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Original Article

Post-Load Plasma Glucose Increase (PG-gap) as a Risk Factor for Developing Dysglycemia in Patients with Transfusion-Dependent β-Thalassemia (β-TDT): Retrospective Analysis over 8 Years

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Abstract. ***Background:*** **Abnormal glucose homeostasis in transfusion-dependent β-thalassemia (β-TDT) patients requires early detection and intervention. However, current diagnostic criteria for patients with a normal oral glucose tolerance test (OGTT) may fail to detect a significant proportion of high-risk individuals.**
Objectives: **The main objective of this study was to evaluate in β-TDT patients with normal fasting plasma glucose (FPG) and glucose tolerance (NGT), the plasma glucose (PG) incremental rise gap during OGTT, defined as the difference between 2h-PG and FPG (PG-gap), as an early predictor index associated with future risk of developing dysglycemia and thalassemia-related diabetes mellitus (Th-RDM).**
Research design, patients, and methods: **58 β-TDT patients, recruited from three Thalassemia centers (Iran, Italy, and Greece), were selected for the study. The patients underwent a routine OGTT, and the PG-gap between 2-h PG and FPG (2-h PG - FPG) was calculated. The patients were categorized into three groups based on the results: "Low post-load" when the gap was < 20th percentile (≤ 10 mg/dL), Group A; "Medium post-load" when the difference was distributed between the 20th and < 75th centiles (> 10 mg/dL and < 30 mg/d), Group B; and "High post load" ≥75th percentile (≥ 30 mg/d) Group C.**
Results: **Follow-up was available for 6 years in all 58 patients, including 8-year data in 45 patients. The incidence of dysglycemia, namely, isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), IFG plus IGT, isolated high 1-h PG (>155 mg/dL), after OGTT, and thalassemia-related diabetes mellitus (Th-RDM), was significantly lower in Groups A and B (27/45 patients) compared to Group C (18/45 patients) (χ^2: 4.8214; P=0.028). Three patients in group C ("High post-load gap") developed Th-RDM. At the last evaluation, the serum ferritin (SF) level was < 800 µg/L in 13/45 (28.8%) patients, between ≥ 800 µg/L and < 1,500 µg/L in 17/45 (37.7%) patients, between ≥ 1,500 µg/L and < 3,000 µg/L in 14/45 (31,1%) patients, and ≥ 3,000 µg/L in**

1/45 (2.3%) patients. Multiple linear regression was used to determine the variables contributing to the 2h-PG at the last follow-up. Only two variables, SF and age, were significantly associated with 2h-PG at last follow-up (t-stat: 2.3941; P=0.0203 and t-stat: 2.0918; P=0.0414, respectively). The other variables [BMI, pre-transfusional hemoglobin level, serum alanine aminotransferase (ALT), and positive family history for diabetes type 1 or 2 did not contribute significantly.
Conclusions: **The findings suggest that a high post-load plasma glucose gap (≥ 75th percentile or ≥ 30 mg/dL) is associated with a progressively increasing risk of glucose dysregulation over the next 6 to 8 years. These findings underscore the importance of a personalized approach to assessing the risk of early glucose metabolic disorders in β-TDT patients who are typically classified as normoglycemic.**

Keywords: Transfusion-dependent β-thalassemia patients; Oral glucose tolerance test; Post-load plasma glucose gap; Glucose dysregulation; Risk factors.

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Introduction. In general, pancreatic β-cell dysfunction and abnormal peripheral tissue insulin sensitivity are present in transfusion-dependent β-thalassemia (β-TDT) patients,[1,2] even before glucose levels exceed the thresholds acknowledged as prediabetes by the World Health Organization (WHO)[3] and the American Diabetes Association (ADA).[4] Therefore, early detection of dysglycemia, [isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), IFG plus IGT, isolated high 1-h PG (>155 mg/dL), after oral glucose tolerance test (OGTT)] and thalassemia-related diabetes mellitus (Th-RDM) are crucial for preventing further complications and improving long-term quality of life. The frequency of screening varies based on individual risk factors, such as the severity of genotype and the efficacy of treatment with transfusions, chelation, and other treatments. More frequent testing is suggested for patients with multiple risk factors or those at very high risk.

Current standard of care guidelines recommend an annual screening with a 2-h OGTT for all β-TDT patients aged 10 years and older.[5,6] The threshold value of 100 mg/dL for fasting glucose, as suggested by ADA[4] rather than 110 mg/dL as per the WHO,[3] was recommended by the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) based on the observation that almost half of β-TDT patients with fasting glucose 100-110 mg/dL developed IGT within the next few years.[7] Currently, the high cost and the long test time are the major limiting factors for the integration of OGTT into routine diabetic care. These factors explain the low adherence to annual OGTT in β-TDT patients. Moreover, the standard oral glucose solution is frequently associated with nausea and, in some cases, vomiting.[8]

Therefore, over the years, numerous investigators have sought alternative screening methods for early diagnosis of dysglycemia. Conflicting data have been reported about the diagnostic role of HbA1c and fructosamine in evaluating dysglycemia in β-TDT patients. The use of HbA1c as a screening test for abnormalities of glucose homeostasis in individuals with β-thalassemia major (β-TDT) appears to be less accurate.[9,10] To try to reduce the costs and to address poor patient adherence to OGTT, Dritsa et al.[8] suggested performing OGTT: (a) at the initiation of puberty; (b) in all patients with a fasting plasma glucose above 100 mg/dL, and (c) in any patient with a HOMA-IR index above 1.85, and to perform the test yearly onwards. Adopting these criteria, the researchers obtained a total reduction of 46.4% in the number of OGTTs performed.[11]

An Italian study has shown that in subjects with normal glucose tolerance (NGT), the time required for the PG concentration to return to, or drop below, the fasting PG level following glucose ingestion is dependent on the insulin response during the OGTT and peripheral/hepatic insulin sensitivity.[12] Notably, across the categories of normal 2-h glucose concentrations, those subjects in the higher 2-h-PG group manifested greater insulin resistance, reduced insulin secretion, and oral disposition index (oDI) compared to those with PG concentrations in the lower category.

Therefore, the ICET-A Network promoted a

retrospective, multicenter observational study with its main objective being to determine whether the difference between FPG and 2 h-PG concentrations during OGTT could provide a reliable and simple additional index for predicting the associated risk of dysglycemia in β-TDT patients with normal FPG (< 100 mg/dL) and normoglycemia after glucose load, as defined by current OGTT criteria.

Patients and Methods

a. Study design, Setting, and Participants. This retrospective observational long-term study includes β-TDT patients followed and recruited from three Thalassemia centers (Iran, Italy and Greece), who underwent 2-h OGTT screening between January 2014 and January 2025. β-TDT was diagnosed using complete blood count, hemoglobin HPLC, and molecular characterization of the genotype in 54 of 58 patients.

Eligible criteria for study inclusion were: (a) β-TDT patients receiving frequent blood transfusion and personalized regimes of iron chelation therapy; (b) chronological age ≥10 years (c) availability of 2h- OGTT, (d) normal glucose tolerance (NGT) defined by fasting glucose < 100 mg/dL, 1h -PG < 155 mg/dL, and 120-min PG < 140 mg/dL, and (e) patients' follow-up of no less than 6 and up to 8 years.

The main exclusion criteria included: (a) non-transfusion-dependent thalassemia (NTDT); (b) bone marrow transplanted patients; (c) β-TDT patients with serum alanine aminotransferase (ALT) above twice the upper normal value range (> 80 mU/L); (d) pregnancy; (e) active hepatitis C, and (f) recent intake of medications influencing glucose metabolism (such as: thiazide diuretics, beta-blockers and corticosteroids) (**Figure 1**).

b. Clinical and biochemical measurements. Data collected at baseline OGTT included: age, gender, anthropometric measurements (standing height, weight, and body mass index), patients' medical data (age at first transfusion, age of splenectomy, type and dose of chelating drugs, family history of diabetes, history of alcohol consumption, and relevant biochemical and hematological evaluation.

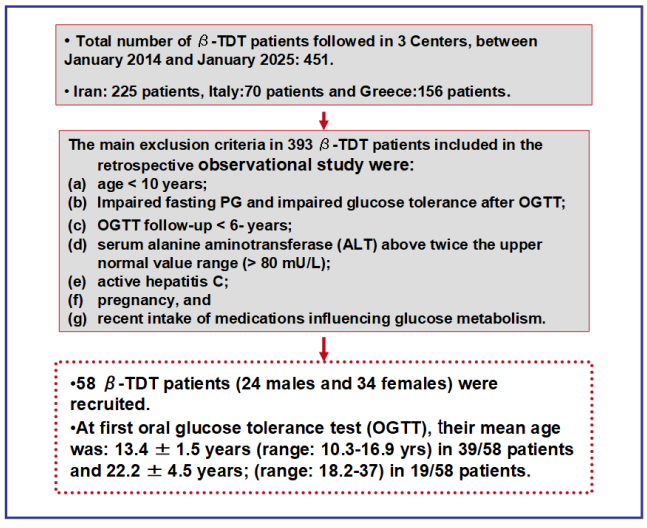

Figure 1. Flow chart for the selection of β-TDT patients for study analysis.

Height and weight were measured according to international recommendations.[13] Body mass index (BMI) was calculated by dividing the weight (Kg) by the square of the height (m^2). Children and adolescents with a BMI between the 5th and 85th percentile were defined as normal weight. A BMI at or above the 85th percentile but below the 95th percentile was considered diagnostic for overweight, and a BMI at or above the 95th percentile was considered diagnostic for obesity, taking into account age and sex. Severe obesity class 2) was defined a BMI >35 Kg/m^2 and < 40 Kg/m^2.[14,15]

Standard methods determined all biochemical parameters. The level of alanine aminotransferase (ALT) was determined by an automated analyser, and iron overload (IOL) was assessed by serum ferritin (SF) in µg/L. IOL was arbitrarily classified as mild (SF:< 800 µg/L), moderate (SF: ≥ 800 µg/L and < 1,500 µg/L), high (SF: ≥ 1,500 µg/L and < 3,000 µg/L), and severe (SF: ≥ 3,000 µg/L). SF was measured by chemiluminescence immunoassay. The 50th centile of reported normal values is 105 µg/L in males and 35 µg/L in females.[16]

c. Oral glucose tolerance test (OGTT). β-TDT patients underwent an OGTT (1.75 g/kg oral glucose, maximum 75 g) after an 8-10 h overnight fast. Venous blood was collected at three intervals (fasting, 1 h, and 2 h after 75 g anhydrous glucose) at baseline. Plasma glucose concentrations were measured by an automated glucose oxidase reaction. OGTT was repeated every two years for at least 6 years.

Glucose tolerance was defined according to the current ADA criteria.[4] Based on plasma glucose concentrations; patients were assigned to one of the following categories of glucose tolerance. Prediabetes was defined by the presence of isolated impaired fasting glucose (i-IFG; fasting PG between 100–125 mg/dL) or isolated impaired glucose tolerance (i-IGT when the 2h-PG during the OGTT was between 140–199 mg/dL) or both. Th-RDM was diagnosed when FPG was ≥ 126 mg/dL or 2 h-PG≥ 200 mg/dL.[15] Moreover, a conventional cutoff of 1h- PG (≥ 155 mg/dL) was used to identify dysglycemia.[17,18]

Statistical analysis. For the statistical analysis, a software program was used and validated, as described by Alder and Roesser.[19] All numeric variables were expressed as mean ± standard deviation (SD), numbers, proportions as percentages (%), and groups were divided into percentiles. The Kolmogorov-Smirnov was used to verify the normality of the distribution of variables. Normally distributed continuous variables were

compared using ANOVA, and non-normally distributed variables were analyzed using the Kruskal-Wallis test. Relationships between variables were determined using Pearson linear correlation for normally distributed variables, Spearman's Rho for quantitative variables that were abnormally distributed, and linear regression analysis. Multiple linear regression analyses were performed using a model in which the dependent variable was the 2h-PG at the last follow-up, with the following baseline variables: age, BMI, pre-transfusional hemoglobin level, SF, ALT, and a positive family history for type 1 or 2 diabetes. The "test stats" used in multiple linear regression provides a confidence interval for the difference between group means, while hiding its calculation for the standard error for that difference. The larger the test stats, the less likely it is that the results occurred by chance. The categorical data were analyzed using the chi-square (χ^2) test. All statistical tests were two-tailed, and p-values < 0.05 were considered to be statistically significant.

Ethics. All patients gave informed consent in accordance with principles of the Declaration of Helsinki and its later amendments in 2020 (www.wma.net), after a detailed explanation of the procedures for performing the OGTT, and the nature and purpose of the study. Moreover, in this retrospective study, patients underwent only routine diagnostic procedures in accordance with current recommendations or guidelines for the management of β-thalassemia. [2,6,7] The study was approved by the local institutional review boards or was waived in accordance with the local legislation and institutional requirements.[20]

Results

a. Characteristics of the study population at baseline. A total of 58 β-TDT patients (24 males and 34 females) were included in the retrospective observational study. At the first OGTT, 39/58 patients (67.2%) were < 18 years (mean age:13.4 ± 1.5 range: 10.3-16.9 years) and 19/58 (32.7%) were ≥ 18 years (mean age: 22.2 ± 4.5; range 18.2-37 years). The mean annual pre-transfusion Hb level was 8.9 ± 0.58 (range: 8-10.1 g/dL). The remaining clinical and laboratory data are summarized in **Table 1**.

Iron chelation therapy was based on three commercially available chelators: Deferioxamine (DFO), Deferasirox (DFX), and Deferiprone (DFP). Each iron chelator was used either as monotherapy or in combination. DFX monotherapy was the most commonly used oral iron chelating agent (31/58; 53.4%), followed by DFO (13/58; 22.4%) and DFP (6/58; 10.3%). 8/58 patients (1.7%) were on combined therapy with DFO + DFP or DFO + DFX. The median serum ferritin (SF) level at baseline of the OGTT was 1,237 µg/L (range: 293-8,133). Monotherapy was generally used if the iron burden was in an acceptable or near-acceptable range, and the dose was adjusted according to 6-monthly SF levels and annual blood consumption per kg of body weight. Thus, the recommended doses of the chelating

Table 1. Summary of clinical and laboratory characteristics at baseline (mean ± SD; median and range) in 58 transfusion-dependent β-thalassemia patients (β-TDT) with normal fasting plasma glucose (PG) and normal glucose tolerance, according to the ADA criteria.

Variables	Transfusion-dependent β-thalassemia patients
Mean age at first OGTT in patients < 18 yrs and >18 yrs	13.4 ± 1.5 and 22.2 ± 4.5
Patients' hematological phenotype /genotype	β0/β0: 44 patients β+/β0: 5 patients β+/β+: 4 patients Not available: 4 patients
Gender distribution	Males:24; Females:34
Positive family history for diabetes type 1 or type 2 diabetes.	10/58 (15.5 %)
Splenectomy	15/58 (24.1 %)
Overweight **Obesity** **Severe obesity**	3/58 (5.1%) 7/58 (12.0%) 2/58 (3.4 %)
Pre-transfusional hemoglobin level (g/dL) **Median and range**	8.9 ± 0.58 9 (7.3 -10.1)
Serum ferritin (µg/L) at OGTT **Median (µg/L) and range**	1,470 ± 1,187 1,237 (367- 8,133)
Alanine aminotransferase (IU/L) (ALT) **Median (IU/L)**	35.0 ± 21.6 30
ALT > 40 IU/L and < 80 IU/L	21/58 (36.8%)
Fasting plasma glucose (FPG) (mg/dL)	85.6 ± 7.7
1-h PG during OGTT (mg/dL) (51/58 patients)	113.3 ± 17.6
2-h PG after OGTT (mg/dL)	108.0 ± 17.0

drugs were for Deferioxamine: 30-50 mg/kg/day over 8-10 hours/day, 4 to 6 days/week, Deferiprone:75 mg/kg/day, in 3 divided oral daily doses, and Deferasirox: 20- 30 mg/kg/day, in a single oral dose. Combination chelation was employed for patients with a high iron burden, iron-related organ injury, or when the adverse effects of chelators precluded the administration of an appropriate dose of chelator. A systematic quantification of adherence to each regimen was not available.

b. Patients' glucose homeostasis categorization at baseline and duration of follow-up: The patients underwent a routine OGTT, and PG-gap levels between 2-h PG and FPG (2-h PG mg/dL - FPG) were calculated. The patients were categorized into three groups based on the results: "Low post-load", when the gap was < 20th percentile (< 10 mg/dL) Group A; "Medium post-load" when the difference was distributed between the 20th and <75th centiles (> 10 mg/dL and < 30 mg/d) Group B; and "High post load" ≥75th percentile (≥ 30 mg/d) Group C **(Figure 2).** The mean total gap (FPG - 2h PG mg/dL) was 19.4 ± 16.2 mg/dL.

In all β-TDT patients, follow-up was available for up to 6 years, and in 45 of 58 patients, it was available for up to 8 years.

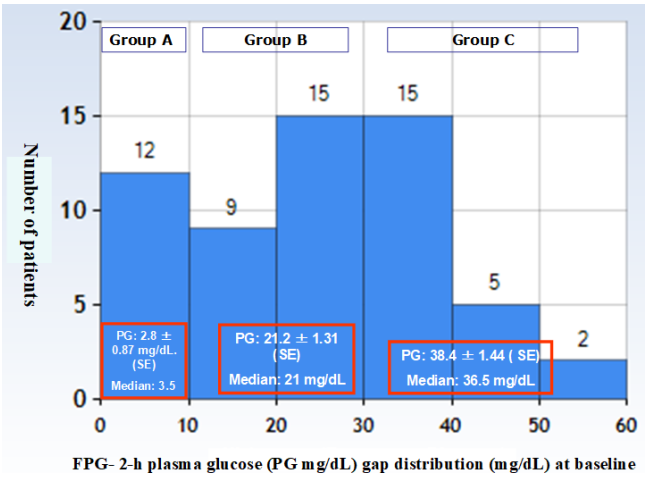

Figure 2. FPG- 2h PG-gap mg/dL gap distribution and mean gap interval (mg/dL ± SE) at baseline in 58 β-TDT patients**.**

c. Evolution of glucose dysglycemia during 8-year follow-up and prevalence in the three subgroups of patients: The evolution of OGTT abnormalities over 2, 4, and 6 years in all 58 enrolled β-TDT patients is illustrated in **Figure 3.**

After 8 years of follow-up, full data were available only in 45 out of 58 β-TDT patients. The detailed distribution of glucose abnormalities is illustrated in **Figure 4.** The total incidence of dysglycemia in Group A (8/45 patients; mean gap interval: 4.2 ± 3.1 mg/dL) plus Group B (19/45 patients; mean gap interval: 21.8 ± 5.3 mg/dL) compared to Group C (18/45 patients; mean

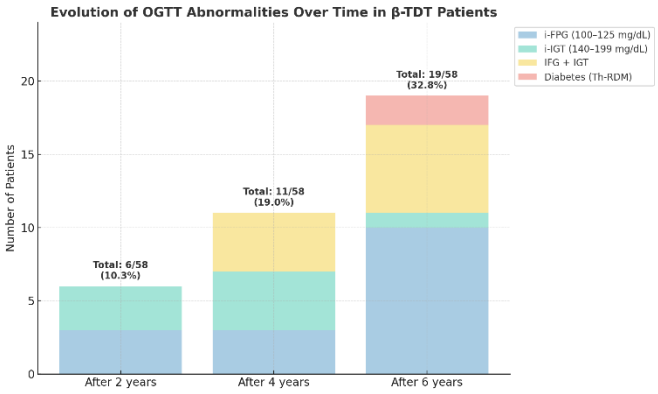

Figure 3. Evolution of glucose abnormalities over time in 58 transfusion-dependent β-thalassemia patients (β-TDT). ***Legend:*** isolated FPG (i-FPG), isolated IGT (i-IGT), IFG plus IGT, isolated high 1h- PG (>155 mg/dL), and thalassemia-related diabetes mellitus (Th-RDM).

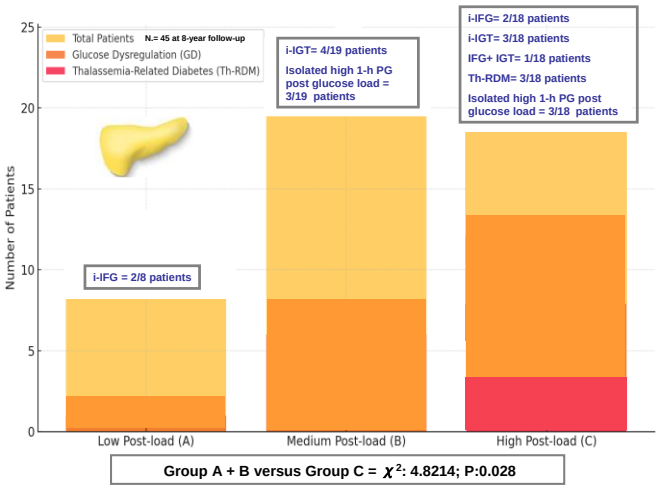

Figure 4. Evolution of glucose dysregulation, using ADA criteria, in 45 transfusion-dependent β-thalassemia patients (β-TDT) after 8 years follow-up and their distribution in relation to postload-fasting plasma glucose (PG) gaps. ***Legend:*** isolated FPG (i-FPG), isolated IGT (i-IGT), IFG plus IGT, isolated high 1 h-PG (>155 mg/dL), and thalassemia-related diabetes mellitus (Th-RDM).

PG gap interval: 29.1 ± 7.0 mg/dL) was significantly lower (χ^2: 4.8214; P=0.028).

d. Serum ferritin (SF) at last observation in 45 patients followed for 8 years: At the last evaluation, the SF level was < 800 µg/L in 13/45 (28.8%) patients, between ≥ 800 µg/L and < 1,500 µg/L in 17/45 (37.7%) patients, between ≥ 1,500 µg/L and < 3,000 µg/L in 14/45 (31,1 %) patients, and ≥ 3,000 µg/L.in 1 patient (23%). No significant difference was documented between the last mean SF level compared to SF at baseline (1,358 ± 800,2 µg/L versus 1,470 ±1,187 µg/L: P: 0.58).

e. Correlations: Pearson or Spearman's Rho correlation coefficients, at baseline and at 8-year follow-up, between 1h- PG levels during OGTT and 2h- PG post-glucose load were statistically significant (r: 0.483; p=0.00033 and r: 0.7025; p< 0.00001, respectively) (**Figure 5)** as

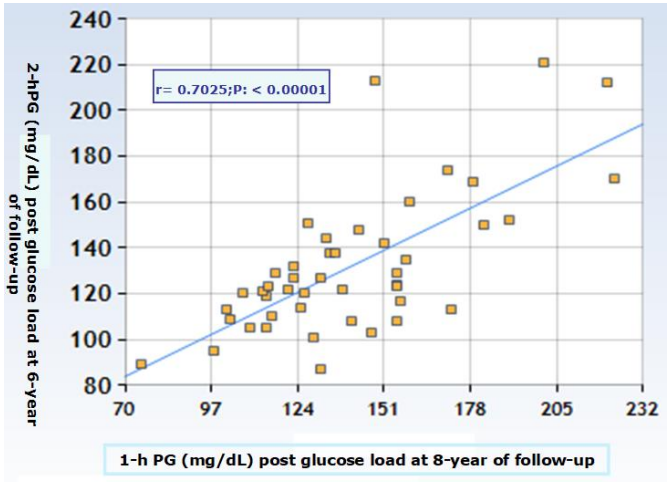

Figure 5. Pearson correlation coefficient (r) between 1-h PG and 2-h PG post glucose load at 8 years of follow-up.

well as between the post-load-fasting PG gap and 2h- PG post-glucose load at baseline (r: 0.5787; p< 0.00001) and at 8-year follow-up (r: 0.31755; p=0.033).

At 8-year follow-up, no Pearson's or Spearman's Rho correlation (2-tailed) was documented between age and SF versus 2h-PG post-glucose load (r: 0.03314; p=0.82 and r: 0.14899; p=0.32, respectively. Moreover, no statistical difference was found in the prevalence of dysglycemia between male and female patients (P = 0.17)**.**

f. Multiple linear regression analysis with 2h-PG-gap level at 8 years follow-up. Multiple linear regression was used to determine 6 variables contributing to the 2h-PG-gap at last follow-up. In particular, the regression procedure indicated that only two variables: SF and age were significantly associated with 2h-PG-gap at previous follow-up (t-stat: 2.3941; p= 0.020 and t-stat: 2.0918; p=0.041, respectively). The other variables [BMI, pre-transfusional hemoglobin level, serum alanine aminotransferase (ALT), and positive family history for diabetes type 1 or 2 did not contribute significantly. In this context, the association with glucose dysregulation with age and SF has been confirmed by previous studies, indicating that this impairment in glucose handling begins in the second decade of life and continues throughout adulthood.[1,2,5-7]

Discussion. Abnormal glucose homeostasis is a common finding in transfusion-dependent β-thalassemia (β-TDT) patients, which worsens with age and non-compliance with chelation therapy. It can occur in the absence of noticeable clinical signs and symptoms. Dysglycemia and thalassemia-related diabetes mellitus in β-thalassemia trait (β-TDT) patients are characterized by varying degrees of reduced insulin secretion and sensitivity, primarily due to iron toxicity on β-cells, even if the complete pathogenesis remains incompletely understood.[5-7,17]

We have documented for the first time that β-TDT patients with NFG and NGT can be stratified for risk of progression to dysglycemia based on the relationship between the FPG concentration and post-load (OGTT) plasma glucose concentration. Interestingly, 1h-PG level during OGTT, at baseline and at 8 years of follow-up, was positively correlated with 2 h-PG post-glucose load, indicating a reduction of β-cell function and insulin sensitivity.[17] Therefore, early intervention measures, including nutritional interventions, regular physical activity, and optimization of iron chelation, should be recommended as preventive strategies.

Moreover, it has been documented that NGT subjects whose PG values decline more rapidly to FPG levels during OGTT have better β-cell function and greater insulin sensitivity compared to NGT subjects whose PG values decline more slowly.[21,22]

The main strengths of this study include the duration of follow-up. However, certain limitations should be acknowledged. The first key limitation is its retrospective nature. Secondly, insulin secretion and action during OGTT were not formally evaluated. However, the clinical applicability of 2h-PG when coupled with FPG for early detection of GD in β-TDT patients has been confirmed in a preliminary study involving 19 normoglycemic β-TDT patients followed at a single Center.[23] The gap between FPG and 2 h-PG post-glucose load was positively correlated with 2h-PG post-load and negatively with FPG and insulinogenic index (IGI). Moreover, IGI was positively correlated with oral disposition index (oDI_{30}) and negatively with 1h and 2h post-PG load. Substantially, across the categories of normal 2h-PG concentrations, the β-TDT patients in the higher 2h-PG group exhibited greater insulin resistance and reduced insulin secretion and oral disposition index (oDI_{30}) compared with those whose PG concentration fell into the lower category, thereby increasing the future risk of impaired glucose tolerance. Thirdly, the relatively small sample size and the variable patient adherence to OGTT limit the generalization of the findings. Another important limitation is that no specific cutoff value for the FPG–2h PG-gap could be established in this study, preventing its immediate use in clinical practice. Furthermore, the insulin sensitivity varies during puberty; it appears to be highest before the onset of puberty, reaches its nadir midway through maturation, and subsequently recovers by the end of puberty. Notably, three patients of group C ("High post-load gap": ≥ 30 mg/dL) developed Th-RDM. The PG gap, after OGTT, in β-TDT patients in mid-advanced adolescence was statistically different compared to β-TDT prepubertal patients (22.5 ± 6,7 versus 11.9 ± 14.3; P: 0.029) but not versus young adult β-TDT patients (26.0 ± 13.5; P:0.42), supporting a significant decline of insulin secretion and persistence of reduced insulin

sensitivity. Finally, the relatively short follow-up duration highlights the need for larger and longer prospective studies to validate the utility of FPG and the 2-hour post-load glucose PG-gap as early and reliable biomarkers of dysglycemia in β-TDT patients.

Conclusion. These preliminary findings suggest that a high post-load glucose incremental rise (PG-gap: ≥ 75th percentile) in transfusion-dependent β-thalassemia patients with normal fasting PG and PG glucose values after an OGTT should be considered a predictor for developing dysglycemia, with the likelihood of progression increasing over time. Additional prospective follow-up studies are needed to determine the level of risk associated with varying post-load fasting gaps, in order to guide clinical monitoring and interventions.

Author contributions: VDS contributed to the study design, revision of the literature, interpretation of the data, statistical analysis, and drafting the first version of the manuscript. VDS, MF, EV, and TMV are the guarantors of the data included in the manuscript and take full responsibility for its content. VDS and ATS prepared the original figures. ATS, SD, PT, CK, MF, and EV contributed to the critical revision of the manuscript for important intellectual content, editing, and revision. All of the authors approved the final manuscript prior to submission.

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