

The use of oral glucose-lowering agents (GLAs) in β -thalassemia patients with diabetes: Preliminary data from a retrospective study of ICET-A Network

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Abstract. *Objective:* The management of prediabetes and hyperglycemia is an increasingly important aspect of care in patients with thalassemia. In light of the limited evidence about the management of GD (glucose dysregulation) with glucose-lowering agents (GLAs), we have conducted a retrospective survey in TDT and NTDT patients with diabetes mellitus to collect more detailed information on GLA use in order to make preliminary recommendations. *Study design and method:* A questionnaire was prepared and distributed to the tertiary thalassemia care Centers of ICET-A Network. *Results:* Eight thalassemia care Centers [Bulgaria, Greece, Iran, Italy (4 Centers) and Qatar], following 1.554 with transfusion-dependent thalassemia (TDT), 132 (8.4%) with diabetes and 687 with non-transfusion-dependent thalassemia (NTDT), 27 (3.9%) with diabetes, participated in the retrospective survey. The records of 117 TDT patients and 9 NTDT patients with diabetes treated with GLAs were analyzed. Metformin, a biguanide, was the most frequently used drug (47.6%), followed by alpha-glucosidase inhibitors (5.5%), incretins (4.7%) and insulin secretagogues (3.1%). In 68 (61.2) patients GLAs was prescribed as monotherapy, while the remaining 49 (38.8%), who had inadequate glucose control with metformin, were treated with combination treatment. Fifty-one patients of 126 (40.4%) initially treated with oral GLA, for a mean duration of 61.0 ± 35.6 months (range: 12- 120 months), required insulin therapy for better metabolic control. *Conclusion:* This retrospective study covers an unexplored area of research in patients with thalassemia and GD. Oral GLAs appear to be safe and effective for the treatment of diabetes mellitus in patients with thalassemia, and can achieve adequate glycemic control for a substantial period of time. (www.actabiomedica.it)

Key words: β -thalassemia, glucose dysregulation, diabetes, glucose-lowering agents, outcome

Introduction

Type 1 diabetes (T1DM) is the result of pancreatic β -cell destruction and patients are prone to acute complications, such as ketoacidosis. Type 2 diabetes (T2DM) is a complex disorder which involves various degrees of decreased β -cell function, peripheral insulin resistance and abnormal hepatic glucose metabolism. Therefore, when considering appropriate pharmacologic therapy, it is important to determine whether the patient is insulin-deficient, insulin-resistant, or both. Treatment options are divided into non-insulin therapies—insulin sensitizers, insulin secretagogues, alpha-glucosidase inhibitors, incretins, and sodium-glucose cotransporter 2 (SGLT-2) inhibitors—and insulin therapies (insulin and insulin analogues), which act by different mechanisms to reduce the blood glucose levels in order to achieve and maintain optimal glycemic control (1,2).

Two hypotheses have been postulated to explain glycemic dysregulation (GD) in thalassemia. The first supports pancreatic β -cell damage and insulin deficiency, associated with insulin resistance (IR) (3-6). The progressive and early loss of β -cell mass, leading to pancreatic dysfunction, may be due to iron-mediated oxidative stress that triggers apoptosis, volume loss, and fatty replacement (3).

The second hypothesis suggests that the “*primum movens*” is IR which results in impaired fasting glucose (IFG); chronic iron overload and progressive damage of β -cell function later induce impaired glucose tolerance (IGT) or thalassemia related-diabetes (T-RD). The IR has been postulated to be at the level of the liver (due to iron deposition), where it may interfere with insulin's ability to suppress hepatic glucose uptake, and also at the level of muscles, where iron deposits may decrease the glucose uptake. This hypothesis is supported by several studies showing higher fasting plasma insulin concentration with increased IR index and normal plasma glucose, preceding the onset of frank GD in patients with thalassemia (7-11).

The most prevalent types of GD documented in a recent survey by the International Network on Endocrine Complications (ICET-A) of 2.252 transfusion-dependent thalassemia (TDT) patients, were impaired fasting glucose (IFG; 10.4%) and T-RD; 8.6%) (3). The prevalence of GD among 874 non-transfusion-dependent

thalassemia (NTDT) patients was lower compared to TDT patients and was documented at a more advanced age (12). T-RD is distinct and different from T1DM and T2DM, but has features of both (13).

Early diagnosis of prediabetes is essential for the prompt identification of high-risk individuals who will benefit from intensive iron chelation therapy and lifestyle modification. In subjects with T-RD, optimal glycemic control is essential in order to reduce the risk of diabetic complications (4).

The management of prediabetes and hyperglycemia is an increasingly important aspect of care in patients with thalassemia, but few studies have specifically addressed the management of GD with glucose-lowering agents (GLAs) (14-18).

Thus, we conducted a retrospective survey in TDT and NTDT patients with diabetes who were treated with GLAs with the aim of collecting detailed information on GLA use and to prepare preliminary recommendations for their use.

Methods used for the ICET-A survey

In May 2021, the Coordinator (VDS) of ICET-A Network invited the 16 centers of the network to take part in a retrospective analysis of TDT and NTDT patients treated with GLAs for diabetes. The main objectives were to ascertain the different choices of clinicians/diabetologists/endocrinologists in prescribing GLAs in thalassemia patients, and to assess efficacy, safety, duration of treatment and adverse effects of their use (*first step*).

An “ad hoc” questionnaire, prepared by the ICET-A Steering Committee (3 endocrinologists: VDS, ATS and PT, and 2 hematologists SD and CK) including the following information: a) number of TDT and NTDT patients with diabetes who had been treated with GLAs; b) agents and therapeutic regimen used in the Center; c) contraindications and limitations of their use; d) parameters used to assess GLA efficacy; e) disadvantages/side effects encountered at any time during the treatment; e) number of patients who required insulin for a better control after starting with GLAs, and f) duration of GLAs treatment (in months) before switching to insulin treatment (*second step*). Diagnostic criteria for diabetes

in all centers was fasting plasma glucose ≥ 126 mg/dL (≥ 7.0 mmol/L) or 2-h plasma glucose during oral glucose tolerance test ≥ 200 mg/dL (≥ 11.1 mmol/L).

The questionnaire was distributed to 8 participating tertiary thalassemia care Centers [Bulgaria, Greece, Iran, Italy (4 centers) and Qatar]. Inclusion criteria for the study were: patients with TDT and NTDT with diabetes, irrespective of age, and who had been, or were currently, on treatment with GLAs. No exclusion criteria were included in the questionnaire. Requested data of patients with thalassemia and diabetes were collected manually from each center and were later entered using an Excel work sheet designed accordingly (*third step*).

After collection and analysis of data, the ICET-A Steering Committee prepared the first draft of the manuscript (*fourth step*). Later, the participants from the centers were formally requested to review the manuscript content and to participate in the preparation of the final version (*last step*).

Statistical analysis

Numeric variables are expressed as Mean \pm Standard Deviation (SD), range and percent (%).

Ethics

All procedures were in accordance with the 1964 Helsinki declaration and its later amendments. In October 2013 (www.wma.net). The local Ethics Committee was not required for the following reasons: no identifiable private information was collected and an anonymized dataset was analyzed.

Results

a. Survey respondents:

Eight tertiary thalassemia care centers from Bulgaria, Greece, Iran, Italy and Qatar, following 1,554 with TDT (132 with diabetes; 8.4%) and 687 NTDT patients (27 with diabetes; 3.9%), accepted to participate in the retrospective survey.

b. Prescribing patterns, class of oral glucose-lowering agents (GLAs) and duration of therapy:

The records of 117 TDT patients and 9 NTDT patients with diabetes treated with GLA were collected and analyzed. The main reported limitations/concerns for the use of GLA in patients with TDT and NTDT in different centers were:

- a. Patients' age below 15 years
- b. Absence of specific treatment guidelines for the role of GLAs in the treatment of thalassaemic patients with diabetes
- c. Paucity of literature data in patients with thalassemia
- d. Safety profiles in thalassemia
- e. Presence at diagnosis of very low or undetectable C-peptide level
- f. Presence of ketoacidosis at diagnosis of diabetes
- g. Heart failure
- h. Hepatic impairment/cirrhosis
- i. Estimated glomerular filtration rate (eGFR): <30 mL/min/1.73 m²

1) Allergy

Table 1 shows the GLA treatments in the study group at last observation, with biguanides (metformin) as the most frequently used drug (47.6%), followed by alpha-glucosidase inhibitors (5.5%), incretins (4.7%) and insulin secretagogues (3.1%).

In 61.2% of the total cohort, GLA was prescribed as monotherapy. Combination therapy was prescribed in 49 patients (38.8%) because of inadequate metabolic control with metformin alone (Table 2). The most commonly used combination therapies were metformin and acarbose (18 patients; 14.2%) and metformin and glibenclamide (17 patients; 13.4%) (Table 2). The parameters used in different centers to assess the efficacy of GLA treatment are summarized in table 2.

The reported total duration of GLA treatment varied from 3 months to 408 months, mean 77.3 ± 95.11 months and the principal adverse effects documented during GLA treatment are summarized in table 1.

Fifty-one patients of 126 (40.4%) initially treated with oral GLA, for a mean duration of 61.0 ± 35.6

Table 1. Distribution of oral glucose-lowering agents (GLAs) as monotherapy or combined therapy, at last observation, in 117 transfusion- dependent thalassemia (TDT) and 9 non-transfusion-dependent thalassemia (NTDT) patients

Subgroups (%)	Generic name and dosage per day (mg)	Number of patients	Comments and main adverse effects
Insulin sensitizers (47.61%)			
Biguanides	Metformin (500-2000 mg; median:1250 mg)	60	Weight loss Hypoglycemia (1 patient) GI intolerance Increase of liver enzymes (1 patient) Poor efficacy
Insulin secretagogues (3.17%)			
Sulfonylureas	Glicazide (80-160 mg)	2	Hypoglycemia Poor efficacy
Meglitinides	Repaglinide (0.5 mg)	2	GI intolerance Hypoglycemia Poor efficacy
Alpha-glucosidase inhibitors (5.55%)			
	Acarbose (100-300 mg)	7	GI intolerance
Incretins (4.76%)			
Long-acting (7 days): GLP-1 receptor agonists			
DPP-4 inhibitors	Sitagliptin (100 mg) Linagliptin (5 mg)	3 1	Hypoglycemia GI intolerance
Others			
SGLT-2 inhibitors	Canagliflozin (200 mg) Dapagliflozin (10 mg)	1 1	UTIs (1 patient) GI intolerance
Combination with 2 or 3 GLA (38.88%)	Met + Acarb; Met + Gliben; Met + Sitagliptin; Met + Repaglinide; SGLT2 inhibitors + Slow- Met; Met + Dapagliflozin; Met + Gliben +Acarb.	18 17 7 1 1 1 4	N.R.

Abbreviations: DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide- 1; SGLT-2=sodium-glucose cotransporter-2; Met=Metformin; Acarb =Acarbose; Gliben= Glibenclamide; GI=gastrointestinal; UTIs=urinary tract infections; N.R.= not reported.

months (range: 12- 120 months), required insulin therapy for better metabolic control.

Discussion

In the last few decades, along with the significant increase in life expectancy of patients with TDT, new complications have emerged. GD is frequent among TDT patients on conventional treatment with regular blood transfusions and iron chelation therapy. Low serum zinc (Zn) levels or vitamin D deficiency

(VDD) have been reported as potential contributing factors to GD (11).

The development of diabetes in patients with thalassemia may be due to a combination of insulin deficiency and insulin resistance; this deficiency may be caused by iron deposition in β -islet cells, exhaustion of β -cells or a combination of both. GD usually develops during the second-third decade of life even though baseline blood glucose levels are normal (13). Diabetic ketoacidosis (DKA) is uncommon (19), most likely due to the persistence of endogenous insulin secretion associated with an impairment of glucagon secretion (Figure 1) (3).

Table 2. Parameters used to assess efficacy of glucose-lowering agents in different Centers

	Bulgaria	Greece	Iran	Italy (4 centers)	Qatar
Reduction of fasting glucose	Yes	No	Yes	Yes (4)	Yes
Reduction of post - prandial glucose	Yes	Yes	Yes	Yes (2) No (2)	Yes
Reduction of HbA1c	Yes	Yes	No	Yes (3) No (1)	Yes
Reduction of fructosamine	Occasionally	Yes	Yes	Yes (3) No (1)	NA
Other parameters	No	No	CGMS	No (4)	FGMS

Abbreviations: CGMD: Continuous Glucose Monitoring System; FLS: Flash glucose monitoring System; NA: Not available.

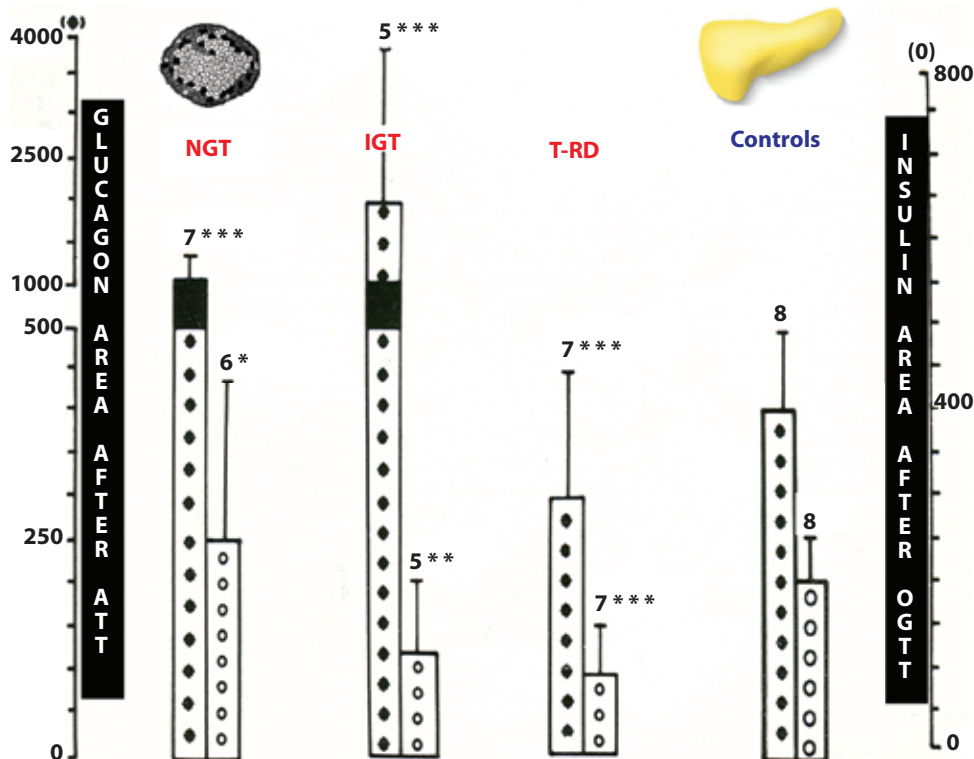


Figure 1. Mean (\pm SD) levels of plasma insulin IRI, U/mL and plasma glucagon (IRG, pmol/L) areas in normal controls (8 patients) and in transfusion-dependent thalassemia patients (TDT) with normal glucose tolerance test (NGT; 7 patients), impaired glucose tolerance (IGT; 5 patients) and thalassemia related-diabetes (T-RD; 7 patients) after oral glucose tolerance test and arginine stimulation test (ATT). P values versus controls: * <0.05 ; ** <0.01 ; *** <0.001 (From: De Sanctis et al. Ref. 3, modified). The insulin area after OGTT was higher in TDT with NGT and IGT and lower in patients with T-RD. A progressive decline in the glucagon area after ATT is present in patients with IGT and T-RD.

Various classes of oral GLAs are currently available for the treatment of GD in thalassemias, and act by different mechanisms to reduce the blood glucose levels and maintain an optimal glycemic control (Table 3).

All centers generally reported successful management of T-RD with GLAs for months or years.

GLAs were chosen, mainly on the basis of low risk for hypoglycaemia and with less complex regimen. The most common reported side effects were gastrointestinal intolerance, followed by hypoglycemia in two patients on treatment with biguanides and DPP-4, and an increase of liver enzymes during treatment with metformin. Although gastrointestinal intolerance

Table 3. Mechanism and site of action of oral glucose-lowering agents (GLAs)

Drug class	Mechanism of action	Primary site of action
Biguanides	Decrease hepatic glucose production; insulin sensitivity in hepatic and peripheral tissues	Liver; peripheral tissues.
Sulfonylureas	Increase insulin release	Pancreas
Thiazolidinediones (TZDs)	Reduce insulin resistance at adipose tissue and skeletal muscle	Peripheral tissues
Meglitinides	Increase insulin release	Pancreas
Alpha-glucosidase inhibitors	Delay carbohydrate absorption	Small intestines
Dipeptidyl-peptidase-4 (DPP-4) inhibitors)	Inhibit DPP-4 activity, prolong incretin action, increase insulin secretion and reduce glucagon secretion (glucose-dependent)	β -cell, stomach, liver
Sodium glucose cotransporter 2 (SGLT2) inhibitors	Inhibit SGLT-2 in the proximal tubules, block glucose reabsorption, glucosuria (act independent of insulin)	Renal tubular SGLT-2 receptor

is frequent, metformin-induced hepatotoxicity is rare. For clinicians, it is important to be vigilant about the occurrence of this rare adverse effect (20).

Management of diabetes in patients with chronic liver disease (CLD), as occurs in thalassemia, is challenging because the liver is the major site of metabolism for most of the GLA agents. For this reason, it seems reasonable to use metformin with caution, up to a maximum dose of 1500 mg/day, in patients with mild/moderate increase of liver enzymes and to avoid its use in patients with severe CLD (21).

Although the present study has several limitations (e.g. sample size that limits the generalization of the findings, retrospective evaluation which relies only on information available in the hospital records, absence of well recognized and validated parameters for the assessment of metabolic control), it provides baseline data that can enhance the quality care of thalassemic patients with diabetes.

In the general population, the assessment of GLA efficacy is done through surrogates (hospitalization, for example) or intermediate endpoints, for example, biochemical ones [plasma fasting glucose, lipid profile and glycated haemoglobin A_{1c}]. The latter is the major tool in the general diabetic population for assessing glycemic control with strong predictive value for diabetes complications (1,2). It reflects the extent of glycation (exposure to glucose) of hemoglobin in the preceding 120 days due to the rate of turnover of red blood cells.

However, monitoring of glycemic control in diabetic patients with thalassemias is different when

compared with the non-thalassemic diabetic population. HbA_{1c} is considered a non reliable indicator of glycaemic control as the levels may be increased or decreased depending on the proximity to transfusion, shortened erythrocyte lifespan. Fructosamine assay suffers from poor reproducibility (large inter-assay variation) and lacks an established target range, which limits its usefulness in monitoring glycaemic control in this group of patients (22,23).

Despite the questionable accuracy of HbA_{1c} in patients with homozygous hemoglobinopathies, Kattamis et al.(24) have reported that in efficiently transfused TDT patients HbA_{1c} can be useful in diagnosis and monitoring treatment of T-RD. Nevertheless, further large studies are needed.

Moreover, there is insufficient evidence to be dogmatic about the ideal glycemic target for patients with thalassemias. Achieving the same target as for those with T1DM [capillary self-blood glucose (CBG) determinations: preprandial: 80 - 130 mg/dL (4.4–7.22 mmol/L), postprandial: <180 mg/dL (< 10 mmol/L), bed time/overnight: 90 - 150 mg/dL (5–8.32 mmol/L)] seems to be a reasonable goal. Thus, patients should be encouraged to perform CBG testing. The regularity of CBG determination will depend on the degree of control and the type of treatment. Continuous glucose monitoring (CGM) and Flash glucose monitoring System (FGMS) may be helpful in selected cases. FGMS, also called 'intermittently viewed CGM', uses a disc device, worn on the arm, that can be scanned with a reader to obtain interstitial glucose results instantly (25). Currently, these devices

do not alert the user to either low or high blood glucose levels.

In conclusion, glucose tolerance in adolescents and young adults with thalassemia may deteriorate with age. Patients with a severe course of T-RD require immediate insulin implementation, while, in a large proportion of patients with GD, oral GLAs appear to be effective in achieving metabolic control of diabetes for several months or years. At this stage a uniform treatment protocol is impossible due to the limited information available in thalassemias. Although ADA still recommends metformin as first-line therapy, the updated Standards of Care have become more focused on other factors rather than solely concentrating on glycemic control (26). Patients who are not responding adequately to metformin monotherapy should advance as quickly as possible to a combination therapy with second-line agents, such as the incretin agents. Incretin agents should also be considered among the first-line options in treating patients for whom metformin is contraindicated or inappropriate (Figure 2). These recommendations, however, raise the problem of having insufficient high quality data about GLAs in thalassemia and to which extent results from the general population can be applied to patients with thalassemias. Therefore, it is recommended that patients should be referred to health professionals with expertise in thalassemia and diabetes when the clinical picture is complex enough to require a multidisciplinary team.

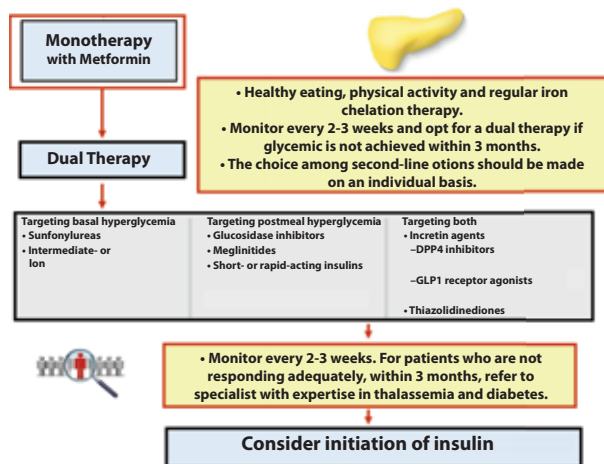


Figure 2. Algorithms for the management with oral glucose-lowering agents in T-RD patients.

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

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