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Original article

Isolated increase of plasma glucose levels at 30 minutes during oral glucose tolerance test (OGTT) in young adult patients with transfusion-dependent β-thalassemia (β-TDT): A possible predictor marker for early development of glucose dysregulation (GD)

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Abstract. *Background:* In the general population, prospective studies have documented that intermediate plasma glucose (PG) at 30-min or 1- hour during a standard oral glucose tolerance test (OGTT) are associated with a high risk of glucose dysregulation (GD) and incidence of diabetes. *Study aims:* The main aim of this retrospective observational study was to determine whether high 30-min-PG levels could be an early indicator of GD in β-TDT patients with an otherwise normal glucose tolerance test (NGT). *Patients and Methods:* A total of 57 β-TDT young adult patients with normal OGTT were re-evaluated, according to the American Diabetes Association guidelines. Indices of insulin secretion and sensitivity were also calculated. Patients were divided into 3 groups (A, B and C), according to 30-min PG evaluated in percentile. *Results:* The first documented cases of GD in the 3 groups of patients were observed after a mean (± SD) interval of 7.2 ± 1.3 years in a patient of Group A (PG level equal or below the 50th percentile); after 6.0 ± 1.7 years in Group B (PG level between the 50th percentile and the 75th percentile) and after 6.3 ± 2.5 years in Group C (PG level above the 75th percentile). Notably, at last consultation, the number of patients with GD was significantly higher in Group C vs. Group A (12/19 vs. 5/19; P: 0.048). In addition, in Group A, an attenuated mean oral disposition index (oDI_{30}) was observed, suggesting impairment of glucose metabolism. In Group B and Group C, a significant inverse correlation between the insulinogenic index (IGI) vs 2-h PG (r = -0.3480; P = 0.037) and a significant positive correlation between IGI and oDI_{30} were documented (r = 0.7727; P < 0.00001). *Conclusions:* Young adult β-TDT subjects with NGT and isolated high 30-min PG > 75th percentile (≥155 mg/dL) may represent a distinct group of patients at a risk for developing GD, likely due to decreased insulin sensitivity and pancreatic β-cell dysfunction. (www.actabiomedica.it)

Key words: oral glucose tolerance test, 30-min pg levels (percentiles), transfusion-dependent β-thalassemia patients, glucose dysregulation, indices of insulin secretion and sensitivity, risk factors

Introduction

In recent years, there has been a growing interest in the study of glucose dysregulation (GD) in patients with β-thalassemia, mainly in those with transfusion-dependent β-thalassemia (β-TDT). The pathogenic mechanisms of GD in these patients are complex and multifactorial. In general, three main factors often co-exist: chronic hypoxia, iron overload (IOL) toxicity and chronic liver disease (1). Iron, mainly secondary to blood transfusions, is accumulated in several organs, particularly the liver, spleen, heart and pancreas. Pancreatic iron loading starts early particularly in patients receiving poor or suboptimal iron chelation therapy (2,3), accelerates after splenectomy (4) and increases with age (1,3). Annual oral glucose tolerance test (OGTT) is a key component of the clinical follow-up; current guidelines recommend annual testing in all β-TDT patients from 10 years of age (5). The data required to diagnose impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes include the determination of fasting PG prior to OGTT and 2-h after the challenge. In clinical practice, insulin levels during OGTT are not assessed routinely. For research purposes, additional blood samples are obtained, and PG and insulin are usually simultaneously measured. Moreover, mathematical surrogate indices of early" and "late-phase" insulin responses, and sensitivity/resistance can be determined to expand the potential additional gains obtained from the assessment of OGTT. The diagnostic role of HbA1c and fructosamine in evaluating GD in β-TDT patients is still being debated. Fructosamine seems to be more specific compared to HbA1c in detecting glucose intolerance and more sensitive for diagnosing diabetes mellitus (DM) (5). Prospective studies have documented that high PG concentrations one hour post glucose load is associated with a higher risk of glucose dysregulation (GD) and incidence of diabetes (6-10). However, the practical implications of using 30-min PG for predicting GD in β-TDT patients, irrespective of glucose tolerance status, have not yet evaluated. The primary objective of this retrospective, observational study was to determine whether different PG cut-offs at 30-min post glucose load, in adult β-TDT patients with NG, may provide useful information for the evaluation of glucose homeostasis and be an early predictor marker for the development of GD over the time. As a secondary objective, the value of surrogate indices of early insulin secretion and insulin sensitivity/resistance was assessed for a better understanding of the pathophysiological changes associated with isolated elevation of 30-min PG level post glucose load.

Subjects and Methods

The study was conducted in the context of an ongoing observational study of the natural history of GD in patients with β-TDT, promoted by the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A).

Setting, study population and research design

The anonymized data of β -TDT patients followed by the same endocrinologist (VDS) at Pediatric Endocrinology and Adolescent Medicine, Outpatient Clinic of St. Anna Hospital of Ferrara (January -September 2010) and Pediatric Endocrinology and Adolescent Medicine Quisisana Outpatient Clinic of Ferrara (October 2010-June 2019), for endocrine or metabolic consultation or second opinion, were reviewed. Eligible criteria for study inclusion were: (a) β-TDT patients receiving routine blood transfusion and chelation treatment; (b) chronological age > 18 years; (c) body mass index (BMI) below 30 kg/m^2; (d) availability of a 2-h OGTT, normal glucose tolerance (NGT) defined by fasting glucose < 100 mg/dL, 60-min PG < 155 mg/dL, and 120-min PG < 140 mg/d, and (e) patients' follow-up for more than 5 years. Exclusion criteria included: non-transfusion-dependent thalassemia (NTDT) patients, patients on steroid treatment or β-blockers, or with incomplete data. The following clinical data were collected at first consultation: demographic characteristics, age at the first consultation, weight, height, medical history, family history of diabetes, history of smoking or alcohol consumption, overall recommended treatments of β-TDT, history of splenectomy, type of iron chelation therapy (ICT), patients' reported adhesion to previous ICT and associated endocrine complications. All clinical

information were collected 1 or 2 days before OGTT screening. Height and weight were measured according to international recommendations (11). Body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m^2). Patients were classified according to BMI as underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), or obese (BMI ≥ 30 kg/m^2). Associated endocrine complications were identified and defined according to previous publications (8,9). The level of serum alanine aminotransferase (ALT) was determined by an automated analyzer (normal range 0–40 mU/L), iron overload (IOL) by serum ferritin (SF); IOL was arbitrarily classified as mild (SF: < 1,000 μg/L), moderate (SF: >1,000 μg/L and < 2,000 μg/L) or severe (SF: >2, 000 μg/L). SF was measured by chemiluminescence immunoassays (Beckman Access Dxl). The 50th centile of reported normal values is 105 μg/L in males and 35 μg/L in females (12).

Assessment of glucose metabolism status

At first evaluation, OGTTs were performed after an 8-10 hr fast, using 1.75 g/kg (max.75 g dextrose monohydrate in 250 mL water). Venous blood samples were collected at baseline and 30', 60', and 120' minutes to determine PG and insulin concentrations. PG was collected in citrate-containing tubes and assessed by glucose oxidase method. As reference for 30-min PG levels, we used the percentiles derived from a different β-TDT cohort, registered during OGTT, in 96 β-TDT patients with NGT= 3rd percentile 98 mg/dL: 25 th percentile: 118 mg/dL; 50 th percentile 141 mg/dL; 75 th percentile: 155 mg/dL and 97 th percentile 187 mg/dL (VDS, unpublised data). β-TDT patients were divided in 3 groups: Group A (30-min PG level equal or below the 50th percentile: ≤141 mg/dL), Group B (30-min PG level above the 50th percentile and below the 75th percentile:142 mg/dL and 154 mg/dL, respectively), and group C (30-min PG level equal or above the 75th percentile: ≥155 mg/dL). Insulin samples were frozen at -60°C and later measured by a commercial chemiluminescence solid phase immunometric assay (Diagnostic Products Corporation, Los Angeles, CA, USA). All insulin samples were tested in duplicate, and the values were expressed in μU/mL. NGT, IFG, IGT and diabetes mellitus (DM) were defined using the criteria of the American Diabetes Association (ADA) (13).

Calculation of insulin secretion and sensitivity/resistance using surrogate indices derived from OGTT

Indices of insulin secretion and sensitivity/resistance were calculated as previously described (14).

The early phase of insulin secretion was assessed using the insulinogenic index (IGI) which was calculated as the incremental change in insulin concentration during the first 30 min after OGTT divided by the incremental change in PG during the same period (IGI: Δ 0-30 insulin/Δ 0-30 glucose min). IGI is considered an acceptable index of β-cell function and can detect subtle disturbances of glucose metabolism also in β-TDT (14). For the determination of insulin sensitivity/resistance the following indices were used: Homeostatic Model Assessment of Insulin Resistance (HOMA- IR), Quantitative Insulin sensitivity Check Index (QUICKI; which is a reciprocal logarithmic transformation of the HOMA-IR), and Matsuda Whole Body Insulin Sensitivity Index ($MI_{0\text{-}120\ min}$) during OGTT. The latter index encompasses both hepatic and peripheral tissue insulin sensitivity. To evaluate the pancreatic β-cell function adjusted for insulin sensitivity, we calculated the oral disposition index (oDI) as the product of IGI and $MI_{0\text{-}120}$. This index reflects the relationship between β-cell function (early-phase insulin secretion) and peripheral insulin sensitivity (hepatic and peripheral tissues). Substantially, oDI is considered to reflect the insulin secretory capacity adjusted for insulin sensitivity (14,15). In subjects with reduced insulin sensitivity, insulin secretion increases but in cases of associated β-cell failure the capacity to compensate decreases resulting in lower oDI.

Statistical Analysis

All numeric variables were expressed as mean ± standard deviation (SD), numbers, proportions as percentages (%), and groups divided into percentiles. The Kolmogorov-Smirnov and Shapiro-Wilk tests were

used to verify the normality of distribution of variables. Comparison of different variables was made using Wilcoxon's signed rank test or Mann-Whitney test. Categorical variables between two independent groups were analysed with Fisher's exact test. Moreover, the data obtained were analysed using Pearson's correlation test for those with normal distribution or Spearman's correlation test for the ones with an abnormal (non- parametric) distribution. For the statistical analysis, a software program was used and validated, according to Alder and Roesser (16). A P value < 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 2020 (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 for a retrospective study was not required because patients underwent only routine diagnostic procedures according to the current recommendations or guidelines (17-20). Moreover, in our retrospective study, no identifiable patients' information was collected and anonymized datasets were analyzed.

Results

At baseline

Patients' characteristics at first consultation

A total of 57 β-TDT patients [23 (40.3%) males] met the inclusion criteria and were enrolled in the study. The mean age of patients was 21.7 ± 4.3 years (range:18-34). All patients were regularly transfused, every 2-3 weeks, with a mean pre-transfusional hemoglobin level of 9.3 ± 0.5 g/dL. Ten patients (17.5 %) had undergone splenectomy. At first consultation, BMI was < 25 kg/m^2 in all but two, who were slightly overweight. The reported age at start of ICT was between 2 and 3 years; their past self-reported adhesion to ICT was: very good (>90%) in 23 patients (40.3%), good (<90% and >70%) in 26 patients (63.1%), unsatisfactory (<70% and >40%) in 6 patients (10.5%) and poor (<40%) in 2 patients (3.5%). At the time of study, 11 patients (19.2%) were on ICT with desferrioxamine (DFO), 17 (29.8%) with deferiprone (DFP), 27 (47.3 %) with deferasirox (DFX), and 2 (3.5 %) with a combination of DFP plus DFP. IOL, assessed by SF, was classified as mild in 41/57 (71.9%), moderate in 9/57 (15.7%), and severe in 7/57 patients (12.2%). The commonest associated endocrinopathy was primary or secondary hypogonadism (males 43.4% and females 55.8%). Moreover, five patients had short stature (≤ 3rd centile), while 2 patients were on thyroxine replacement therapy. Demographics, clinical and laboratory data of study groups are presented in Table 1.

The evaluation of PG levels and surrogate indices of insulin secretion and sensitivity/resistance in the 3 subgroups of β-TDT patients classified on the basis of 30-min PG percentiles are reported in Table 2.

In 14 out of 19 (73.6%) β-TDT patients of Group A, a higher level of 2-h PG compared to FPG was observed. The difference was equal to 29.5 ± 13.3 mg/dL (median 26 mg/dL). The difference of FPG vs 2-h PG, following OGTT, in 16 out of 19 (84.2%) β-TDT patients of Group B was equal to 29.2 ± 12.8 mg/dL (median 26.5 mg/dL) and in14 out of 19 (73.6%) β-TDT patients of Group C was equal to 30.4 + 11.7 mg/dL (median 32.5 mg/dL). Interestingly, the reduction of oDI_{30} index was much more marked in β-TDT patients of Group B and C vs. Group A, suggesting a progression of glucose metabolism deterioration. Moreover, the insulin secretion and insulin sensitivity/resistance indices, HOMA- IR, and Matsuda index, were statistically different in Groups B and/or C versus Group A (Table 2).

Correlations

Correlation analysis between the collected variables including age, ALT, SF, PG during OGTT, and indices of insulin secretion, sensitivity/resistance and β-cell function was performed in the whole group of β-TDT patients. In Group B and Group C, a significant inverse correlation between IGI vs 2-h PG

Table 1. Demographic, clinical and laboratory data in 57 β-TDT patients, at first consultation, classified into three groups, on the basis of 30-min plasma glucose (PG) minute percentiles.

Variables	GROUP A = (n: 19)	GROUP B = (n:19)	GROUP C = (n: 19)	A vs. B P- value	B vs. C P- value
Chronological age (yrs)	20.6 ± 2.7	21.1 ± 4.5	23.1 ± 4.9	0.84	0.25
Gender (Males/Females)	8/11	8/11	7/12	-	-
BMI (Kg/m ^{2})	22.0 ± 2.9	23.1 ± 2.7	22.6 ± 2.5	0.28	0.11
Positive family history for diabetes Type 1 or 2	2	3	4	-	-
Splenectomy	3 (15.7%)	2 (10.5%)	5 (26.3%)	1	0.40
Serum ferritin (μg/L) at time of OGTT (*)	964.5 ± 367.0	1320.2 ± 713.2	824.4 ± 379.9	0.060	**0.011**
ALT (0-40 IU/ L)	35.0 ± 13.2	35.3 ± 20.5	27.0 ± 12.1	0.68	0.52
ALT > 40 IU/L	5/19 (26.3)	5/19 (26.3)	1/19 (5.2%)	1	0.17
Iron chelation therapy					
DFO	4 (21.0%)	5 (26.3%)	2 (10.5%)	-	-
DFP	7 (36.8%)	3 (15.7%)	7 (36.8%)	-	-
DFO $_+$DFP	0 (0%)	2 (10.5%)	0 (0%)	-	-
DFX	8 (42.1%)	9 (47.3%)	10 (52.6%)	-	-

Abbreviations: PG: plasma glucose; ALT:alanine aminotransferase; BMI = Body mass index; DFO: desferrioxamine; DFP: deferiprone: DFX: deferasirox; Group A (30-min PG level equal or below the 50th percentile: ≤ 141 mg/dL), Group B (30-min PG level above the 50th percentile and below the 75th percentile), and Group C (30-min PG level equal or above the 75th percentile: ≥155 mg/dL. Data are presented as mean ± SD; P -values in bold represent significant results. (*) the 50th centile of serum ferritin level in the general population is 105 μg/L in males and 35 μg/L in females.

[Spearman's correlation: r = - 0.3480; P (2-tailed) = 0.037] and a significant direct correlation between IGI and oDI$_{30}$ (Pearson's correlation: r = 0.7727; P: < 0.00001) were documented. Moreover, in Group B and Group C no significant correlation was observed between 30-min PG and SF (Pearson's correlation: r = -0.0367; P:0.79) and no significant correlations were observed between insulin sensitivity indices and other clinical and laboratory parameters, including age, splenectomy status, PG levels during OGTT, liver enzyme (ALT) and iron overload level, assessed by SF levels.

Outcomes of glucose metabolism, at last observation, and percentages of GD across different 30-min PG percentiles

After the first consultation, an annual 2-h OGTT, according to ADA criteria, was suggested to the referring centers. Moreover, an endocrine evaluation in patients with GD was also suggested. The first documented GD in the 3 groups of patients was observed after 7.2 ± 1.3 years in Group A, after 6.0 ± 1.7 years in Group B and after 6.3 ± 2.5 years. in Group C. The follow-up interval between the 3 groups of patients was not statistically significant (Group A vs. Group B = P: 0.93; Group A vs. Group C = P: 0.18 and Group B vs. Group C= P: 0.28). Notably, the number of patients with GD, based on ADA criteria, was higher in Group C vs. Group A (12/19 vs. 5/19; Fisher exact test: P: 0.048). A detailed presentation of results, at last consultation, is reported in Table 3. All patients were on oral chelation monotherapy [45/57 on DFX (78.9%) and 12/57 on DFP (21%)]. Compared to baseline, the mean SF level was lower at 695.2 ± 243.8 μg/L vs. 1026.2 ± 530.6 μg/L (P: < 0.0001).

Discussion

To our knowledge, this is the first study who has explored the clinical utility of isolated high 30-min PG (≥ 154 mg/dL), in a subgroup of β-TDT patients with normal glucose tolerance, assessed by ADA criteria.

Table 2. Demographics, plasma glucose (PG) levels and surrogate indices of insulin secretion and sensitivity/resistance in the three groups (A, B and C) of 57 β-TDT patients with different 30-min PG percentiles during OGTT, at first consultation.

Variables	GROUP A = (n: 19)	GROUP B = (n:19)	GROUP C = (n: 19)	P- value A vs. B / A vs. C	P- value B vs. C
Chronological age (yrs) - Range	20.6 ± 2.7 (18-26)	21.1 ± 4.5 (18-34)	23.1 ± 4.9 (18-32)	0.84/0.059	0.25
Gender (Males/Females)	8/11	8/11	7/12	-	-
Fasting PG (mg/dL) - Range	86.7 ± 8.3 (71-97)	90.8 ± 6.3 (82-99)	90.6 ± 5.6 (80-98)	0.10/0.41	0.92
PG 30-min (mg/dL) during OGTT- Range	119.4 ± 13.4 (94-141)	147.6 ± 3.4 (144-152)	163.6 ± 5.4 (155-173)	**< 0.0001/ <0.0001**	**<0.0001**
PG 1-h (mg/dL) during OGTT - Range	118.2 ± 17.4 (82-145)	134.2 ± 10.7 (110-156)	133.6 ± 17.7 (79-152)	**0.001/ 0.009**	0.90
PG 2-h (mg/dL) during OGTT - Range	106.4 ± 13.8 (75-127)	116.2 ± 19.3 (101-138)	111.7 ± 18.8 (76-128)	0.080/ 0.080	0.43
QUICKI	0.35 ± 0.02	0.38 ± 0.035	0.36 ± 0.022	0.05/0.15	0.18
HOMA-IR	1.70 ± 0.68	1.23 ± 0.52	1.89 ± 1.58	**0.025**/0.63	0.16
Insulinogenic Index (IGI)	1.17 ± 0.71	0.58 ± 0.25	0.65 ± 0.32	**0.001/ 0.006**	0.61
MATSUDA Index (MI 0-120)	7.5 ± 2.7	9.0 ± 4.4	3.8 ± 1.9	0.21/ **< 0.0001**	**< 0.0001**
Oral Disposition Index (oDI)	8.0 ± 4.3	4.2 ± 1.5	4.0 ± 1.8	**0.0009/ < 0.0001**	0.71

Abbreviations: PG: plasma glucose; ALT: alanine aminotransferase (normal values: <40 mU/ml); OGTT: Oral glucose tolerance test; NGT: normal glucose tolerance; QUICKI: Quantitative Insulin sensitivity Check Index; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance.

Over a 7-year of follow-up, two thirds of patients developed some form of glucose dysregulation and 3/19 (15.7%) patients (Group C) with normal glucose tolerance (NGT) developed 1-hour PG post glucose load ≥ 155 mg/dL, despite mild IOL (SF levels 695.2 ± 243.8 μg/L) assessed at last consultation. Moreover, in 14 out of 19 patients (73.6%) of Group A, we found that 2-h PG level was higher than FPG. The difference was equal to 29.5 ± 13.3 mg/dL (median 26 mg/dL). Normally, time to return to or fall below the FPG level, after glucose ingestion, depends on the insulin response during the OGTT and both peripheral and hepatic insulin sensitivity. The faster the 2 h-PG level declines to the FPG level, the more efficient the subject is in disposing of the glucose load (21). Our patients manifested an attenuated oDI_{30} index, suggesting an impairment of glucose metabolism. Masrouri et al (22). have reported that a difference, in normoglycemic subject, between 2-h PG and FPG ≥ 9 mg/dL was associated with a higher risk of prediabetes/type 2 diabetes development. The mechanisms leading to a decrease of oDI_{30} index remain unclear, but low physical activity, reduced muscle mass (23,24) and low-grade of cytokines release (IL-1, IL-6 and TNF-α), due to iron overload (25,26), could be potential contributors to decreased insulin sensitivity. Our study has several limitations. First, iron overload was assessed by SF and did not incorporate the findings of advanced pancreatic MRI imaging methods into the data analysis. However, the utility of pancreatic MRI has not yet been validated for the very early changes of glucose homeostasis after glucose load. Second, during follow-up, patients at referring centers had OGTT performed at irregular intervals, which could affect the precision

Table 3. Evolution of OGTT in 57 β-TM patients with different 30 - min PG percentiles (Groups A, B and C) at last consultation.

Variables	GROUP A = (n: 19)	GROUP B = (n:19)	GROUP C = (n: 19)
NGT and PG	10/19 (52.6%)	6/19 (31.5%)	2/19 (10.5%)
30-min high PG	PG > 50th and < 75th percentile: 1/19 (5.2%)	Persistent high PG: > 50th and < 75th percentile: 3/19 (15.7%)	Persistent high PG > 75th percentile: 2/19 (10.5%)
1-h PG post glucose load ≥ 155 mg/dL	3/19 (15.7%)	2/19 (10.5%)	3/19 (15.7%)
ADA criteria (*):			
IFG	2/19 (10.5%)	1/19 (5.2%)	1/19 (5.2%)
IGT	3/19 (15.7%)	2/19 (10.5%)	5/19 (26.3%)
IFG plus IGT	0 (0%)	5/19 (26.3%)	4/19 (21%)
Th-RDM	0 (0%)	0 (0%)	2/19 (10.5%) (**)

Abbreviations: PG: plasma glucose; ADA: American Diabetes Association criteria; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; Th-RDM: Thalassemia- related diabetes mellitus; (*) At last consultation: Fisher exact test- Group A vs. B*:* P = 0.49; Group A vs. C: P = 0.048; Group B vs. C: P = 0.33; (**): 6 and 10 years after the first consultation.

of data presentation. Third, GD and diabetes were diagnosed based on a single screening OGTT. Fourth, it is important to note that the commonly used surrogate indices of early glucose secretion and sensitivity should be used cautiously especially when comparing patients of mixed genders and ethnic heterogeneity (27). Finally, the study was conducted in a selected group of Italian β-TDT patients referred for consultation or second opinion and thus lacks ethnic heterogeneity. Nevertheless, it has also several strengths including the meticulous selection of β-TDT patients with NGT, the simultaneous four points measurements of PG and insulin during OGTT, the assessments of β-cell secretion and insulin sensitivity indices, and the long-term follow-up of patients.

Conclusions

Based on our current knowledge this is the first long-term follow-up study examining the relationship between increase of isolated 30-min PG levels and glucose homeostasis in β-TDT patients. Young adult β-TDT patients with NGT and isolated 30-min PG equal or above the 75th percentile (≥155 mg/dL) were in a 'danger zone' for developing a deterioration of glucose metabolism. Our results should be validated by further larger, multiethnic and prospective studies to confirm whether high 30-min PG level during OGTT may be considered cost-effective in the assessment of glucose homeostatis in β-TDT patients.

Conflict of Interest: 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.

Authors Contribution: VDS designed the study, analysed data and wrote the first original draft of manuscript. All authors revised critically the manuscript content, edited it for intellectual content and contributed to discussion All authors revised the final version and approved the submitted version.

Declaration on the Use of AI: Not used.

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