup>[5]</sup> Furthermore, no association was found between the positive family history of diabetes and the development of glucose metabolism disorders. Positive family history of diabetes had also no significant impact on the development of glucose metabolism disorders in patients with thalassemia major.<sup>[5]</sup> We found no relationship between desferal administration and the development of diabetes, which could be due to insufficient knowledge of the transfusion procedure and desferal dose. In addition, some patients refused to take desferal at some time. The results of studies in Italy<sup>[7]</sup> and Shiraz<sup>[8]</sup> indicated that irregular administration of desferal is an effective risk factor for the development of glucose metabolism disorders. However, we did not find any direct relationship between the above mentioned with glucose metabolism disorders since we did not have all the accurate information on the deferral transfusion procedure in the past, especially among patients under 10 years of age. Regarding the effect of iron and TIBC on the development of glucose metabolism disorders, our results showed that serum-free iron

level proportional to blood level and desferal is constantly changing, and the amount of iron deposition in the tissue can contribute to the development of endocrine disorders. TIBC varies considerably according to the serum iron level and decreases as the serum iron level is elevated and seems that it has no impact on the development of glucose metabolism disorders.<sup>[3]</sup> No relationship was found between glucose metabolism disorders, serum iron levels, and TIBC based on the results of the present study.<sup>[5]</sup> In addition, Chern<sup>[5]</sup> detected ferritin serum as an effective risk factor for the development of glucose metabolism disorders. In another study by Shamsirsaz *et al.*, ferritin level in thalassemic patients with endocrine disorders was significantly higher. The evidence also shows that serum ferritin levels <2500 µg/L can lead to a powerful prognosis marker among the thalassemic patients.<sup>[13]</sup> Khalifa also did not find a statistically significant relationship between ferritin levels and glucose metabolism disorders,<sup>[6]</sup> which were in line with the results of our study. This is because the ferritin is representative of iron overload within the last 3 months, whereas the development of glucose metabolism disorders seems to be affected by the interaction with excess iron. Prevalence of diabetes mellitus, IFG, and IGT is greater than the general population.<sup>[13]</sup> Age, amount of blood transfusion per month, and duration of blood transfusion over lifetime are among the factors that can increase the duration of exposure to pancreatic iron overload and consequently elevated glucose tolerance disorders.<sup>[14]</sup>

## CONCLUSION

Although we did not find any correlation between how to receive desferal and the development of glucose tolerance disorders, it seems that high prevalence of glucose tolerance disorders among the patients with thalassemia major is due to irregular or inadequate administration of desferal or poor quality of received desferal, because the removal of the excess iron from body is dependent on the administration of an iron chelating agent including desferal. Therefore, according to surveys and results from different studies, endocrine evaluation must be carried out regularly in patients with beta-thalassemia major, especially those over 10 years of age. Regarding the results of glucose tolerance disorders, our findings indicated that glucose tolerance test is a necessary screening tool and fasting blood glucose has not been adequately justified as a diagnostic criterion. In addition, patients with IFG and IGT should receive nutritional counseling as a medically necessary preventive service to delay or slow down progression from thalassemia to overt diabetes using adherence to proper nutrition. Therefore, it is necessary for these patients to perform a glucose tolerance test every 6 months and take insulin when the disease develops into diabetes. Although we found no relationship between the desferal dose and its transfusion time for the prevention of endocrine disorders development, we claim that providing adequate and accurate knowledge for patients regarding the impacts of regular use and early administration

of desferal will reduce the incidence of endocrine disorders in the future.

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