Acta Biomed 2021; Vol. 92, N. 3: e2021240 DOI: 10.23750/abm.v92i3.11733

Letter to Editor

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

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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 thalassemia.

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 Total: M/F (Age range)	**TDT patients tested with OGTT (Criteria used)**	**IFG (%)** M/F Age range	**IFG+IGT (%)** M/F Age range	**IDDM (%)** M/F Age range	**NIDDM (%)** M/ F Age range	**Total number of patients with GD after OGTT**
Bulgaria (1)	**26**	**4 (15.3%)**	**0**	**0**	**0**	**4**
39	**(WHO)**	3/1	-	-	-	**(15.3%)**
23/16 (1-18)		> 10 years	-	-	-	
Bulgaria (2)	**42**	0	**2 (4.8%)**	**3 (7.1%)**	**1 (2.4%)**	**6**
44	**(WHO)**	0	0/2	3/0	0/1	**(14.3%)**
22/22 (1-59)		0	11-13	31-52	25	
Greece	**347**	**12 (3.4%)**	**0**	**10 (2.9%)**	**51 (14.7%)**	**73**
359	**(ISPAD and**	6/6	-	6/4	19/32	**(21%)**
176/183 (0.4-63)	**WHO)**	29-57	-	39-63	29-59	
Iran	**NA**	**NR**	**NR**	**64 (9.1%)**	**44 (6.2%)**	**NA**
700	**(ADA)**	-	-	35/29	24/20	
388/312 (1-51)		-	-	7-51	18-38	
Italy (1)	**56**	**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)	**77**	**3 (3.9%)**	**2 (2.6%)**	**6 (7.8%)**	**1 (1.3%)**	**12**
82	**(WHO)**	1/2	1/1	0/6	1/0	**(15.6%)**
30/52 (1-64)		32-40	32-43	43-55	64	
Italy (3)	**147**	**4 (2.7%)**	**13 (8.8%)**	**23 (15.7%)**	**3 (2.0%)**	**43**
147	**(ADA)**	2/2	8/5	8/15	0/3	**(29.2%)**
74/73 (25-56)		25-40	41-56	45-53	27-49	

Italy (4) **135** 85/41 (1-59)	**85** **(WHO)**	**0** - -	**1 (1.2%)** 0/1 50	**6 (7%)** 3/3 38-54	**10 (11.8%)** 6/4 38-63	**17** **(20%)**
Kingdom of Saudi Arabia **146** 77/69 (1-52)	**137** **(WHO)**	**59 (43 %)** 34/25 11-47	**11 (8 %)** 5/6 11-47	**9 (6.5%)** 3/6 17-47	**2 (1.4%)** 2/0 29-47	**81** **(59.1%)**
Oman **100** 44/56 (6-41)	**97** **(WHO)**	**2 (2%)** 1/1 24-25	**7 (7.2%)** 3/4 22-29	**11 (11.3%)** 4/7 14-40	**5 (5.1%)** 2/3 16-34	**25** **(25.7%)**
Qatar **140** 78/62 (14-40)	**90** **(ADA)**	**14 (15.5%)** 10/4 20-24	**13 (14.4%)** 8/5 25-31	**7 (7.7%)** 3/4 28-40	**7 (7.7%)** 3/4 28-40	**41** **(45.5%)**
Sri Lanka **154** 80/74 (11-44)	**152** **(ADA)**	**33 (21.7%)** 19/14 13-38	**0** - -	**22 (14.4%)** 7/15 11-44	**1 (0.65%)** 0/1 18	**56** **(36.8%)**
Turkey **154/152** 80/74 (11-44)	**NA** **(WHO)**	**NR** NR NR	**NR** NR NR	**6 (12.5%)** 3/3 NR	**0** - -	**NA**
United Kingdom **92** 44/48 (18-59)	**92** **(ADA)**	**7 (7.6%)** 4/3 24-48	**10 (10.9%)** 5/5 25-49	**25 (27.2%)** 13/12 28-59	**10 (10.9%)** 4/6 26-54	**52** **(56.6%)**
Total **2252**	**1348** **(59.8%)**	**141** **(10.5%)**	**59** **(4.4%)**	**195** **(8.6%)**	**138** **(6.1%)**	**419** **(31.0%)**
Total number of patients with NTDT followed in the 14 Centers	**NTDT patients tested with OGTT (Criteria used)**	**IFG (%)**	**IFG+IGT (%)**	**IDDM (%)**	**NIDDM (%)**	**No. of patients with GDs after OGTT**
874 **(1-87)**	**378** **(WHO/ADA)**	**20 (5.3%)** 7/13 (18-46)	**4 (1.1%)** 3/1 (24-47)	**12 (1.0%)** 7/5 (30-87)	**10 (2.6 %)** 3/7 (25-54)	**46 (12.1%)**
P value	-	**0.004**	**0.003**	**< 0.00001**	**< 0.00001**	**< 0.00001**

Legend = TDT: transfusion-dependent β-thalassemia; NDTT: non-transfusion-dependent β-thalassemia; M: Males; F: Females; ADA: American Diabetes Association; WHO: World Health Organization; ISPAD: International Society for Pediatric and Adolescent Diabetes; FPG: Fasting plasma glucose; IGT: Impaired glucose tolerance; IDDM; Insulin-dependent diabetes mellitus; NIDDM: Non insulin-dependent diabetes mellitus; GD: Glucose dysregulation, NA: Not available; NR: Not reported.

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.

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Received: 1 May 2020 – Accepted: 6 May 2021
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