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Original Article

Could Plasma Glucose (PG) Increment (PG%) Expand the Clinical Weight of OGTT? Preliminary Findings in 19 TDT Patients (β-TDT) with Normal Glucose Tolerance

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Abstract. ***Background*: Worldwide, glucose dysregulation (GD) and diabetes mellitus are common complications in transfusion-dependent β-thalassemia (β-TDT) patients. Impaired insulin sensitivity and insulin secretion are both involved in the deterioration of glucose tolerance from a normal to a glucose-intolerant state.**
Objective: **The main aim of the present study was to evaluate the plasma glucose (PG) increment (PG %) retrospectively at two h during oral glucose tolerance test (OGTT) over fasting plasma (FPG) concentration as a simple parameter to recognize early β-cell dysfunction in normoglycemic β-TDT patients with NGT and different severities of iron overload (IOL).**
Patients and Methods: **A total of 19 β-TDT young adult patients with normal OGTT were re-evaluated according to the American Diabetes Association (ADA) guidelines. Venous blood samples were collected at baseline and at 30, 60, and 120 minutes to determine PG (mg/dL) and insulin concentrations (μIU/mL). The time required for the PG concentration to return to the fasting level was calculated by computing the percentage increment of 2-h PG with respect to FPG (PG%), using the formula [(2-h PG-FPG)/FPG]x 100. The early phase of insulin secretion (IGI) and sensitivity were assessed by validated surrogate indices calculated from parameters obtained during the four-point OGTT.**
Results: **The mean age of patients was 30.3 ± 5.7 (range: 23.10- 44.3). The mean ± SD, median, and range of PG% increment between 2 h-PG and FPG were 35.5 ± 20.2, 38.7, and 0 - 68.2 mg/dL, respectively. The PG% increment was negatively correlated to the patient's age, FPG, and IGI, and positively correlated with 2-h PG post-glucose load. IGI was negatively correlated with 1-h and 2-h PG after post-glucose load and positively correlated with oral disposition index (oDI).**
***Conclusions*: The PG% increment is a simple, useful screening parameter that can expand the clinical weight of OGTT and can provide valuable metabolic information on β-cell dysfunction.**

Keywords: Oral glucose tolerance test; Plasma glucose increment (PG %); Transfusion-dependent β-thalassemia patients; glucose dysregulation; Indices of insulin secretion/sensitivity; Risk factors.

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Introduction. Worldwide, glucose dysregulation (GD) is common in transfusion-dependent β-thalassemia (β-TDT) patients and has been attributed to an early and progressive decline of β-cell secretion, along with reduced insulin sensitivity in the liver and/or skeletal muscle or both.[1,2] Both defects can be demonstrated long before overt diabetes. They may differ in different stages of glucose tolerance from normal glucose regulation (NGT) to prediabetes (impaired fasting glucose: IFG and/or impaired glucose tolerance: IGT) and overt diabetes (thalassemia-related diabetes mellitus: Th-RDM). The prevalence of GD and Th-RDM increases with age and the magnitude of iron overload, and affects a significant proportion of patients.[1-3] Apart from iron overload (IOL), other factors responsible for organ damage include chronic hypoxia due to anemia, patients' genotype, history of splenectomy, obesity, hepatic steatosis, chronic liver disease, particularly chronic active hepatitis C infection, and zinc deficiency.[4-7] The prevalence of Th-RDM in 3,382 β-TDT patients, followed by 18 centers, reported by the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) was 12.2 ± 9.7% (median: 13.2 %).[8]

Although determining the optimal method for early identification of β-TDT patients at risk for deteriorating glucose homeostasis remains challenging, current guidelines recommend annual glucose tolerance test screening (OGTT: 1.75 g glucose/kg body weight, maximum: 75 g) starting from the age of 10 years. Plasma glucose (PG) is measured at least at baseline and two hours after a dextrose anhydrous load.[2,3] Despite its effectiveness, OGTT has limitations; it is time-consuming, laboratory-dependent, laborious, and poorly tolerated by some patients.[8] Notably, a high percentage of suboptimal or poor adherence (mean rate: 41.3%) to annual OGTT screening was reported by the ICET-A Network.[8] Moreover, in low- and middle-income countries, screening for GD in β-TDT patients poses particular challenges, in particular, where healthcare centers are overcrowded, understaffed, and insufficiently resourced.

Over the years, many investigators have tried to find alternative screening methods for the early diagnosis of GD with limited success.[9-12] Continuous glucose monitoring systems (CGMS) are a reliable and valid device for evaluating glucose metabolism.[13] However, further studies with a larger sample size are needed before their validation. Thus, new biomarkers for predicting future GD and diabetes, either alone or in combination with PG post-glucose load measurement, have been tested.

To improve the consistency and quality of information derived from OGTT in the general population, there has been a renewed interest in the increment of 2-h PG post-glucose load with respect to fasting plasma glucose (FPG) concentration.[14] It has been reported that NGT subjects, whose post-load PG concentration returned quickly to baseline, had a lower risk for developing type 2 diabetes after a follow-up of 8 years when compared to subjects with a slower PG fall to baseline.[15] Therefore, improving the reliability of testing would improve its clinical predictive value and would provide more meaningful data.

The main aim of this study was to analyze the clinical utility of PG at two h during OGTT over FPG concentration and to correlate its increment (PG%) to surrogate indices of β-cell secretion and sensitivity in β-TDT patients with normal glucose tolerance (NGT) and a different severity of IOL, assessed by serum ferritin (SF).

Subjects and Methods

Study population, inclusion, and exclusion criteria. The anonymized data of β-TDT patients followed by the same endocrinologist (VDS) from October 2010 to October 2024 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 iron chelation therapy; (b) chronological age > 18 years; (c) availability of four points 2-h OGTT, and (d) β-TDT patients with NGT as defined by American Diabetes Association (ADA) criteria: FPG < 100 mg/dL and 120-min PG during OGTT < 140 mg/dL.[16] The main exclusion criteria included: (a) non-transfusion-dependent thalassemia (NTDT); (b) bone marrow transplanted patients;(c) β-TDT patients with body mass index (BMI) above 30 kg/m^2; (d) pregnancy; and (e) patients taking medications affecting glucose metabolism.

Data collection and anthropometric measurements. The following clinical data were collected at the first consultation: demographic characteristics, age at the first consultation, weight, height, medical history, and overall recommended treatments, type of iron chelation therapy (ICT), family history of diabetes, history of smoking or alcohol consumption, and previous history of splenectomy.

Height, weight, and body mass index (BMI) were measured according to standardised procedures. 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).[17]

Study procedures and assays. 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 using the glucose oxidase method. The time required for the PG concentration to return to the fasting level was made by computing the percentage increment of 2-h PG in respect to FPG (PG%), using the following formula: [(2-h PG-FPG)/FPG]x 100.[18] PG is expressed in mg/dL and insulin concentration in μIU/mL.

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). The insulin values were expressed in μU/mL.

The level of serum alanine aminotransferase (ALT) was determined by an automated analyzer (normal range 0–40 mU/L), 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.[19]

Data processing and statistical analysis. 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 /Δ 0-30 glucose min). IGI_{30} is considered an acceptable index of β-cell function in β-TDT patients.[20] An IGI_{30} value < 0.4 was considered indicative of a defective acute insulin response.[21]

For the determination of insulin sensitivity/resistance, the following indices were used: Matsuda Whole Body Insulin Sensitivity Index (MI_{0-120}) and oral disposition index (oDI), as the product of IGI_{30} and MI_{0-120}. Matsuda index is a marker of whole-body insulin sensitivity, and the oDI index reflects the relationship between β-cell function (early-phase insulin secretion) and peripheral insulin sensitivity (hepatic and peripheral tissues).[20,22] 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.

The updated index of the homeostatic model assessment (HOMA-2 IR) was used by the HOMA-2 calculator software released by the Radcliffe Department of Oxford.[23] The model establishes an equilibrium point for PG, insulin, C-peptide, and proinsulin in the fasting state to replicate physiological reality in reference individuals. For HOMA 2% B and HOMA 2% S, a normal value of 100% was assigned. A lower HOMA-2 % B is associated with loss of pancreatic response and a lower HOMA-2% % S is associated with insulin resistance.[23]

Statistical analysis. Data are presented as mean ± SD, except where otherwise indicated. The normality of the distribution of continuous variables was verified using the Kolmogorov-Smirnov test. For comparison of different variables, Student t-test, Wilcoxon's signed rank test, and Mann-Whitney test were used appropriately. Pearson linear correlation for normally distributed variables, and Spearman for quantitative variables, abnormally distributed, were used. For the statistical analysis, a software program was used and validated, according to Alder and Roesser.[24] A two-sided 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.[25,26] Moreover, in our retrospective study, no identifiable patients' information was collected, and anonymized data sets were analyzed.

Results

Patients' characteristics at baseline. A total of 19 β-TDT patients [12 (63.1%) females] met the inclusion criteria and were enrolled in the study. The mean age of patients was 30.3 ± 5.7 years (range: 23.10- 44.3).

All patients were regularly transfused, every 2-3 weeks, with a mean pre-transfusional hemoglobin level of 9.1 ± 0.3 g/dL. Six patients (31.5 %) had undergone splenectomy.

At first consultation, BMI was < 25 kg/m^2 in all but four, who were slightly overweight (2 males and 2 females; BMI: 26.8 ± 0.88 Kg/m²). The reported age at start of iron chelation therapy (ICT) was between 2 and 3 years. At the time of study, all patients were on oral mono- or combined (5/19; 26.3%) iron chelation therapy (**Table 1**). In 4 patients, the IOL was severe, and in 3, it was moderate. In the remaining 12 patients, it was mild (SF:573.6 ± 205.8 μg/L) (**Figure 1).**

The commonest associated endocrinopathy was

Table 1. Summary of clinical and laboratory characteristics in 19 transfusion-dependent β-thalassemia patients (β-TDT) with fasting plasma glucose (FPG) <100 mg/dL and normal glucose tolerance, according to the ADA criteria, at the time of OGTT.

Variables	Results
Mean age (yrs)	30.3 ± 5.7
Gender distribution	Males:7; Females:12
Positive family history for type 1 or type 2 diabetes	4/19 (21 %)
History of splenectomy	6 /19 (31.5 %)
Body Mass Index (BMI: Kg/m²)	22.6 ±2.6
Pre-transfusional hemoglobin level (g/dL)	9.1 ± 0.3
Serum ferritin (µg/L) at OGTT	1,054.3 ± 720.6 (Range: 271-2,324)
Alanine aminotransferase (ALT: IU/L)	31.7 ± 11.2 (Range:17-57)
ALT > 40 IU/L	3/19 (15.7%)
Iron chelation therapy at the time of OGTT	- DFX monotherapy: 13/19 (68.4%)
	- DFP monotherapy: 1/19 (5.2%)
	- Combined therapy (DFO + DFP):5/19 (26.3%)

Legend: **BMI** = Body mass index; **DFP:** deferiprone; **DFX:** deferasirox.

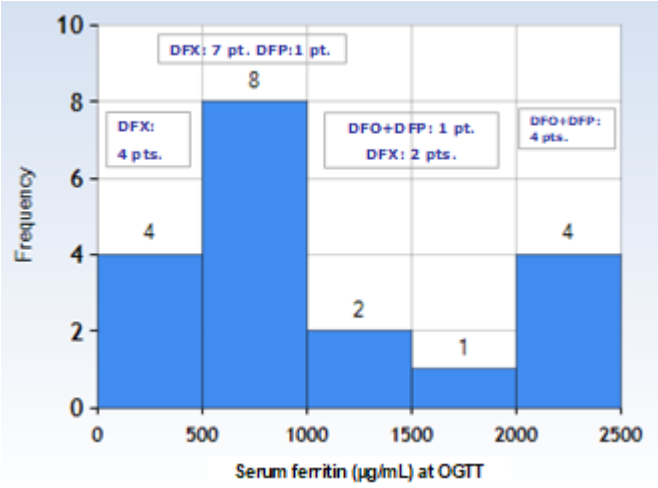

Figure 1. Distribution of serum ferritin levels in 19 β-TDT patients with normal glucose tolerance test.

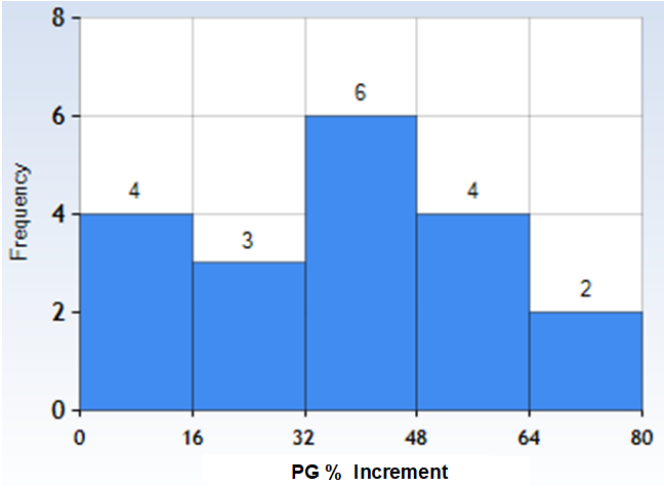

Figure 2. Distribution of PG% increment in 19 β-TDT patients with normal glucose tolerance.

primary or secondary hypogonadism [3/7 males (42.8%) and 9/12 females (75%)]. All except three female patients were on hormone replacement therapy with sex steroids. Moreover, 2/19 (10.5%) patients had short stature (≤ 3rd centile), while one female (8.3%) patient was on thyroxine replacement therapy for mild primary hypothyroidism.

Plasma glucose and surrogate indices of insulin secretion and sensitivity/resistance during OGTT at first consultation. The mean ± SD, median, and range of PG% increment between 2 h-PG and FPG in the 19 β-TDT patients were 35.5 ± 20.2, 38.7, and 0- 68.2 mg/dL, respectively **(Figure 2).** PG% increment in 7 β-TDT male patients was 29.9 ± 17.7 mg/dL, and in 12 β-TDT female patients was 38.7 ± 21.6 mg/dL (P: 0.37).

In 5/19 patients (26.3%), the PG peak post-glucose load was observed at 60 minutes. A lowish IGI was detected in 8/9 patients (88.8%) with PG% increment > 32 mg/dL.

Correlations. The PG% increment was negatively correlated to the patient's age, FPG, and IGI, and positively correlated with 2-h PG post-glucose load. IGI was negatively correlated with 1-h and 2-h PG after post-glucose load and positively correlated with oDI_{30}. A detailed analysis of the correlation between different variables is reported in **Table 2**.

Discussion. Because of increasing longevity of patients with β-TDT, the prevalence of GD and thalassemia related diabetes mellitus (Th-RDM) has increased. Early diagnosis of GD is essential for the timely identification of high-risk TDT patients who may benefit from intensive iron chelation therapy, lifestyle modification and, in selected cases, pharmacotherapy.

The OGTT is used to classify subjects as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetes. During the OGTT, insulin action and secretion modulate the rate of increase and decrease in PG and the time required for PG to peak and to return to the fasting levels.[27] The first phase of insulin secretion and hepatic insulin resistance indices are important determinants of the initial rise of PG following glucose ingestion. The rate of decline in plasma glucose concentration back towards the fasting PG levels seems

Table 2. Correlations between PG% and insulinogenic index (IGI) vs. clinical, laboratory characteristics, and surrogate indices of insulin secretion and sensitivity/resistance in 19 β-TDT subjects.

Variables	β-TDT subjects PG% (no.19)	β-TDT subjects IGI_{30} (no.19)
Age	**r: - 0.5064; P: 0.027**	r: 0.2259; P: 0.35
Body Mass Index	r: - 0.1957; P: 0.42	r: 0.0864; P: 0.72
Alanine aminotransferase	r: -0.2151; P: 0.37	r: - 0.0456; P: 0.85
Serum ferritin	r: 0.2396; P: 0.32	r: 0.1254; P: 0.60
Fasting PG	**r: - 0.6397; P: 0.0032**	r: 0.1783; P: 0.46
PG 30 minutes during OGTT	r: 0.1827; P: 0.45	r: - 0.3521; P: 0.13
PG 1-h during OGTT	r: 0.3291; P: 0.16	**r: - 0.4717; P: 0.041**
PG 2-h during OGTT	**r: 0.9294; P: <0.00001**	**r: - 0.5943; P: 0.0073**
HOMA 2-IR	r: - 0.256; P: 0.29	r: 0.2627; P: 0.27
Insulinogenic Index$_{30}$ (IGI_{30})	**r: - 0.5396; P: 0.017**	=
MATSUDA Index (MI_{0-120})	r: 0.4514; P: 0.052	r: - 0.4212; P: 0.073
Oral disposition index (oDI)	r: - 0.2681; P: 0.26	**r: 0.8158; P: 0.000021**
HOMA- 2 % B	r: - 0.0213; P: 0.93	r: 0.2015; P: 0.40
HOMA- 2 % S	r: 0.3227; P: 0.17	r: - 0.2929; P: 0.22

to depend primarily on late-phase insulin secretion and muscle insulin sensitivity. The Mexican-American San Antonio Heart Study found that patients with 2-h PG levels higher than FPG had a 2.33-fold higher risk of developing type 2 diabetes over 7-8 years of follow-up.[15]

In the present study, we tried to extract metabolic information from the PG% during OGTT. Our results confirm, for the first time in patients with β-TDT, that PG% can expand the clinical weight of OGTT screening by simply implementing a more powerful and informative calculation that indirectly discloses the measure of insulin secretion and insulin sensitivity.

The following preliminary novel results emerged from our retrospective observational study:

(a) First, PG% was inversely correlated with the Insulinogenic Index (IGI_{30}). IGI_{30} is a measure of the early phase of insulin secretion in response to glucose load during the first 30 minutes of OGTT. Therefore, a higher PG% (greater rise in 2-h PG relative to FPG) is associated with lower early-phase insulin secretion (lower IGI). This suggests that β-TDT patients with a larger glucose increment after glucose load have an impaired early insulin response, a hallmark of β-cell dysfunction.

(b) Second, PG% was directly correlated with the absolute values of 2-h PG during the OGTT. The correlation is consistent with the hypothesis that impaired early insulin secretion (low IGI_{30}) leads to poorer glucose control after a glucose load due to reduced insulin sensitivity not compensated by a sufficient increase in insulin secretion. Therefore, PG% could reflect the fine-tuning between insulin secretion and sensitivity.[28]

(c) Third, a lower IGI index was associated with higher glucose levels at both 1-h and 2-h during the OGTT, further supporting the role of β-cell dysfunction in glucose dysregulation. In addition, the positive correlation of IGI_{30} with the oral Disposition Index (oDI_{0-120}), which is a measure of β-cell function adjusted for insulin sensitivity, suggests that patients with better early insulin response have better overall glucose regulation and insulin sensitivity. Substantially, subjects whose PG values fall faster to FPG levels during OGTT have greater insulin sensitivity and better β-cell function compared to NGT subjects whose PG values fall more slowly. Therefore, the presence of both a reduction in insulin secretion and insulin sensitivity suggests a peculiar aspect of β-TDT-related glycemic phenotype.

Some limitations of this study warrant consideration. First, the small single study population of β-TDT and the lack of longitudinal data are the major limitations and, thus, clearly need replication in a larger cohort of patients with long-term follow-up. Second, the study setting was a single center, so generalizability should be considered with caution. Third, the β-cell function measurements were generated by using mathematical models derived from OGTT instead of the gold-standard technique. Overall, they are unable to reconstruct the exact architecture of the severity of the defects in β-cell function and insulin sensitivity herein reported. However, measuring IGI_{30} and oDI_{0-120} has several advantages; it involves less complex protocols, requires less cost, and utilizes a physiological route of glucose administration. Moreover, they have been validated against the euglycemic clamp.[29] Finally, prospective studies are required to corroborate our findings further, evaluate their implications for specific outcomes, and assess the benefits of therapeutic interventions targeting early glucose abnormalities. This would allow early

intervention aimed at preserving pancreatic β-cells and helping to prevent or delay the development of GD and Th-RDM.

Conclusions. PG% is a simple, useful screening parameter that can expand the clinical weight of OGTT and provide valuable metabolic information on β-cell dysfunctions in β-TDT patients at potential risk of neurometabolic deterioration. Moreover, it may provide a more personalized OGTT screening interval approach to β-TDT patients with NGT and PG% near or below the FPG value (low PG%).

Author contributions. VDS contributed to the literature review, database design, statistical analysis, interpretation of the data, and drafting of the manuscript. ATS, SD, PT, and CK contributed to the critical revision of important intellectual content and editing and revision of the manuscript. VDS is the guarantor of this work and takes responsibility for the integrity and accuracy of the data analysis. All of the authors approved the final manuscript prior to submission.

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