Prevalence of glucose dysregulation (GD) in patients with β-thalassemias in different countries: A preliminary ICET-A survey

Vincenzo de Sanctis 1, Ashraf Soliman 2, Ploutarchos Tzoulis 3, Shahina Daar 4, Antonis Kattamis 5, Polyxeni Delaporta 5, Mohamed A. Yassin 6, Mehran Karimi 7, Duran Canatan 8, Soad Al Jaouni 9, Maria Conetta Galati 10, Giuseppe Raiola 11, Giuseppe Messina 12, Saveria Campisi 13, Forough Saki 14, Dulani Kottabachchi 15, Valeria Kaleva 16, Kristina Petrova 16, Atanas Banchev 17, Christos Kattamis 18

1 Coordinator of ICET-A Network (International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine) and Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy; 2 Department of Pediatrics, Division of Endocrinology, Hamad General Hospital, Doha, Qatar and Department of Pediatrics, Division of Endocrinology, Alexandria University Children’s Hospital, Alexandria, Egypt; 3 Department of Diabetes and Endocrinology, Whittington Hospital, University College London, London, UK; 4 Department of Haematology, College of Medicine and Health Sciences, Sultan Qaboos University, Sultanate of Oman; 5 Thalassemia Unit, Division of Pediatric Hematology-Oncology, First Department of Pediatrics, University of Athens, “Agia Sofia” Children’s Hospital, Athens, Greece; 6 National Center for Cancer Care and Research, Medical Oncology Hematology Section HMC, Doha, Qatar; 7 Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; 8 Medical Director of Antalya Genetic Diseases Center, Antalya, Turkey; 9 Head Division of Pediatric Hematology Oncology, Department of Hematology Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia; 10 Department of Pediatric Haematoncology, Thalassaemia and Prenatal Diagnosis Regional Center, Pugliese-Ciaccio Hospital, Catanzaro, Italy; 11 Department of Paediatrics, Pugliese-Ciaccio Hospital, Catanzaro, Italy; 12 UOSD Microcitemia, Grande Ospedale Metropolitano “Bianchi- Melacrino- Morelli”, Reggio Calabria, Italy; 13 UOSD Thalassaemia, Umberto I’ Hospital, Siracusa, Italy; 14 Shiraz Endocrinology and Metabolism Research Center, Shiraz, Iran; 15 Thalassaemia Care Unit, Colombo North Teaching Hospital, Sri Lanka; 16 Varna Expert Center for Coagulopathies and Rare Anemias; 17 Pediatric Hematology-Oncology, University Hospital “Tzaritza Giovanna - ISUL”, Sofia, Bulgaria; 18 First Department of Paediatrics, National Kapodistrian University of Athens, Greece.

To the Editor,

The prevalence of diabetes mellitus (DM) in β-thalassemia varies from 9.7% to 29% and the overall prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) is 17.2% and 12.4% respectively in transfusion dependent thalassemia (TDT) patients (1). The highest prevalence of IFG and IGT has been observed in countries of the Middle East (27.8%) and the Mediterranean coast (15.1%) (2). Therefore, early detection of glucose dysregulation (GD) plays an important prevention role and is an area of considerable research interest for patients with thalassemias.

The current international guidelines recommend annual screening for GD in all patients with transfusion-dependent (TDT) from the age of ten years (2). Annual screening becomes even more important in the light of evidence showing that intensive chelation regimen (monotherapy or combined) in the early stages of glucose abnormalities can improve insulin secretion and normalise glucose metabolism (3). Similar GD recommendations are not available for patients with non-transfusion-dependent thalassemia (NTDT) (4).

The International Network on Endocrine Complications in Thalassaemia (ICET-A) aims to encourage research in the field of growth disorders and endocrine complications in thalassaemia (5), and works to attract the interest of young physicians to the world of thalassaemia.

In December 2020, the ICET-A promoted a preliminary multi-country survey with the aim of assess-
ing the prevalence of GD in patients with TDT and NTDT followed in 14 centers of the ICET-A Network. TDT refers to the patients who require regular blood transfusions for survival since early life, while NTDT refers mainly to patients who do not need regular transfusions, though they may require occasional transfusions in certain circumstances, such as surgery, pregnancy or infection (6).

An ad hoc questionnaire was prepared and distributed by email to participating centers. As defined by the American Diabetes Association (ADA) criteria, a fasting plasma glucose between 100 and 125 mg/dl (5.6 – 6.9 mmol/L) is termed IFG, while the WHO proposes a cut-off value of 110 mg/dl (6.1 mmol/L) plasma glucose for IFG. Because the new WHO and ADA classification are based on the pathogenesis of the disease and not on its treatment, and thalassemia-related diabetes (TRD) is a distinct clinical entity caused either by insulin insufficiency and variable insulin resistance, we decided to use the old terminology: Insulin-dependent diabetes mellitus (IDDM) and Non insulin-dependent diabetes mellitus (IDDM) for the data presentation of patients.

The results of the survey of the overall prevalence of GD in patients with TDT are summarized in table 1. The most prevalent GD were IFG (10.4%) and IDDM (8.6%). The prevalence of GDs among NTDT patients was lower compared to TDT patients and was documented at a more advanced age.

A number of important observations emerged from this retrospective survey: 1) the high prevalence of GD in TDT patients suggest a revaluation of general management of these patients especially in regard to intensive chelation therapy as well as lifestyle modifications is extremely important; 2) GD in NTDT patients is less common than in TDT patients (12.1% vs. 31.0%) and is usually documented later in life; and 3) a number of TDT patients with DM retained a residual capacity to secrete insulin, at least in the earlier stages of their disease, responding to oral antidiabetic agents (6.1%).

In conclusion, in the last four decades, there has been a rapid increase in the survival of thalassemia patients due to an improvement in diagnosis and treat-

### Table 1. Types and prevalence of glucose dysregulation (GD) in patients with β-thalassemias (TDT and NTDT) in different countries.

| Patients with TDT | TDT patients tested with OGGTT (Criteria used) | IFG (%) | IFG+IGT (%) | IDDM (%) | NIDDM (%) | Total number of patients with GD after OGGTT |
|-------------------|-----------------------------------------------|---------|-------------|----------|-----------|-------------------------------------------|
|                   | Total: M/F (Age range)                          | M/F     | M/F         | M/F      | M/F       |                                           |
| Bulgaria (1)      | 26 (WHO)                                       | 4 (15.3%)| 0           | 0        | 0         | 4 (15.3%)                                 |
|                   | 39 (WHO)                                       | 3/1     | -           | -        | -         |                                           |
|                   | 23/16 (1-18)                                   | > 10 years| -           | -        | -         |                                           |
| Bulgaria (2)      | 42 (WHO)                                       | 0       | 2 (4.8%)    | 3 (7.1%) | 1 (2.4%)  | 6                                          |
|                   | 44 (WHO)                                       | 0       | 0/2         | 3/0      | 0/1       | (14.3%)                                   |
| Greece            | 176/183 (0.4-63)                               | 12 (3.4%)| 0           | 10 (2.9%)| 51 (14.7%)| 73 (21%)                                  |
|                   | 347 (ISPAD and WHO)                            | 6/6     | -           | 6/4      | 19/32     |                                           |
| Iran              | 388/312 (1-51)                                 | 29-57   | -           | 39-63    | 29-59     |                                           |
| Italy (1)         | 700 (ADA)                                      | NA      | NR          | 64 (9.1%)| 44 (6.2%) | NA (18.3%)                                |
|                   | 56 (ADA)                                       | 3 (5.3%)| 0           | 3 (5.3%) | 3 (5.3%)  | 9                                          |
|                   | 66 (ADA)                                       | 0/3     | -           | 2/1      | 2/1       | (16%)                                     |
|                   | 31/35 (1-57)                                   | 39-50   | -           | 47-57    | 45-52     |                                           |
| Italy (2)         | 82 (WHO)                                       | 3 (3.9%)| 2 (2.6%)    | 6 (7.8%) | 1 (1.3%)  | 12 (15.6%)                                |
|                   | 30/52 (1-64)                                   | 1/2     | 1/1         | 0/6      | 1/0       |                                           |
|                   | 147 (ADA)                                      | 32-40   | 32-43       | 43-55    | 64        |                                           |
| Italy (3)         | 147 (ADA)                                      | 4 (2.7%)| 13 (8.8%)   | 23 (15.7%)| 3 (2.0%)  | 43 (29.2%)                                |
|                   | 74/73 (25-56)                                  | 2/2     | 8/5         | 8/15     | 0/3       |                                           |
ment. With the increased lifespan, the comorbidities associated with the disease have begun to appear. Among them, GD is the most frequent and, potentially, the most severe, aggravating the patients’ quality of life and prognosis.

Many unresolved issues in the relation to this very peculiar form of TRD still persist, such as: advantages and limitations of imaging, biomarkers for detecting high-risk patients, outcome of GD, long-term benefits of oral antidiabetic agents and assessment of microvascular complications (retinopathy, nephropathy) and neuropathy. These may be clarified by new studies over the next few years.

Conflicts 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.

References

1. De Sanctis V, Soliman A, Tzoulis P, et al. Early detection of glucose dysregulation (GD) in patients with β-thalassemia major: Review of current diagnostic criteria and the ICET-A survey. Curr Trends Endocrinol. 2021;11:1-11.
2. He LN, Chen W, Yang Y, et al. Elevated Prevalence of Abnormal Glucose Metabolism and Other Endocrine Disorders in Patients with β-Thalassemia Major: A Meta-Analysis. Biomed Res Int 2019;2019:6573497.
3. Farmaki K, Angelopoulos N, Anagnostopoulos G, et al. Ef-
fect of enhanced iron chelation therapy on glucose metabolism in patients with b-thalassaemia major. Br J Hematol. 2006;134:438-444.

4. Karimi M, Cohan N, De Sanctis V, Mallat NS, Taher A. Guidelines for diagnosis and management of Beta-thalassemia intermedia. Pediatr Hematol Oncol. 2014;31:583-96.

5. De Sanctis V, Soliman AT. ICET-A an Opportunity for Improving Thalassemia Management. J Blood Disord. 2014;1:1-2.

6. Chuncharunee S, Teawtrakul N, Siritanaratkul N, Chueamuangphan N. Review of disease-related complications and management in adult patients with thalassemia: A multi-center study in Thailand. PLoS One 2019;14:e0214148

---

Received: 1 May 2020 – Accepted: 6 May 2021

Correspondence

Vincenzo De Sanctis, MD
Coordinator of the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A)
Via Paolo V, 25
44121 Ferrara, Italy
Tel: +39 0532 770243
E-mail: vdesanctis@libero.it