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Original article

Long-term retrospective study on the conversion rate from prediabetes to diabetes in transfusion dependent thalassemia (TDT) patients: The experience of a single tertiary care Center in Iran

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Abstract. *Background:* The prevalence of glucose dysregulation (GD) in patients with thalassemia increases with age. *Objectives:* This retrospective study aimed to characterize the natural history of prediabetes and identify risk factors associated with the progression to diabetes among transfusion-dependent thalassemia (TDT) patients. *Research Design and Methods:* We retrospectively reviewed annual oral glucose tolerance test (OGTT) data from 108 out of 700 Iranian TDT patients diagnosed with diabetes mellitus (DM). *Results:* Prediabetes was diagnosed at a mean age of 21.3 ± 5.9 years. The mean serum ferritin (SF) level at prediabetes diagnosis was 3,869 ± 2,805 ng/mL. The average time for conversion from prediabetes to DM was 3.8 ± 2.0 years, with a mean age of 25.0 ± 6.5 years at DM diagnosis. A parental history of diabetes was reported in 87% of the patients. There was a direct correlation between the age at prediabetes diagnosis and the age at DM diagnosis (r = 0.9391, P: < 0.00001), as well as with fasting plasma glucose (FPG) at DM diagnosis (r = 0.7065, P: < 0.00001). SF levels at prediabetes diagnosis were also associated with SF levels at the time of DM diagnosis. *Conclusions:* Identifying high-risk patients remains challenging; however, a parental history of diabetes, elevated SF levels, and younger age at prediabetes diagnosis were significantly associated with the progression to DM in TDT patients with a normal body mass index. (www.actabiomedica.it)

Key words: Transfusion-dependent thalassemia (TDT), prediabetes, diabetes mellitus, progression rate, risk factors, Iran

Background

According to the severity of phenotype, β-thalassemias are classified as transfusion-dependent thalassemia (TDT) and non–transfusion-dependent thalassemia (NTDT). TDT entails lifelong regular transfusion requirement for survival. Non-transfusion-dependent thalassemias (NTDT) is a term used to label patients who do not require such lifelong regular transfusions for survival, although they may require occasional or even frequent transfusions in certain clinical settings and for defined periods of time (1).

Prevalence of glucose dysregulation (GD) in patients with thalassemia increases with age and is greater in subjects with severe mutations (2).

In prediabetes, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) indicates glucose levels higher than normal but not in the diabetes range. Early screening offers a window for treatment that may prevent or delay progression of the disease and its complications.

Diagnostic criteria of prediabetes are based on biochemical parameters, and include at least one of the following conditions: isolated impaired fasting plasma glucose (i-FPG), isolated impaired glucose tolerance (i-IGT), IFG plus IGT and altered glycated hemoglobin (HbA1c) (3). However, several studies have reported a lack of agreement between HbA1c and glucose-based tests in patients with TDT (4-7). Moreover, there is currently no consensus regarding the diagnostic criteria for prediabetes. The American Diabetes Association (ADA) defines prediabetes as a FPG of 100 to 125 mg/dL (8) while the World Health Organization (WHO) considers a higher FPG from 110 to 125 mg/dL (9).

In the general population, the prevalence of prediabetes depends on age, gender, ethnicity, geographical region of residence, body mass index (BMI), parental history of diabetes and socioeconomic status (10). The proportion of individuals with prediabetes who progress to type 2 diabetes (T2D) over a ten-year period varies from 13%-52% with an annual progression rate of 1% - 12.5% (11). However, the time period of progression from prediabetes to T2D appears to be shorter in children than in adults (12).

Nevertheless, the predictors and the rate of progression from prediabetes to DM in TDT patients has not been fully characterized in published studies (13-15).

Therefore, in July 2023 the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) (16) promoted a long-term retrospective survey study on the conversion rate of prediabetes to diabetes mellitus (DM) in patients with TDT.

Four out 12 Centers for the Thalassemias Care (2 in Italy, 1 in Oman and 1 in Iran), taking part to the ICET-A Network, participated in the study. As a first step, Oman and Italy evaluated and compared the natural course of prediabetes to diabetes in two groups of β-TDT patients who started iron chelation therapy (ICT) before the age of 6 years and between 6 and 10 years, and characterized the trajectories of fasting and post glucose load, insulin sensitivity and insulin secretion, assessed by HOMA2-%S and HOMA2-%β, in a subgroup of β-TDT patients followed annually for 4 years before the diagnosis of DM (17). Notably, the age at diagnosis of prediabetes in 18 β-TDT patients was directly correlated with the age at diagnosis of DM (r: 0.6925, P: 0.0014).

After reviewing the current evidence and addressing remaining research gaps, the main goal of the present long-term retrospective study was to evaluate in a large group of TDT patients the progression rate from prediabetes to DM and the risk factors of conversion to diabetes among those with prediabetes, and as secondary aim, to describe the demographic characteristics, biochemical and diagnostic parameters in TDT patients with prediabetes followed in a single tertiary care Center in Iran.

Patients and methods

Study design and patient population

Data were retrospectively collected from a cohort of 700 TDT patients regularly followed or referred to the Thalassemia Clinic and Metabolism Research, Hospital and Outpatient Clinic, affiliated with the Shiraz University of Medical Sciences (Iran), recruited from January 2015 to 15th September 2023. Only those who converted from prediabetes to DM were selected for the present study.

Information on medical history, age, sex, family history of diabetes (first or second degree), pre-transfusional hemoglobin (Hb) level, assessment of iron overload by serum ferritin, history of splenectomy and presence of associated endocrine complications were collected. Height and weight were measured using standard techniques and pubertal stages were evaluated according to Tanner's criteria.

Body mass index (BMI) was calculated as body weight divided by the square of height and categorized as underweight (<20 kg m^2), normal weight (20–24.9 kg m^2), overweight (25–29.9 kg m^2) and obesity (≥30 kg m^2) in adult subjects. A child was diagnosed

as overweight if the BMI was at the 85 th percentile but less than the 95 th percentile for age and sex, and as obese if the BMI was at the 95 th percentile for age and sex (18). Associated endocrine complications were defined according to our previous reports (19-22).

Eligibility criteria

The main criteria for study inclusion, as reported by the ICET-A survey protocol, were: (a) TDT patients diagnosed on the basis of clinical and laboratory data using hemoglobin HPLC and/or molecularly characterized genotype (23); (b) annual screening with 2-h oral glucose tolerance test (OGTT), assessed at baseline and 120' min after glucose load; (c) IFG diagnosed according to ADA criteria (8); and (d) conversion from the diagnosis of prediabetes to DM. The key exclusion criteria included: (a) non-transfusion dependent thalassemia patients (NTDT); (b) bone-marrow transplanted patients; (c) TDT patients using drugs affecting glucose metabolism; (d) presence of associated chronic illnesses besides TDT, such as HIV positivity and chronic kidney diseases; (e) TDT patients pharmacologically treated for prediabetes, and (f) patients without regular follow-up.

Assessment of iron overload

Iron overload was assessed by serum ferritin (SF) level. Iron overload was arbitrarily classified as mild (SF:< 1000 ng/mL), moderate (SF: >1000 ng/mL and < 2000 ng/mL) or severe (SF: >2000 ng/mL) (17).

Serum ferritin was measured in the last years by immunoradiometric or chemiluminescence immunoassays. The normal reference range values are 30–350 ng/mL in males and 15–150 ng/mL in females (24).

Statistical analysis

Qualitative variables are presented as means ± standard deviations (SD), medians, and percentages.

Data were analyzed to construct histograms, assessing the normality of distribution. Data with skewness between –0.5 and 0.5 were considered fairly symmetrical. Skewness values between –1 and –0.5 or between 0.5 and 1 indicated moderate skewness, while values less than –1 or greater than 1 suggested high skewness.

Regarding kurtosis, values near zero were indicative of normal distribution. For quantitative variables, Student's t-test was applied for comparisons between two groups when data were normally distributed. The Wilcoxon-Mann-Whitney test was utilized for non-normally distributed data. The relationship between two variables was assessed using Pearson's correlation for normally distributed data and Spearman's correlation for non-normally distributed data. The Chi-square ($\chi 2$) test was employed to compare frequencies of qualitative variables across different groups.

Data analysis focused specifically on the diagnosis of prediabetes and diabetes mellitus (DM). All statistical analyses were conducted using Stata version 11.0 (StataCorp, Texas, USA). A two-tailed P-value threshold of <0.05 was considered statistically significant.

Ethics

All participants gave informed consent in accordance with principles of the Declaration of Helsinki and its later amendments in October 2013 (www.wma.net) after a detailed explanation of the procedures for performing the OGTT test, the nature and purpose of the study, and the patient's benefits for collecting such information. Ethics approval was not required because the OGTT is considered to be part of optimal diagnostic procedures according to current guidelines (2,13-15) no identifiable private information was collected, and an anonymized dataset was analyzed.

Results

Transfusional management and iron chelation therapy changed over the years. Patients were splenectomized when transfusion requirements of packed red cells increased to 180–220 ml/kg/yr and/or in the presence of other signs of hypersplenism such as leukopenia, thrombocytopenia or massive spleen.

One hundred and eight out of 700 TDT patients with DM were eligible to be included in the study

They were born from 1982 to 2013 (median 1997) (Figure 1).

The diagnosis of prediabetes was made at the mean age of 21.3 ± 5.9 years (Figure 2). The mean SF level at the diagnosis of prediabetes was 3,869 ± 2,805 ng/mL (median: 2,780; range: 536-9,600) (Figure 3).

52/106 (48.1%) TDT patients with prediabetes presented with isolated IFG (i-IFG) as first manifestation of abnormality of GD and 56/108 (51.8%) patients presented with IFG plus IGT. None was diagnosed with isolated IGT (i-IGT). Detailed patients' information at the diagnosis of prediabetes is reported in table 1. At the diagnosis of prediabetes, 43/52 (82.6 %) patients with i-IFG and 36/56 (64.2%) patients with IFG plus IGT presented a severe iron overload (SF level above 2.000 ng/mL), suggesting a poor adherence to ICT.

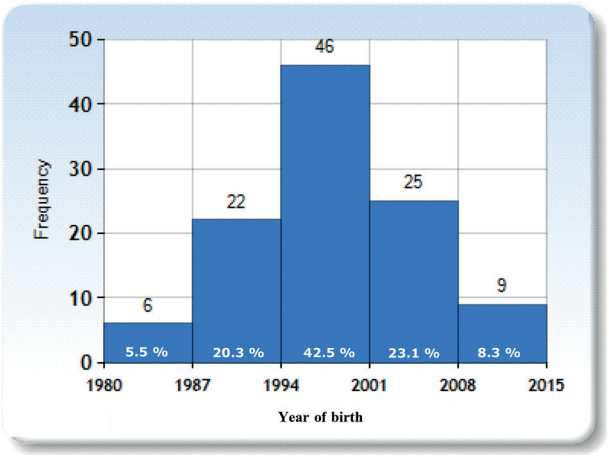

Figure 1. Distribution of TDT patients with diabetes in relation to the year of birth

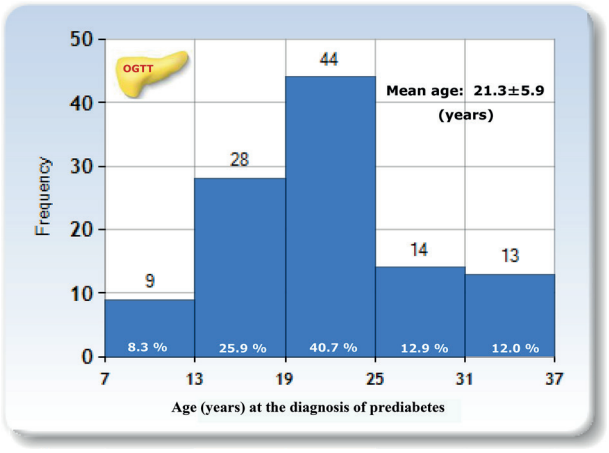

Figure 2. Distribution of TDT patients with prediabetes by age groups.

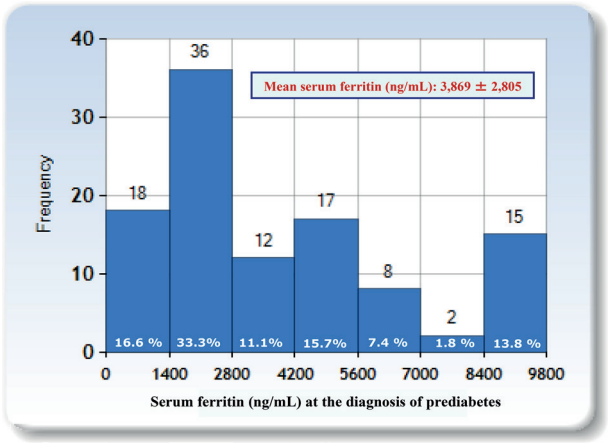

Figure 3. Distribution of serum ferritin (ng/mL) in TDT patients at the diagnosis of prediabetes.

Notably , in 28 TDT patients (53.8%) with prediabetes the i-FPG level was between 6.0-6.39 mmol/L (108-115 mg/dL) and in the remaining 24 patients (46.1%) between 6.4-6.79 mmol/L (115.2-122.2 mg/dL). The 3th percentile value of FPG was 6.11 mmol/L (110 mg/dL), the 97th percentile value was 6.74 mmol/L (121 mg/dL) and the 50th percentile value was 6.38 mmol/L (114 mg/dL).

The intraindividual coefficients of variation for FPG in patients with i-IFG and IFG plus IGT were: 95% CI= 6.342 - 6.458 and 95% CI= 6.3857- 6.5143, respectively. The intraindividual coefficients of variation for FPG in male and female patients with i-IFG was: 95% CI=6.3701- 6.5299 and 6.2688 - 6.4112, respectively; and in male and female patients with IFG plus IGT was: 95% CI= 6.3347 - 6.5053 and 95% CI=6.3573 - 6.5627, respectively.

The mean time interval for conversion from prediabetes to DM was 3.8 ± 2.0 years (95% CI: 3.423 – 4.177).

The mean age at the diagnosis of DM in 108 /700 TDT patients (15.4%) was 25.0 ± 6.5 years (Figure 4). In the majority of patients (40.7%) the diagnosis of DM was done in the second and third decade of life

Table 1. Demographic characteristics, biochemical and diagnostic parameters (mean and standard deviation) in transfusion-dependent thalassemia (TDT) at the diagnosis of isolated impaired fasting glucose (i-IFG) and IFG plus impaired glucose tolerance (IFG plus IGT).

Total number of patients with transfusion-dependent thalassemia (TDT)	52 (i-IFG)	56 (IFG+IGT)	P value
Male/Female	27/25	28/28	0.99
Mean age (years)	22.3 ± 7.0	20.3 ± 4.6	0.036
Lowest age (years)	7	9	=
Highest age (years)	35	32	=
Skewness	0.25336	-0.51625	=
Kurtosis	-0.26998	0.21956	=
History of splenectomy (n. and%)	23/52 (44.2 %)	13/56 (23.2 %)	0.021
Family history of diabetes (first and second degree) (n. and%)	45/52 (86.5%)	49/56 (87.5%)	0.87
Serum ferritin (ng/mL)	4,265 ± 3,081	3,501 ± 2,493	0.15
Fasting plasma glucose (mmol/L) and 2-h after oral glucose tolerance test (OGTT)	6.40 ± 0.21 6.43 ± 0.28	6.45 ± 0.24 8.63 ± 1.17	0.25 < 0.0001
Mean conversion rate from prediabetes to diabetes mellitus (years) and median (years)	4.26 ± 2.26 5	3.44 ± 1.74 4	0.041 =

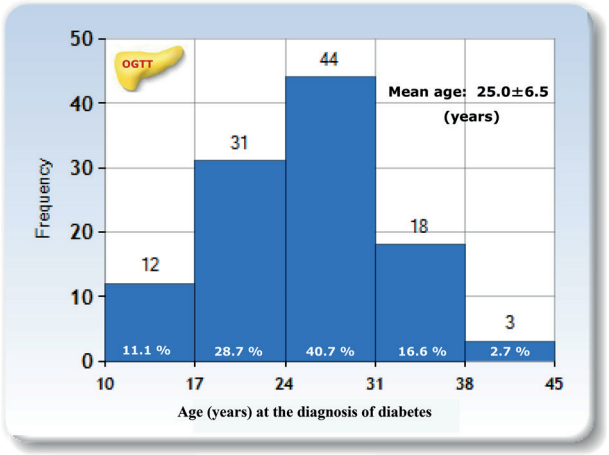

Figure 4. Distribution by age groups of TDT patients at the diagnosis of diabetes.

(69.4%). The mean SF level, at the diagnosis of DM, was 3,767 ± 2,519 ng/mL (median: 3,041; range: 434 - 10,958) (Figure 5).

As illustrated in table 2, rapid conversion to DM was associated with male gender, combined IFG plus IGT rather than isolated IFG, and younger age. However, family history of DM and SF were not predictors of a more rapid course of progression to DM. Of note, hypogonadotrophic hypogonadism, despite being a marker of pituitary iron overload, as well as splenectomy were associated with slower rather than more rapid progression to DM.

Correlations

The age at the diagnosis of prediabetes was directly correlated with the age at diagnosis of DM (r: 0.9391, P: <0.00001) (Figure 6) and with the FPG at the diagnosis of diabetes (r: 0.7065, P:< 0.00001). No statistically significant correlations were observed with other variables included in the study.

Discussion

A wide range of α- and β-thalassemia mutations have been detected in the Iranian population, with a total of 39 different β-globin mutations identified. This suggests the presence of multiethnic groups in the country. In Iran, there are 18,983 patients carrying hemoglobinopathies, 3,750,000 carriers of β-thalassemia and 198 medical centers affiliated to 64 medical universities and faculties (25,26). In the Fars province, the most prevalent β-thalassemia mutations are IVS II-1 G:A and IVS I-6 T:C, with frequencies of 31% and 15%, respectively (26).

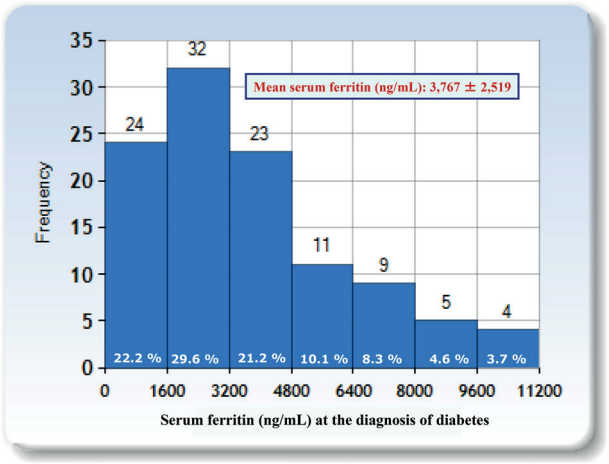

Figure 5. Distribution of serum ferritin (ng/mL) in TDT patients at the diagnosis of diabetes The 3rd percentile value for the conversion rate from prediabetes to diabetes was 1 year and the 97 th percentile value was 7 years. For a better understanding of factors involved in the progression rate of prediabetes, we selected two subgroups of patients that were arbitrarily classified as "rapid prediabetes conversion rate"(≤ 2 years; Group A- RPCR) and "slow prediabetes conversion rate"(≥ 7 years; Group B- SPCR). A detailed description of the two subgroups and the diagnosis of associated endocrine complications registered at prediabetes are reported in table 2.

Transfusion-dependent thalassemia (TDT) patients are at a high risk for developing prediabetes and diabetes mellitus (DM). The natural history of prediabetes, including isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and the combination of IFG and IGT, can follow one of three courses: persistence, reversion to normal glucose tolerance, or progression to diabetes. This progression is distinct from that in type 1 diabetes, as it does not involve a complete absence of insulin secretion (11, 27-29).

In this retrospective study conducted at a tertiary care center in Iran, the diagnosis of prediabetes (i-IFG and IFG plus IGT) and DM in TDT patients was reported at a mean age of 21.3 ± 5.9 years (95% CI: 20.1–22.4) and 25.0 ± 6.5 years (95% CI: 23.7–26.2), respectively. Most patients with prediabetes were identified by fasting plasma glucose (FPG) levels ≥ 6.11 mmol/L (≥110 mg/dL). This suggests that OGTT may not be cost-effective for screening in this context. However, it's important to note that FPG mainly reflects hepatic glucose output, providing only a crude index of insulin resistance. The 2-hour post-glucose (2-h PG) concentration during OGTT also reflects insulin secretion capacity. In patients with IGT, this indicates a more advanced stage of risk for progression to diabetes. Therefore, while FPG is more practical and less expensive than OGTT, relying solely on FPG could overlook a significant number of patients with IGT, as evidenced in both TDT patients (30,31) and the general population (32).

Parental history of diabetes, high serum ferritin (SF) levels, and younger age at prediabetes diagnosis were significantly associated with the progression to DM. However, body mass index (BMI), gender, and pretransfusional hemoglobin (Hb) levels, despite a suboptimal transfusion regimen, were not significant predictors of conversion. Interestingly, in the "slow prediabetes conversion rate" group, a higher percentage of females (83.3%) was observed compared to males (16.6%), as well as a history of splenectomy in females. This suggests that females might tolerate iron toxicity better than males, although studies on the impact of gender on TDT patient survival have reported variable results (33,34). Post-splenectomy, a rapid rise in SF levels and a decrease in total body iron storage capacity have been documented, leading to increased iron concentration in organs other than the spleen (35,36). These findings underscore the importance of a sex-specific approach in assessing diabetes risk in TDT patients.

A parental history of diabetes was reported in 87% of patients in our study. Similar to other Middle Eastern and North African countries, Iran has one of the highest prevalences of diabetes worldwide (37). The prevalence of diabetes among Iranian adults aged 25-65 has risen over the years, from 8.4% in 2004 to 12.2% in 2019. Contributing factors include genetics, obesity, physical inactivity, urbanization, and poor nutritional habits (38-40). Bahar et al. (41) reported a relative risk for developing DM and insulin resistance in carriers of β-thalassemia.

At the diagnosis of prediabetes, a high proportion of patients with i-IFG (82.6%) and IFG plus IGT (64.2%) presented with severe iron overload (SF level above 2,000 ng/mL), indicating poor adherence to iron chelation therapy. SF levels did not

Table 2. Demographic characteristics, biochemical and diagnostic parameters (mean and standard deviation) in transfusion-dependent thalassemia (TDT) with "rapid prediabetes conversion rate"(Group A- RPCR) and "slow prediabetes conversion rate" (Group B -SPCR).

Total number of patients with transfusion-dependent thalassemia (TDT)	Group A (n. 34) (RPCR)	Group B (n.18) (SPCR)	P value
Male/Female	19/15	3/15	0.015
Mean duration of progression rate from prediabetes to diabetes mellitus (years)	1.38 ± 0.49	7.16 ± 0.38	< 0.0001
Number and % of patients with isolated FPG at the diagnosis of prediabetes	16/34 (47%)	17/18 (94.4%)	0.0008
Mean age (years) at diagnosis of diabetes	20.7 ± 6.7	30.4 ± 0.9	< 0.0001
History of splenectomy (n. and%)	8/34 (23.5%)	10/18 (55.5%)	0.0079
Family history of diabetes (first and second degree) (n. and%)	27/34 (79.4%)	17/18 (94.4%)	0.12
Body mass index (Kg/m^2) at the diagnosis of diabetes mellitus	20.5 ± 1.9	20.1 ± 2.2	0.52
Mean pre-transfusional Hb level (g/dL) at the diagnosis of diabetes	7.6 ± 0.7	7.7 ± 0.8	0.66
Serum ferritin (ng/mL) at the diagnosis of diabetes mellitus	4,451 ± 2,738	3,792 ± 3,038	0.27
Associated endocrine complications at the diagnosis of prediabetes:	=	=	=
1. HH in males (n. and %)	=	=	=
2. HH in females (n. and %)	8/18 (44.4%*)	0/3 (0%)	0.15
3. Secondary amenorrhea (n.)	1/15 (6.6%*)	1/15 (6.6%)	1
4. Primary hypothyroidism (n. and %)	3/15 (20%*)	12/15 (80%)	0.0012
5. Hypoparathyroidism (n. and %)	2/34 (5.8%)	2/18 (11.1%)	0.49
6. Hypocortisolism (n. and %)	4/34 (11.7%)	4/18 (22.2%)	0.32
7. More than 2 endocrine complications (n. and %)	3/34 (8.8%)	3/18 (16.6%)	0.40
	8/34 (23.5%)	8/18 (44.4%)	0.12

Legend: (*) = 1 male and 3 female TDT patients were prepubertal.

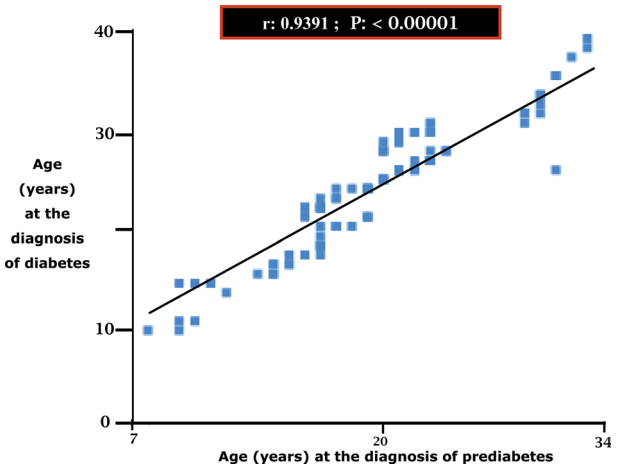

Figure 6. Correlation between age at diagnosis of prediabetes vs. age at diagnosis of diabetes mellitus in TDT patients.

correlate with patient age or pre-transfusion Hb levels. Younger age at diagnosis of prediabetes, independent of other factors, was associated with a higher prevalence and faster progression to diabetes, suggesting an accelerated decline in pancreatic β-cell function among adolescents and young adults with TDT. This trend has been observed in patients followed in Oman and Italy (17). Recent studies, including one by Rujito et al. (42), have identified mutations in diabetes-related genes (HNF4A, PTPN, KCNJ11, and PPAR gamma) in thalassemia patients, suggesting a susceptibility to DM and exacerbation of iron deposition in the pancreas, impacting glucose homeostasis.

OGTT is the gold standard for screening, recommended to be carried out annually from the age of ages 10 years, possibly combined with insulin secretion determination (31). While identifying the optimal method for assessing glucose homeostasis

deterioration remains challenging, the 'rapid prediabetes conversion rate' observed in our study reinforces the utility of annual OGTT screening.

Our study's main strengths include a large sample size and a relatively long-term follow-up (mean: 3.8 years; median: 4 years; range: 1-8 years). However, limitations must be acknowledged. The study population was recruited from a single Iranian Thalassemia Center, potentially limiting the applicability of findings to other ethnic groups or geographical regions. The severity of patients' genotypes was not fully available. Iron overload was assessed solely by SF levels, and other significant parameters, such as liver enzymes and the effects of different iron chelating agents, were not analyzed. Lastly, the progression to diabetes was not compared with regression rates, although a previous long-term study showed varied outcomes among TDT patients with combined IFG/IGT (15).

In conclusion, to our knowledge, this retrospective study represents the largest investigation to date on the long-term conversion rate from prediabetes to diabetes in transfusion-dependent thalassemia (TDT) patients. Identifying high-risk individuals is a challenging task, yet our findings indicate that a parental history of diabetes, elevated serum ferritin levels, and a younger age at prediabetes diagnosis are significantly associated with the progression to diabetes mellitus (DM) in TDT patients with a normal body mass index (BMI). These identified risk factors are crucial, as they provide valuable insights for clinicians, enabling them to implement targeted diagnostic and therapeutic interventions in the comprehensive management of TDT patients.

Moreover, our study reinforces the complex interplay of genetic, biochemical, and demographic factors in the progression of glucose dysregulation in TDT patients. It underscores the need for individualized, gender-specific approaches in the management of these patients, highlighting the importance of regular and comprehensive screening practices. Through these findings, we aim to contribute to the optimization of clinical strategies, ultimately enhancing the quality of life and health outcomes for patients with transfusion-dependent thalassemia.

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Conflict of Interest Statement: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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