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Characterisation of transfusion-dependent prediabetes using continuous glucose monitoring: The Haemoglycare study

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ABSTRACT

Aims: Continuous Glucose Monitoring (CGM) may help detect early dysglycemia in Transfusion-Dependent Thalassemia (TDT) patients, though previous reports suggest it may overestimate prediabetes prevalence. This study analyzed glucose-related metrics in TDT patients with negative diabetes screening tests, compared with healthy controls. A secondary objective was to assess the association between TAR140 > 6 % and clinical/laboratory characteristics of patients.

Methods: Patients resulted negative to the screening tests for glucose disorders were compared to healthy controls using CGM system for 7 days.

Results: This study involved 39 participants (19 patients, 20 controls). HbA1c was falsely elevated in patients, despite normal mean glucose and GMI. Standard deviations and coefficients of variation were higher in patients than controls.

No healthy control but 7/19 (37 %) TDT patients presented the interval TAR140 > 6 %. Significant differences were observed between "really euglycaemic" TDT patients (TAR140 ≤ 6 %) and "hyperglycemic" ones (TAR140 > 6 %) in terms of GMI, mean glucose and TAR140%. Comparing the glucose metrics of TDT euglycaemic patients (TAR140 ≤ 6 %) and healthy controls, no significant difference was reported. No differences in iron overload indexes were found between the hyperglycemia and euglycemia groups.

Conclusions: CGM reliably detects prediabetes in 37 % of TDT patients. TAR140 > 6 % may serve as a diagnostic cutoff.

1. Introduction

In patients with β-thalassemia, iron overload due to a regimen of chronic transfusions is responsible for significant multi-organ toxicity affecting the heart, liver, bone, and endocrine glands, with considerable morbidity and mortality [1,2].

Diabetes mellitus (DM) is a complication of Transfusion-Dependent Thalassemia (TDT) with a variable incidence of 3 %–10.5 %. Meanwhile, the incidence of Impaired Glucose Tolerance (IGT) among patients with TDT (prediabetes) ranges from 7 % to 24 % [3–5]. Although DM's aetiology is connected to iron overload in different tissues that control mechanisms of carbohydrate homeostasis, including the pancreas and liver, controversy about its aetiology persists. Both insulin deficiency and insulin resistance have been reported in patients with β-thalassemia [2]. Other factors, including individual sensitivity to damage from iron accumulation, zinc deficiency, and collagen accumulation (i.e. secondary to increased activity of procollagen-proline dioxygenase) impact the risk of developing DM [3]. Because IGT and DM are conditions observed even in patients who are transfused well and regularly chelated, the parameters currently used to diagnose iron

Abbreviations: CGM, continuous glucose monitoring; GMI, glucose management indicator; HbF, fetal hemoglobin; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; OGTT, oral glucose tolerance test; TAR140%, time spent with blood glucose greater than or equal to 140 mg/dl; TBR, time below range; TDT, transfusion-dependent thalassemia; TIR, time in range.

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overload (e.g. serum ferritin, liver iron concentration, and cardiac iron concentration) cannot detect early and preclinical damage of the pancreas or other endocrine glands [4]. Indeed, because endocrine organs have a superior reserve capacity, the clinical manifestations concerning them may appear years after silent iron accumulation [5].

DM's onset is generally gradual and insidious. Although patients with mild disorders such as IGT and impaired fasting glucose (IFG) may be asymptomatic, those conditions pose additional risks to cardiac function [6].

Diagnosing prediabetes and DM early is therefore important. Unfortunately, the normal screening tests for glucose metabolism disorders such as fasting blood glucose and glycated hemoglobin (HbA1c) fail in the early diagnosis of such patients. HbA1c, in particular, is not a reliable indicator for patients who have received transfusions because the results can be falsely increased or decreased depending on the proximity to the transfusion, the reduced lifespan of the erythrocytes and the test used [7,8]. The oral glucose tolerance test (OGTT) remains the only validated screening test [1,2]. However, its procedure is complex and time-consuming for patients and healthcare professionals and is not a feasible method for screening all patients worldwide [1].

Continuous Glucose Monitoring (CGM) systems, by contrast, are a new technology that measure the concentration of glucose in the interstitial fluid using a sensor placed under the skin. Most CGM systems used today show levels of accuracy that, among patients with diabetes, allow therapeutic modifications without confirmation using capillary glycaemia [9]. The use of Continuous Glucose Monitoring (CGM) in diagnosing dysglycemia in the general population is currently an area of active research. Some studies suggest that CGM can help detect early glucose metabolism alterations, the quality and quantity of evidence supporting its use for formal diagnosis remain limited. Current guidelines still rely on fasting glucose and OGTT for diagnosing prediabetes and diabetes, though CGM-based metrics such as Time in Range (TIR) and glucose variability are gaining recognition for their predictive value in assessing metabolic risk [10].

To date, the use of CGM systems among patients with thalassaemia has shown an incidence of prediabetes as high as 70 % in the second or third decade of life [11]. However, research has also revealed only occasional increases of glycaemia above the threshold values for the diagnosis of DM [12,13]. Among patients affected by DM, the analysis of CGM should ignore the single peak values recorded but should consider how long glycaemia remains above normal values (i.e. glucose-related metrics) [14], because glycaemia can occasionally but briefly exceed normal ranges even among healthy individuals [15]. For that reason, determining the correct use and interpretation of the results of CGM is important, especially for patients with TDT at a high risk of glucose metabolism disorders.

Against that background, the primary objective of our study was to analyse glucose-related metrics in an adult population of patients with thalassaemia who received negative results on traditional screening tests for DM compared with healthy controls. The secondary objective, meanwhile, was to compare time spent with blood glucose greater than or equal to 140 mg/dl (TAR140%) $>$ 6 % with the clinical and anamnestic characteristics of participating patients.

2. Methods

2.1. Sampling and recruitment

The present study was supported by a grant from the Regione Campania (Italy).

Patients for the sample were randomly selected from among adult patients suffering from TDT followed at the Pediatric Hematology and Oncology Unit of the University of Campania "L. Vanvitelli". Following standardised protocols, all patients were on a chronic transfusion regimen to maintain a pre-transfusional haemoglobin of approximately 9.5 g/dL (i.e. 2 units of packed red blood cells every 2–3 weeks) and on standard chelation therapy. All patients also tested negative for screening tests for DM (i.e. fasting glycaemia and OGTT scores).

Healthy controls were also recruited among medical residents and doctors who were at least 18 years old, had no chronic illness or medications that might affect glucose metabolism, had normal OGTT scores, had no positive islet autoantibodies, and had a body mass index (BMI) $<$ 25.0 kg/m^2, fasting glycaemia $<$ 100 mg/dl, HbA1c $<$ 5.7 % (39 mmol/mol), and Homeostasis Model Assessment index (HOMA-IR) $<$ 2.5. Female participants pregnant at the time of enrolment were ineligible.

All procedures performed in our study were approved by the Institutional Research Committee of the University of Campania "Luigi Vanvitelli" (n°916; 28 Jul 2016). All participants provided their informed written consent to participate in the study.

2.2. Demographic and clinical characteristic

A case report form was specifically designed and completed by clinicians (i.e. diabetologists or haematologists) to record the participants' demographic and clinical data, namely age, sex, height, weight, duration of illness, and other medical conditions (i.e. family history of diabetes, endocrine disorders, and cigarette smoking habit). Last, HOMA-IR was calculated as a parameter for evaluating insulin resistance.

2.3. Study design

According to the American Diabetes Association (ADA) guidelines [13], 2 h-glucose value $\geq$ 140 mg/dl (7.8 mmol/L) and $<$ 199 mg/dl (11 mmol/l) during OGTT is diagnostic for prediabetes. Moreover, 2 h glucose value $\geq$ 200 mg/dl (11.1 mmol/L) during OGTT or a random glucose value (at any time of the day without regard to time since the previous meal) $\geq$ 200 mg/dl(11.1 mmol/L) are both diagnostic for diabetes mellitus. All patients and controls had to test negative on the OGTT and fasting glucose test. Specifically, their glucose levels were assessed exclusively at fasting and at 2 h both within normal ranges.

All participants (subjects and controls) meeting the inclusion and exclusion criteria received a *Medtronic Guardian™ 4 sensor* for seven days. At the end of the monitoring, the glucose sensor data was analyzed in *Carelink™ System software.*

Glucose metrics considered for the analysis were: Glucose Management Indicator (GMI), mean glucose (m g/dl), glycemic variability as Standard Deviation (SD), Coefficient of Variation (CV), time spent with glycemia greater than or equal to 200 mg /dl (TAR200%, median), time spent with blood glucose greater than or equal to 140 mg/dl (TAR140%, median), time spent with blood glucose less than 70 mg/dl (TBR $<$ 70 %, median).

The endpoints of our study were to record the number of participants who exceeded or equalled the glycaemic value of 140 mg/dl or 200 mg/dl so as to record how long participants remained with glucose values above those cutoffs (i.e. TAR140% and TAR200%, respectively).

Last, we used the value $\leq$ 6 % of TAR140% as an index of normality, as done on healthy controls in past research [15].

2.4. Statistical analysis

Because no previous studies have involved analysing glucose-related metrics in patients with thalassaemia, the sample size for our study was calculated during a pilot study. Therein, the first eight patients were compared with 15 healthy controls, and a power analysis (i.e. independent samples *t* test) for the parameter TAR140%, a minimum sample of 24 participants (i.e. 12 patients and 12 controls) was determined.

To date, no standardised analytical method allows using glycaemic sensors for diagnosing DM, meaning that clear references of normality for glucose-related metrics are unavailable. To make the results of our study as accurate as possible, we compared the glycaemic data of patients and healthy controls. We selected healthy controls with the same clinical and demographic characteristics as the cases to minimize

potential confounding factors and ensure that any observed differences in glucose metrics could be attributed to the presence of Transfusion-Dependent Thalassemia (TDT) rather than differences in age, sex, or other baseline characteristics.

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 25.0, with a two-sided significance level of 0.05. To assess signi��cant differences between patients with thalassemia and healthy controls, we used the chi-square test for qualitative variables and the *t* test for independent samples or the non-parametric Mann–Whitney *U* test for quantitative variables depending on the results of the Kolmogorov–Smirnov normality test. In the case of normal distribution, we verified the hypothesis of homoscedasticity using Levene's test before performing the *t* test for independent samples. The *t* test for unequal variances was used if the hypothesis was not confirmed. Last, to compare TAR140 > 6 % and TAR140 ≤ 6 %, we used the non-parametric test directly due to the small sample size, and, again, the *t* test for unequal variances was used if the hypothesis was not confirmed.

3. Results

This study involved 39 participants, 19 thalassemic patients and 20 healthy volunteers. The demographic characteristics of the study population are reported in Table 1.

3.1. Analysis of glucose-related metrics: Overall comparison of patients with thalassaemia and healthy controls

3.1.1. HbA1c, mean glucose and GMI

We observed a statistically significant difference between the mean HbA1c of the two groups (i.e. patients and controls). Mean HbA1c was higher among patients with TDT than controls (6.7 vs. 5.2 %, 49 vs. 33 mmol/mol; $p < 0.001$). That finding contrasts the absence of significant differences in mean glucose and GMI (i.e.GMI is estimating HbA1c% from CGM) between the groups (104 ± 11.5 vs. 101 ± 6 mg/dl, p = n.s.; 5.34 ± 0.4 vs. 5.29 % ± 0.1, p = n.s.). All data are reported in Table 2.

3.1.2. Glycaemic variability according to standard deviations (SD) and coefficients of variation (CV)

The difference in the mean *SD* of glucose values derived from the CGM was significant in both groups (17.93 ± 4.22 vs. 14.55 ± 2.2, $p = 0.003$), as was the difference in CV (17.22 ± 3.6 vs. 14.42 ± 1.94, $p = 0.004$). All data appear in Table 2.

Fig. 1 graphically illustrates the difference in glycaemic variability between healthy controls and patients with thalassaemia, including increments of glucose levels (i.e. glycaemic peaks) in both groups. Glycaemia generally increased more among patients than controls, and 2 h after glucose levels began to increase, the levels normalised in both groups.

3.1.3Numbers of participants with high glucose values (≥ 140 mg/dl and ≥ 200 mg/dl).

Among the patients, one with thalassaemia presented glucose values ≥200 mg/dl, whereas none of the controls ever exceeded that value. Considering the reference value of 140 mg/dl, 16 of 19 patients and 17 of 20 controls equalled or exceeded that glucose threshold on at least one occasion throughout CGM (84 % vs. 85 %). Therefore, no statistically significant difference in the number of participants with high glucose values emerged in either group. All data are reported in Table 2.

3.1.3. Time spent in hyperglycaemia or in hypoglycaemia: TAR ≥ 200 %, TAR ≥ 140 %, TBR < 70 %

No statistical difference emerged in median TAR ≥ 200 %, median TAR ≥ 140 %, or median TBR < 70 % in the two groups overall. Considering TAR ≥ 140 % greater than 2 %, more patients with thalassaemia exceeded that value than controls (52 % vs. 20 %; $p = 0.034$). Even more significant was the difference in the number of patients with TDT who spent more than 6 % of the time with glucose levels ≥ 140 mg/dl (37 % of cases vs. 0 % of controls; $p = 0.003$). None of the controls spent more than 6 % of the time with glucose values ≥ 140 mg/dl. All data are reported in Table 2.

3.1.4. Time spent in hyperglycaemia (TAR140 > 6 %): Comparison between "euglycaemic" and "hyperglicaemic" patients with TDT

A comparison of patients with TDT with a TAR140 > 6 % (i.e. hyperglycaemia) and patients with a TAR140 ≤ 6 % (i.e. euglycaemia) revealed a significant difference in the GMI% (5.70 vs. 5.1; $p < 0.001$) of the mean glucose (116 vs. 96.5; $p < 0.001$) and TAR140% (10 vs. 1.5; $p < 0.001$).

Table 1
Demographic and clinical characteristics of participating patients with thalassemia ($n = 19$) and healthy controls ($n = 20$).

	Patient with thalassemia (cases) n = 19	*Healthy volunteers (controls) n = 20*	p
Age,y (mean ± SD)	39.53 ± 8.35	35.55 ± 6.62	n s
Male, n (%)	4 (21 %)	5 (25 %)	n s
BMI,kg/m2 (mean ± SD)	22.59 ± 3,3	22.75 ± 2.2	n s
HOMA-IR (mean ± SD)	1.27 ± 0.74	1.07 ± 0.69	n s
Family history of diabetes, N (%)	14 (73.7 %)	12(60 %)	n s
Cigarette smoking habit, N(%)	4 (21 %)	5 (25 %)	n s

BMI Body mass index.
HOMA-IR Homeostatic model assessment for insulin resistance.

Table 2
Comparison of glycated hemoglobin (HbA1c) and continuous glucose monitoring (CGM) glucose metrics between patients and controls *p value < 0.05.

	Patient with thalassemia (cases) n = 19	*Healthy volunteers (controls) n = 20*	p
GMI,% (mean ± SD)	5.34 ± 0.4	5.29 ± 0.1	n s
HbA1c mmol/mol (mean ± SD) % (mean ± SD)	49 ± 9.81 6.7 ± 0.9	33 ± 2.18 5.2 ± 0.2	<0.001
Mean glucose, mg/dl (mean ± SD)	104 ± 11.5	101 ± 6	n s
SD,mg/dl (mean ± SD)	17.93 ± 4.22	14.55 ± 2.2	0.003*
CV,% (mean ± SD)	17.22 ± 3.6	14.42 ± 1.94	0.004*
Number of participants with Glucose values ≥ 200 mg/dl	1/19 (5 %)	0/20 (0 %)	n s
Number of participants with Glucose values ≥ 140 mg/dl	16/19 (84 %)	17/20 (85 %)	n s
TAR ≥ 200,% (median; IQR)	0 (0–0)	0 (0–0)	n s
TAR ≥ 140,% (median; IQR)	3 (1–9)	1.5 (1–2)	n s
TBR < 70,% (median; IQR)	1 (0–3)	1 (0–1)	n s
Number of participants with. TAR ≥ 140 2 %	10/19 (52 %)	4/20 (20 %)	0.034
Number of participants with. TAR ≥ 140 > 6 %	7/19 (37 %)	0/20 (0 %)	0.003

GMI (Glucose Management Indicator- reporting period 7 days).
SD (Standard Deviation-reporting period 7 days).
CV (Coefficient of Variation-reporting period 7 days).
TAR ≥ 200 % (Time above Range ≥ 200 mg/dl; >11.1 mmol/L) reporting period 7 days.
TAR ≥ 140 %(Time above Range ≥ 140 mg/dl; >7.78 mmol/L) reporting period 7 days.
TBR < 70 % (Time below Range < 70 mg/dl; <3.89 mmol/L) reporting period 7 days.

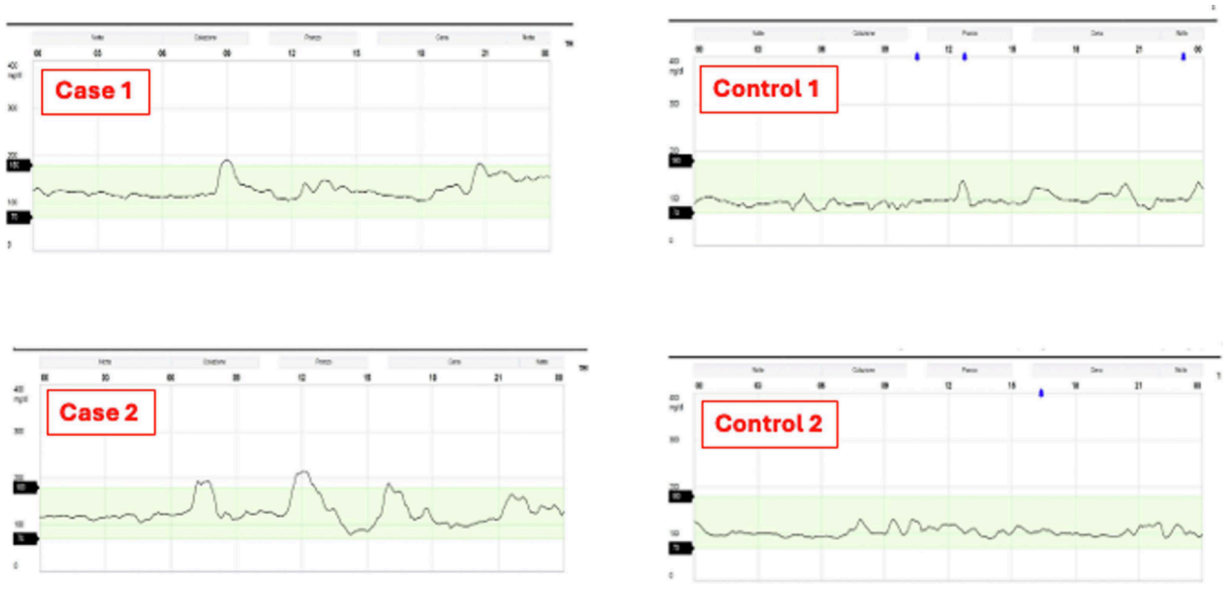


Fig. 1. Glycaemic variability and glycaemic peaks in TDT patients and healthy controls: daily glucose profile graph by continuous glucose monitoring.

No differences surfaced between the groups with hyperglycaemia and euglycaemia in terms of age, BMI, HOMA-IR, ferritin, transferrin saturation index, glycosylated haemoglobin, thyroid-stimulating hormone, or numerous other associated endocrine diseases, liver iron concentration, and cardiac T2* values shown by magnetic resonance imaging.

Last, when patients with euglycaemia ($n = 12$) were compared with healthy controls ($n = 20$), no differences in GMI, mean glucose, CV, TAR200%, TAR140%, TBR70%, age, BMI, or HOMA-IR were found. All data are reported in Table 3.

4. Discussion

Recent recommendations confirm the need for screening glucose metabolism disorders in all patients with haemoglobinopathies, especially transfusion-dependent patients, starting from 10 years of age [1]. The aim of such screening is to detect abnormal glucose homeostasis (i.e., prediabetes) that could lead to type 2 diabetes. Prediabetes is characterized by impaired fasting glucose, impaired glucose tolerance, and/or elevated HbA1c [13]. However, traditional screening methods for thalassemia patients remain debated due to HbA1c testing limitations and the restricted availability of validated alternatives such as fructosamine in TDT [1]. For these reasons, OGTT remains the gold standard for diagnosing DM in haemoglobinopathies. However, the OGTT is time-consuming, posing challenges in specialized care settings due to patient reluctance and heavy clinical workloads. Even for high-risk patients, compliance with OGTT screening is low [16]. Thus, developing an easy-to-perform and acceptable screening method that minimizes clinical burden is critical for identifying and managing glucose disorders in this high-risk group.

CGM may play a role as an alternative. CGM is a straightforward, cost-effective method to study glycemia in real-life settings, capturing glucose responses over multiple days instead of focusing solely on the 2-hour window following a glucose load. While CGM is not universally validated for diagnosing DM or prediabetes, it has been studied as an alternative to OGTT in various high-risk groups: obese patients [17,18], cystic fibrosis patients [19,20], preclinical type 1 DM patients [21–23], pregnant women [24,25], and kidney transplant recipients [26]. For thalassemia patients, CGM shows promise for early detection of glucose metabolism abnormalities.

In our study, we aimed to expand on available data and characterize glucose-related changes in TDT patients.

We included only patients with TDT who tested negative on fasting glucose and OGTT screening. Mean HbA1c levels were significantly higher in TDT patients compared to healthy controls, despite no significant differences in mean glucose levels or CGM-derived GMI between the groups. Since HbA1c can be calculated from mean glucose [27], a normal CGM glucose average conflicts with elevated HbA1c levels. These discrepancies, likely caused by disease-related factors such as elevated fetal hemoglobin, confirm that HbA1c is unreliable for diagnosing DM in TDT patients [1]. Our findings are consistent with Bhatti et al., who reported elevated HbA1c levels in thalassemia patients compared to controls and suggested using CGM for diabetes and prediabetes diagnosis [28]. Recent studies have questioned the reliability of fructosamine as a marker for glucose homeostasis in pediatric patients with beta-thalassemia. Gomber et al. [29] found no significant difference in fructosamine levels between thalassemic patients and healthy controls, nor between those with normal and abnormal glucose tolerance, suggesting that fructosamine may not accurately reflect glucose metabolism in this population. Additionally, the Guidelines for the Management of Transfusion-Dependent Thalassaemia (4th edition, 2021) do not endorse the use of fructosamine for monitoring glucose homeostasis in thalassemic patients, indicating a lack of consensus on its clinical utility in this context. For this reason, we did not measure fructosamine in our study.

Although mean glucose levels were similar between groups, glucose variability metrics (e.g., SD and CV) were significantly higher in TDT patients. This aligns with findings from other studies where CV increases from normoglycemic states to prediabetes [30,31]. Glucose variability is linked to diabetic vascular complications [32,33], highlighting its clinical relevance. Even with normal CGM-estimated HbA1c (GMI), high glycemic variability in TDT patients could signal increased diabetes-related risks.

Our study identified one TDT patient (5 %) with glucose values $\geq$ 200 mg/dl (DM range) and 16 patients (84 %) with glucose values $\geq$ 140 mg/dl (prediabetes range). These results align with Soliman et al., who observed glycemic abnormalities in 75 % of TDT patients using CGM [11]. Soliman also noted that OGTT detected abnormalities in only 31.25 % of cases, suggesting CGM may overestimate glucose dysregulation. Similarly, in our study, 85 % of healthy controls showed at least one glucose value $\geq$ 140 mg/dl during CGM. Such isolated peaks do not necessarily indicate a glucose metabolism disorder, underscoring the importance of analyzing time spent above thresholds.

Healthy controls spent a median of only 1.5 % of time with glucose

Table 3
Comparison of glucose metrics, medical and demographic data of "hyperglicemic" (TAR140 > 6 %) thalassemic patients (n = 7) and "euglycemic" (TAR140 ≤ 6 %) ones (n = 12). ∮ The last column shows the results of the comparison between euglycemic thalassemic patients (n = 12) and healthy controls (n = 20). *p value < 0.05.

	Cases TAR140 > 6 % (n = 7)	*Cases TAR140 ≤ 6 % (n = 12)*	p	*Controls (n = 20)*	p ∮
GMI %(median; IQR)	5.70 (5.60 – 5.80)	5.1 (5 – 5.3)	<0.001*	5.15 (5.1 – 5.4)	n s
Mean glucose mg/dl (median; IQR)	116 (112 – 120)	96.5 (93.5 – 100.5)	<0.001*	100 (97 – 103.5)	n s
CV %(median; IQR)	16.7 (13.7 – 24)	17.2 (15.2 – 18.78)	n s	14.5 (13.2 – 16.65)	n s
TAR ≥ 200 % (median; IQR)	0 (0 – 0)	0 (0 – 0)	n s	0 (0 – 0)	n s
TAR ≥ 140 % (median; IQR)	10 (8 – 16)	1.5 (0.5 – 2.5)	<0.001*	1.5 (1 – 2)	n s
TBR < 70 %(median; IQR)	1 (0 – 1)	1 (0.5 – 4.5)	n s	1 (0 – 1)	n s
AGE y (median; IQR)	38 (34–50)	35 (33.5 – 44)	n s	33 (32 – 40)	n s
BMI (median; IQR)	20.40 (18.72 – 24.50)	23.24 (21.71 – 25.50)	n s	22.5 (20.5 – 25.0)	n s
HOMA-IR (median; IQR)	1.1 (0.85 – 1.40)	1.12 (0.7 – 1.31)	n s	1.1 (0.7 – 1.30)	n s
Duration of blood transfusion therapy (median; IQR)	38 (34 – 50)	35 (33.5 – 44)	n s		
LIC (median; IQR)	4.9 (4 – 11.35)	11.8 (7.31 – 14.11)	n s		
Cardiac T2* (median; IQR)	31.83 (29.2 – 32.46)	32.09 (28.94 – 34.58)	n s		
Ferritin last 5 years ng/ml (median; IQR)	988 (767 – 1833)	1290 (805.95 – 1365.5)	n s		
TSI last 5 years (median; IQR)	114 (96 – 134)	106 (102 – 110.5)	n s		
HbA1c mmol/mol (median; IQR) %	50 (48–54)	54 (48–57)	n s		
(median; IQR)	6.7 (6.5 – 7.1)	7.1 (6.5 – 7.4)			
TSH last 5 years mIU/L (median; IQR)	19.25 (7.3 – 24.02)	19 (10.3 – 30.6)	n s		
Number of other endocrine diseases (disorders of growth or sexual development, hypotyroidism, adrenal insufficiency) (median; IQR)	0 (0 – 1)	0 (0 – 0.5)	n s		

GMI (Glucose Management Indicator- reporting period 7 days).
SD (Standard Deviation-reporting period 7 days).
CV (Coefficient of Variation-reporting period 7 days).
TAR ≥ 200 % (Time above Range ≥ 200 mg/dl; >11.1 mmol/L) reporting period 7 days.
TAR ≥ 140 %(Time above Range ≥ 140 mg/dl; >7.78 mmol/L) reporting period 7 days.
TBR < 70 % (Time below Range < 70 mg/dl; <3.89 mmol/L) reporting period 7 days.
BMI Body Mass Index.
LIC Liver Iron Overload with Magnetic Resonance Imaging.
T2* value with Cardiac Magnetic Resonance Imaging.
TSI transferrin saturation index.
TSH thyroid-stimulating hormone.

values ≥ 140 mg/dl, with none exceeding TAR140 > 6 %. To better evaluate the diagnostic utility of TAR140 > 6 %, we divided TDT patients into two groups: "euglycemic" (TAR140 ≤ 6 %) and "hyperglycemic" (TAR140 > 6 %). Significant differences emerged between these groups for GMI, mean glucose, and TAR140% (p < 0.001). Notably, no significant differences in CGM metrics were found between euglycemic TDT patients and healthy controls, supporting TAR140 > 6 % as a threshold for prediabetes (Table 3).

Spending more than 6 % of time with glucose values ≥ 140 mg/dl increases mean glucose and CGM-estimated HbA1c, potentially exposing TDT patients to higher cardiovascular risks. Recent findings show that maintaining normal glucose ranges (TIR and TITR) reduces microvascular complication risks in DM patients [32,34]. Thus, TDT patients' cardiovascular risk may also be assessed by analyzing TAR metrics.

We also sought to determine the clinical and laboratory characteristics of hyperglycaemic patients with TDT by comparing them with euglycaemic patients. No differences were found in age, BMI, HOMA-IR, liver iron overload with magnetic resonance imaging (i.e. liver iron concentration), T2* value with cardiac magnetic resonance imaging, ferritin, transferrin saturation index, glycosylated haemoglobin, thyroid-stimulating hormone, or the number of other associated endocrine diseases. Those findings show that, in our study, glycaemic abnormalities were not correlated with the iron overload index or the duration of blood transfusion therapy. Even parameters normally used in defining metabolic syndrome (i.e. BMI and HOMA-IR) do not seem to be important for identifying individuals at risk among patients with TDT. Our findings are similar to those observed by others [2,3] and they emphasize the need for further studies to investigate the pathogenesis of dysglycemia in thalassemic patients.

The strengths of our study include its originality, the use of a well-matched control group, and its focus on CGM-derived metrics such as TAR140 > 6 %. Another strength is the longer observation period compared to previous studies (i.e. 3 days vs. 7 days). Limitations include a small sample size and cross-sectional design, which limit generalizability and preclude causal conclusions. Additionally, one-week CGM monitoring excludes long-term variability in glucose metrics. Future multicenter studies with longitudinal designs are essential to validate these findings, explore long-term CGM variability, and determine CGM's predictive value for dysglycemia and cardiovascular risks in TDT patients. Cost-effectiveness and integration into clinical workflows should also be evaluated to assess CGM's feasibility in routine screening for this high-risk group.

5. Conclusions

Although fasting venous glycaemia and the OGTT are the only validated tests for diagnosing DM, IFG, and IGT among patients with TDT, we believe CGM may become increasingly relevant for diabetes screening in this population.

In our study, CGM identified 37 % of patients with prediabetes. These cases had not been detected using traditional screening tests, highlighting the high sensitivity of glucose sensors to dysglycaemia when appropriate cutoffs and parameters are applied. Our data define the profile of transfusion-dependent prediabetes using a TAR140 > 6 % cutoff.

Notably, analysis of our data revealed that 7 of 19 TDT patients classified as euglycaemic per traditional methods were prediabetic. Diagnosis cannot rely solely on occasional high glucose values but rather on sustained hyperglycaemia, specifically TAR140 > 6 %. In response, diabetologists need to initiate timely prophylactic interventions to reduce cardiovascular risk, such as ferrochelation therapy, zinc supplementation, and dietary–behavioural education.

Providing a correct interpretation of glucose-related metrics from CGM in TDT patients was the chief objective of our study. Diabetologists and haematologists can adopt CGM in early screening stages for glucose

metabolism disorders, as part of follow-up after pathological OGTT results, or in monitoring preventive or curative DM therapy. The method is repeatable, well-tolerated by patients, and its lower costs compared to OGTT make it feasible for healthcare facilities. Given the high sensitivity of CGM in detecting glucose abnormalities, its future role in screening and monitoring TDT patients warrants further exploration. CGM could serve as an adjunct tool to traditional screening methods, allowing for earlier identification of at-risk individuals and facilitating personalized interventions. Its ability to track glycemic trends over time, rather than relying on isolated glucose measurements, makes it a valuable candidate for long-term metabolic monitoring. Further studies with larger patient cohorts are necessary to confirm our findings.

Ethics approval statement.

All procedures performed in our study were approved by the Institutional Research Committee of the University of Campania "Luigi Vanvitelli" and it was conducted according to the Declaration of Helsinki. Participants have provided written consent.

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CRediT authorship contribution statement

Angela Zanfardino: Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation. **Gulsum Ozen:** Writing – review & editing, Validation, Investigation, Data curation. **Giorgia Ippolito:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Domenico Roberti:** Writing – review & editing, Formal analysis, Data curation. **Silverio Perrotta:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis. **Dario Iafusco:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **Emanuele Miraglia del Giudice:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Data curation. **Maddalena Casale:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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