Acta Biomed 2023; Vol. 94, N. 3: e2023178 DOI: 10.23750/abm.v94i3.14805

Review

Recent advancements in glucose dysregulation and pharmacological management of osteoporosis in transfusion-dependent thalassemia (TDT): an update of ICET-A (International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine)

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Abstract. *Purpose of review:* The aim of this short review is to provide an update on glucose homeostasis, insulin secretion and pharmacological management of osteoporosis in transfusion-dependent thalassemia (TDT). *Recent findings:* A retrospective study, documenting the changes in glucose-insulin homeostasis from early childhood to young adulthood, has advanced our understanding of the evolution of glucose regulation in patients with TDT. Magnetic Resonance Imaging (T2* MRI) is considered to be a reliable tool to measure pancreatic iron overload. Continuous glucose monitoring systems (CGMS) can be used in early diagnosis of glucose dysregulation and in disease management in patients with already diagnosed diabetes. Oral glucose-lowering agents (GLAs) are effective and safe for the treatment of diabetes mellitus (DM) in patients with TDT, achieving adequate glycemic control for a substantial period of time. Current modalities for the management of osteoporosis in adults with TDT include inhibitors of bone remodeling such as bisphosphonates and denosumab as well as stimulators of bone formation (e.g., teriparatide), Considering the unique characteristics of osteoporosis associated with TDT, early diagnosis, treatment initiation and treatment duration are critical issues in the management this special population. *Conclusions:* Advances in the care of TDT patients have led to improved survival and quality of life. Nevertheless, many chronic endocrine complications still remain. Their routine screening and a high index of suspicion are imperative in order to provide timely diagnosis and treatment. (www.actabiomedica.it)

Key words: Transfusion-dependent thalassemia, short stature, growth and endocrine disorders, risk factors, osteoporosis

Introduction

Clinically, β-thalassemias can be classified as transfusion-dependent thalassemia (TDT) or β thalassemia major (β-TM) and non–transfusion-dependent thalassemia (NTDT) or thalassemia intermedia (TI) according to the severity of clinical and hematological phenotypes. Current treatment of TDT patients consists of regular lifelong blood transfusions (starting before the age of 2-3 years) and efficient iron chelation regimes to prevent and treat the consequent iron load and organ toxicity. Conversely, patients with NTDT usually maintain hemoglobin (Hb) levels between 7 and 10 g/dL and may require transfusions sporadically during pregnancy, intercurrent illnesses, surgery or regular transfusions in later life to prevent or treat late complications such as pulmonary hypertension and extensive medullary expansion (1).

With the optimization of transfusion and chelation regimens, and the availability of new imaging techniques that allow assessment of iron overload (IOL) in several organs, TDT has changed from a pediatric disease with poor life expectancy to a chronic disease with an open ended prognosis. Nevertheless, hepatic, cardiovascular and mainly endocrine complications still occur. The etiology of endocrine complications is multifactorial and partially unknown although IOL is the major factor. Many diagnostic and therapeutic approaches of endocrine disorders and associated complications remain to be elucidated.

The aim of the present update, promoted by the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A), was to prepare a short update of recent advancements in glucose dysregulation (GD) and osteoporosis in patients with TDT.

Glucose homeostasis and insulin secretion

It is well known that diabetes mellitus (DM) as well as milder forms of GD are common complications in patients with TDT. Since 2018, several studies have advanced our knowledge on the pathogenesis, natural history and management of GD in TDT patients.

a. Prevalence and pathogenesis of glucose dysregulation

The prevalence of GD varies substantially between studies. A recent international survey, organized by the ICET-A, included data on 1,348 patients with TDT and 378 with NTDT. Among individuals with TDT, the reported prevalence was 10.5% for impaired fasting glycemia (IFG; fasting glucose ≥ 100 mg/dL), 4.4% for the combination of IFG and impaired glucose tolerance (IGT; 2-hour glucose on oral glucose tolerance test 140-199 mg/dL), and 14.7% for DM. In those with NTDT, GD had lower prevalence and developed later in life, with frequency of 5.3% for IFG, 1.1% for the combination of IFG and IGT, and 3.6% for DM (2).

The identification of predictors for GD has been the subject of intense scientific interest. A cross-sectional study of 200 patients with TDT confirmed the well-known association of elevated serum ferritin (in this study when it exceeds 2,500 ng/ml) and body mass index (BMI > 25 kg/m²) with development of DM (3).

The potential role of insulin growth factor -1 (IGF-1) in the pathogenesis of DM in individuals with TDT is debated. For this reason, a retrospective study assessed the serum levels of IGF-1 in 34 adults with TDT and different degrees of glucose regulation. Participants with DM had the lowest

IGF-1 concentration, followed by those with IFG or IGT, while those with normal glucose homeostasis had significantly higher IGF-1 levels. A negative correlation was found between serum IGF-1 and fasting glucose and Homeostasis Model Assessment Insulin Resistance Index (HOMA-IR), confirming the association of low IGF-1 levels with development of GD. The question remains whether this association implies a risk factor or the cause, and whether low IGF-1 by itself can contribute to dysglycemia (4).

A retrospective study of 25 patients with TDT and DM elucidated the pathogenesis of hyperglycemia, describing in detail its clinical and biochemical characteristics. In comparison to those with normoglycemia, patients with DM were characterized by higher serum alanine aminotransferase (ALT) and basal insulin levels, higher HOMA-IR, and more frequent presence of hypogonadism. The conclusion of the authors was that iron overload and liver dysfunction lead to a

combination of insulin resistance and decreased ability for insulin secretion (5).

b. Pancreatic siderosis assessed by Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (T2* MRI) is considered to be a reliable tool to measure pancreatic IOL. A prospective validation study conducted by Meloni et al.(6) demonstrates that the T2* MRI may be transferred between MRI scanners by various vendors and centers representing a precise and reproducible method for quantifying pancreatic iron deposition, thus enabling its non-invasive assessment. T2* value of >33 ms refers to normal pancreatic tissue, 10-33 ms to pancreatic tissue with mild IOL, 2.5-10 ms to moderate IOL, and <2.5 ms to severe IOL (7).

Although one large cross-sectional study by Wahidiyat et al. (7) demonstrated no significant difference in pancreatic iron deposition between children and adults (P: 0.387), a prospective multicenter

observational study including 1079 patients (7-53 years of age) (8) and a prospective cross-sectional study including 90 children (9) suggests that pancreatic iron accumulation is an age-dependent process starting in early childhood. The excess iron directly damages pancreatic β-cells, resulting in cell death, insulin deficiency and, as a consequence, DM (10).

Nevertheless, various research groups have reported a nonsignificant difference in pancreatic IOL assessed by MRI between patients with TDT and nondiabetic patients (7,11-13). In addition, no correlation was found between pancreatic or hepatic iron and glucose/insulin levels in patients diagnosed with DM based on the OGTT (14) and between pancreatic MRI values and fructosamine levels, fasting blood glucose, insulin, C-peptides, and HOMA-IR indexes (14). In a large group of 1,079 TDT patients, 82.9% with normal glucose tolerance had a measurable iron in the global pancreas, demonstrating the low specificity of pancreatic IOL for the GD. These findings supported the hypothesis that pancreatic IOL may require a latent time to generate IGT and overt DM (8).

Interestingly, heart disease and pancreatic IOL are closely related, the latter being a reliable indicator of heart failure, arrhythmias, and myocardial dysfunction in the absence of cardiac iron; furthermore, a link between TDT-genotype and levels of pancreatic IOL has been postulated (15).

c. Screening for glucose dysregulation in patients with TDT

With respect to the optimal screening of individuals with TDT, a single-centre study assessed the diagnostic value of simultaneous measurement of glucose and insulin levels during an oral glucose tolerance test (OGTT) in 43 patients with TDT. The conclusion was that the majority of normoglycemic individuals exhibited impairment in insulin secretion, with either high basal insulin levels or delayed peak insulin secretion at 60 or 90 minutes rather than at 30 minutes post oral glucose loading. These abnormal insulin responses are valuable indices that predict the development of dysglycemia in patients with TDT (8).

A review summarizing recent studies in combination with personal experience and expert opinions, recommended screening for GD with OGTT, preferably combined with measurement of insulin levels, starting from the age of 10 years, biannually thereafter until the age of 16 years, and subsequently annually. The threshold value of 100 mg/dL for fasting glucose, as suggested by the American Diabetes Association (ADA) rather than 110 mg/dL as per the World Health Organisation, was recommended on the basis of the observation that almost half of individuals with fasting glucose 100-110 mg/dL will develop IGT within the next few years (16).

d. Continuous Glucose Monitoring (CGM)

Current American Diabetes Association recommendations include screening for DM in "at risk populations" with either random HbA1c values, fasting glucose, or an oral glucose tolerance test (OGTT) (17). However, as hemoglobinopathies and transfusions are known to affect HbA1c analyses, its utility in thalassemia is limited. Depending on the test performed, the shorter erythrocyte lifespan, rapid erythrocyte turnover and the proximity to the transfusion may incorrectly decrease the results (18). OGTT also

has its limitations as results are not always reproducable and can change over time.

The use of continuous glucose monitoring systems (CGMS) appears to diagnose more, and earlier glucose dysregulation compared to HbA1c, fasting glucose, and OGTT in TDT patients (19-21). The value of CGMS over other diabetes screening approaches is that it obtains minute-by-minute glucose readings as opposed to single-point measurements. This provides an opportunity to record elevated blood glucose levels over the course of a day, as well as glucose excursions related to meals and activities of daily living (22). In patients with TDT the CGMS can be used in early diagnosis of glycemic abnormalities and in disease management in patients with already diagnosed diabetes.

In a study including 200 patients with TDT, El-Samahy et al. (23) compared OGTT and CGMS in assessing glucose homeostasis. Twenty patients with random blood glucose ≥ 140 mg/dL (7.8 mmol/L) were studied using an OGTT and CGMS for four days. During OGTT, 30% of these patients had IGT and 35% had DM while during CGMS 35% had IGT and 65% had DM. The percentage of diabetic patients diagnosed by CGMS was significantly higher than that with OGTT (P: 0.012).

The advantage of the glucose sensor compared to OGTT was also confirmed by the study of Soliman et al. (24) who investigated 16 adolescents with TDT (19.75 ± 3 years) using an OGTT and CGMS for 3 days. During OGTT, 25% had IFG, 12.5% had IGT and one had diabetes. Using CGMS, 25% had diabetes and 56% of the patients had IGT (24).

These findings suggest that, in comparison to other screening tests, the CGMS is a sensitive method for detecting early GD and provides the potential for a more accurate assessment of glucose homeostasis in TDT patients. However, CGMS is not yet approved as a diagnostic method for TDT patients, the devices are expensive, and the system is not widely used as yet in TDT. To create a consensus on screening parameters/ thresholds, such as the number of glucose spikes necessary to indicate prediabetes or diabetes and its association with clinical outcomes, further information is required (14).

e. Evolution of glucose homeostasis in patients with TDT

A retrospective study, documenting the changes in glucose-insulin homeostasis from early childhood to young adulthood, has advanced our understanding of the evolution of glucose regulation in patients with TDT. The main findings were that the primary defect is usually insulin resistance, followed by impaired insulin secretion, and that IFG at an early age represents a risk factor for GD later in life (25).

Another retrospective study shed light on the significance of isolated hyperglycemia 1-h after glucose load during oral glucose tolerance test (OGTT). Patients with TDT and normal fasting and 2-h glucose values on OGTT were compared on the basis of normal (< 155 mg/dl) or high (≥ 155 mg/dl) 1-hour glucose values. Isolated 1-h hyperglycemia may serve as a single biomarker to detect patients with iron overload and liver impairment since it is independently associated with elevated serum ferritin and alanine aminotransferase levels. In addition, isolated 1-h hyperglycemia was associated with development of GD in 84% of cases over a 5-year follow-up period (26).

A third retrospective study showed that patients with TDT and combined IFG and IGT, followed-up for a mean period of 7.7 years, have a 22.4% likelihood of developing DM, 55.2% to remain unchanged and a 22.4% possibility to improve glucose status (27).

There is paucity of evidence on glucose status of patients with TDT and mild iron overload. Therefore, two studies evaluated glucose homeostasis in individuals with TDT and low ferritin levels. The first longitudinal study periodically examined the glucose homeostasis in 11 adults with TDT and persistently low serum ferritin values below 800 ng/mL, for a median follow-up of 5 years. While there were no cases of DM, 63% of participants had abnormal glucose regulation, more often IGT, at the baseline, while stabilization of glycemic indices was observed over the next 5 years (28).

The second study, including 14 TDT patients with serum ferritin < 500 ng/mL and 10 with ferritin 500-1,000 ng/mL, reported that 62.5% of those patients had GD, usually IGT, but no cases of DM (29). Substantially, both studies found that the burden of dysglycemia applies even to patients with low fer-

ritin values. Removal of iron from the pancreas is challenging, and the three available iron chelators (deferrioxamine, deferiprone or deferasirox) in monotherapy have an equivalent efficacy (30).

f. Management of DM

Despite the high prevalence of DM in patients with TDT, there is limited evidence about its management. In this context, taking into account the lack of high-quality data on the use of oral glucose-lowering agents (oral GLAs) in patients with TDT and DM, a retrospective survey in 8 thalassemia care centres, including 1,554 patients with TDT and 687 with NTDT was performed. The records of 117 TDT patients with DM and 9 with NTDT treated with oral GLAs were analysed. The most frequently used antidiabetic medication was metformin (in 47.6%), followed by acarbose (5.5%), gliptins (in 4%), and insulin secretagogues (gliclazide and repaglinide in 3.1%). As many as 40.4% of patients, who were initially treated with oral GLAs for a mean duration of 61 months, later required insulin therapy. This retrospective study suggests that oral GLAs are effective and safe for the treatment of DM in patients with thalassemias, achieving adequate glycemic control for a substantial period of time (31).

In view of the high prevalence of zinc deficiency in patients with TDT, two studies have been recently conducted to evaluate the effect of zinc supplementation on glucose homeostasis. The first study compared cross-sectional differences in markers of glucose regulation and zinc status in 9 patients with TDT and DM, 20 patients with no DM and 10 healthy controls. Zinc deficiency was more common in individuals with TDT and DM, indicating that hypozincemia may contribute to glucose dysregulation. Afterwards, the participants with TDT and DM were supplemented with zinc at a dose of 25 mg per day for 3 months which resulted in a decrease of fasting glucose and an increase of insulin sensitivity (32).

The second study was a randomized controlled trial which assessed the effect of zinc supplementation on glucose homeostasis in patients with TDT and DM. Eighty children were randomly assigned to oral zinc of 40 mg per day for 12 weeks or a placebo. Children in the intervention group had a significant decrease in serum ferritin, fructosamine (indicative of better glycemic control), and HOMA-IR (suggestive of reduced insulin resistance), and higher fasting C-peptide (providing evidence for increased insulin secretion) (33).

In summary

Recent studies have confirmed iron overload, liver dysfunction, and high BMI as risk factors for the development of DM in individuals with TDT, while preliminary data have raised the question whether low IGF-1 levels could also contribute to dysglycemia. With regards to screening for GD, CGMS classifies a larger proportion of TDT patients with prediabetes or DM compared to OGTT, the current gold standard diagnostic test. However, large studies are warranted to evaluate the diagnostic value of CGMS in the early detection of GD and to define the reference values of various glycemic parameters. Recent evidence about the evolution of glucose regulation in patients with TDT suggests that insulin resistance is usually the primary defect, followed by impaired insulin secretion, while isolated 1-hour hyperglycemia during OGTT indicates a very high likelihood of developing GD within 5 years. Interestingly, preliminary data report that GD is highly prevalent even amongst TDT patients with mild iron overload and low serum ferritin. In the field of optimal management of GD, zinc supplementation has shown promising results with lowering of fasting glucose, and increasing both insulin secretion and sensitivity. Finally, retrospective data support the use of oral antidiabetic agents, especially metformin, in patients with TDT and DM, with good efficacy for a substantial time period.

Practical approach to pharmacological management of osteoporosis

Osteoporosis and the associated increased fracture risk is a common complication in adults with βTM, reaching up to 60%, even in patients with adequate transfusion and iron chelation (34).

Current modalities for the management of osteoporosis in adults with TDT include inhibitors of bone

remodeling such as bisphosphonates and denosumab as well as stimulators of bone formation (e.g., teriparatide), while no data are available regarding the efficacy and safety of selective estrogen receptors modulators (SERMS), parathyroid hormone related peptide (PTHrP) agonist, abaloparatide and the sclerostin antibodies, romosozumab. Considering the unique characteristics of osteoporosis associated with TDT (i.e., younger age of the patients, compromised bone quality due to iron overload and possible under-transfusion, and the presence of other endocrinopathies that negatively affect bone metabolism), early diagnosis, treatment initiation and treatment duration are critical issues in the management this special population.

a. Bisphosphonates

Bisphosphonates (BPs), especially alendronate (35) and zoledronate (36-38) are the most widely used anti-osteoporotic medications for the prevention and treatment of bone loss in TDT patients. In most of the studies, bone mineral density (BMD) gains were comparable or even greater than those reported with the same agents in postmenopausal osteoporosis (39), although no data are currently available for their antifracture efficacy in patients with TDT associated osteoporosis (39).

The duration of oral alendronate in the currently published studies does not exceed 3 years, thus the safety of their administration for longer periods remains unknown.

For zoledronate the regimens that have been used differ from the regimes in postmenopausal osteoporosis, consisting of 4 mg every 3 (36,37) or 6 months (37), resulting in a cumulative dose much higher than the dose administered for postmenopausal osteoporosis (5 mg yearly).

Interestingly, BMD at all skeletal sites [lumbar spine (LS), femoral neck (FN) and radius] continued to increase up to 24 months after discontinuation of 1-year zoledronate treatment with both the 3-monthly and the 6-monthly regimen (38), allowing for potential longer intervals between zoledronate infusions (e.g.,12 -or 18-month intervals or 2 yearly) (40).

For the given treatment period, BPs were generally well-tolerated, and the type as well as the frequency of reported adverse events were as expected from the studies in postmenopausal and senile osteoporosis, consisting of mild upper gastrointestinal toxicity (alendronate) (34), and "flu-like" reaction in a small proportion of TDT subjects after the first infusion (zoledronate) (36,37).

Given the young age of TDT patients, concerns regarding the long-term and reproductive safety of BPs (41), should be carefully evaluated. Only three cases (2 females, 1 male) of osteonecrosis of the jaw (on alendronate 70 mg weekly administered for 3.5-4 years) (42), after tooth extraction and one case of atypical femoral fracture in a 36-old male with TDT who had been treated with zoledronate for 3 years and was off-treatment for 1 year before the event (43), have been reported so far. There are, as yet, no reports of pregnancy in patients on BPs and currently, for women who intend to conceive, treatment with BPs should be discontinued and be reinstituted after delivery (44).

b. Denosumab

Denosumab, in the 60 mg S.C. 6-monthly dose, has also proved efficacious in significantly increasing LS and FN BMD over a period of 1 year in patients with TDT associated osteoporosis.

Available data regarding the safety profile of denosumab in these patients have been reassuring. Reported adverse events were mild gastrointestinal problems (nausea, abdominal pain, diarrhea), headache and fever, while hypocalcemia was observed in less than 10% of cases (45,46). Special concerns of denosumab safety in these patients include: (i) the potential increased risk of upper respiratory system and gastrointestinal infections in a population that is already more prone to these events due to disease-dependent factors such as splenectomy, heart disease, and other comorbidities and (ii) the "rebound" phenomenon with substantial BMD loss following denosumab discontinuation. Regarding the former, close surveillance of TDT patients under treatment with denosumab is recommended. As for the latter, taking into account the results from studies in postmenopausal osteoporosis and the data from BPs studies among TDT patients, sequential administration of zoledronate or alendronate is expected to mitigate BMD losses following denosumab discon-

tinuation, especially among TDT patients treated for up to 2.5 - 3 years (47,48).

c. Teriparatide

Teriparatide is the most widely used osteoanabolic agent approved worldwide for the management of severe postmenopausal, male, and glucocorticoid-induced osteoporosis, but data on TDT patients are scarce. A recently published (49) case series of 11 patients with TDT associated osteoporosis (mean age 45 ± 4.38 years) treated with teriparatide for a mean duration of 18.7 ± 7.0 months reported significant improvements in BMD at the lumbar spine (19% and 22%) and total hip (13% and 14.2%), at 12 and 24 months, respectively. Almost 45% of the cohort reported side effects, including bone pain (5/11), muscle pain (4/11) and fever, while no fracture was reported during the study period (49). However, since the duration of teriparatide treatment is limited to 2 years, and discontinuation is followed by progressive loss of BMD (50), subsequent treatment with oral or i.v. BPs is needed in order prevent further bone loss (48,51,52). There are currently no data available on combination regimes of teriparatide with antiresorptive agents (i.e., zoledronate or denosumab) in patients with TDT, although favorable results have been reported in postmenopausal osteoporosis (51,53).

In summary

Based on available data on postmenopausal osteoporosis and TDT patients, an initial 1 to 3-year course of zoledronate or up to 5 years oral BPs would be a relatively safe approach. Alternatively, a 3 to 5 years course of denosumab is also an option. Two years of treatment with teriparatide could be considered in cases of severe osteoporosis with fractures and should always be followed by a course of oral BPs of 1-2 years or one course of iv. administered 5mg of zoledronate (53).

Conclusions

Several key advances have been made in the care of patients with TDT in the past five decades. Improved survival has led to an increased longevity that has been associated with newly recognised comorbidities or evolving complications. These not only add new challenges to all those taking care of adult TDT patients, but also give important messages for the delivery of care to younger patients with the disease who are likely to live much longer if appropriate care is started early in life. GD and osteopenia/osteoporosis are common complications even in patients who have received an adequate transfusional regime and iron chelation therapy, and their prevalence increases with increasing age. A systematic review, of 25 studies, including 4,934 patients with thalassemias, reported a prevalence of fractures in 18% (95% CI, 16–19%; I^2 = 89.0%) in TDT and 7% (95%CI, 4–10%; I^2 = 94.2%) among patients with NTDT (54). Therefore, early recognition of GD, osteopenia/osteoporosis and proper management are of paramount importance.

Optimisation and delivery of a high standard of care and the close collaboration between pediatricians and their adult counterparts is, and should remain, the main focus for managing the life-long disease of TDT patients. Moreover, patients with TDT need comprehensive care, preferably in a centralized thalassemia Unit, that should incorporate a multidisciplinary team including cardiologist, hepatologist, endocrinologist and reproductive medicine specialist.

Acknowledgments: We thank Prof. Christos Kattamis, βhalassemia Unit, First Department of Paediatrics, National Kapodistrian University of Athens, Greece, for his encouragement and clinical advices.

Funding: None

Ethic Committee: Not requested as review paper.
Conflict of interest statement: 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.

Authors contribution: Conceptualization: (VDS and SD); Literature research for glucose dysregulation (PT, AB and IM) and for osteoporosis (MPY); Original writing: (PT, AB, IM and MPY) Introduction, conclusions, revision and editing of manuscript (SD and VDS). All authors have read and approved the final version of the manuscript, ensuring that questions related to the accuracy and integrity of any part of the work were appropriately analyzed and discussed.

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Received: 23 April 2023
Accepted: 23 May 2023
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