Iranian Journal of Blood & Cancer

Guideline

Guideline for the Diagnosis and Treatment of Diabetes Mellitus in Patients with Transfusion-Dependent Thalassemia

Mohammad E. Khamseh[1], Mojtaba Malek[2], Nahid Hashemi-Madani[1], Fariba Ghassemi[3], Neda Rahimian[1], Amir Ziaee[3], Mohammad Reza Foroughi-Gilvaee[3], Pooya Faranoush[3], Negin Sadighnia[3], Ali Elahinia[3], Vahid Saeedi[1], Mohammad Reza Rezvany[3], Mohammad Faranoush[3,*]

[1] Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences (IUMS), Tehran, Iran.

[2] Research Center for Prevention of Cardiovascular Disease, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences (IUMS), Tehran, Iran.

[3] Pediatric Growth and Development Research Center, Institute of Endocrinology Iran University of Medical Sciences Tehran Iran.

ARTICLE INFO

Article History:
Received: 26/07/2023
Accepted: 21/09/2023

Keywords:
Thalassemia
Blood transfusion
Diabetes

***Corresponding authors:**
Mohammad Faranoush
Pediatric Growth and Development Research Center, Institute of Endocrinology Iran University of Medical Sciences Tehran Iran.
Email: Faranoush47@gmail.com

Abstract

Thalassemia major hemoglobinopathy requires regular blood transfusions, often leading to iron overload due to repeated transfusions and increased intestinal iron absorption. The association between thalassemia major and metabolic complications, including diabetes and metabolic syndrome, has been recognized due to iron overload, insulin secretion impairment, insulin resistance, hepatic dysfunction, and other endocrine complications. These hormonal imbalances can also influence glucose metabolism and contribute to the development of metabolic syndrome. It's essential for individuals with thalassemia major to undergo regular monitoring of their glucose metabolism, including periodic assessments of fasting blood glucose, oral glucose tolerance tests, and measurement of Fructosamine. Early detection and management of diabetes and metabolic syndrome in thalassemia major patients are crucial to minimize complications and optimize overall health. Medical management may involve a combination of regular blood transfusions, iron chelation therapy to reduce iron overload, lifestyle modifications such as a healthy diet and physical activity, and, if needed, pharmacological interventions for glycemic control. Close collaboration between hematologists and endocrinologists is often necessary to provide comprehensive care for individuals with thalassemia major and metabolic complications.

Please cite this article as: Khamseh ME, Malek M, Hashemi-madani N, Ghassemi F, Rahimian N, Ziaee A, Foroughi-Gilvaee MR, Faranoush P, Sadighnia N, Elahinia A, Saeedi V, Rezvany MR, Faranoush M. Guideline for the Diagnosis and Treatment of Diabetes Mellitus in Patients with Transfusion-Dependent Thalassemia. Iranian Journal of Blood and Cancer. 2023;15(4):293-303.

1. Introduction

One of the most common hemoglobinopathies worldwide associated with blood transfusions and iron overload is thalassemia syndrome. Diabetes is a common and severe complication in patients with blood transfusion-dependent thalassemia (1). These patients require frequent blood transfusions to control their anemia, which can lead to an increased risk of developing diabetes due to iron accumulation in the body. Iron accumulation in the body can lead to an increase in reactive oxygen species (ROS) production, which can cause cell death and fibrosis. This can, in turn, affect the endocrine glands and cause various complications (2, 3). The management of diabetes in thalassemia patients is complex and requires a multidisciplinary approach involving endocrinologists, hematologists, and diabetes educators. The prevalence of glucose intolerance and diabetes in young adults with thalassemia has been reported to be 17-24%, progressively increasing with advancing age (4, 5). The highest percentage of diabetes occurs in thalassemia patients in their second and third decades of life. The prevalence of diabetes in thalassemia patients in Iran has been reported to be 9.5% (95% CI 7.8-11.3) (6). The prevalence of diabetes in thalassemia patients varies among different populations and is influenced by factors such as age, genetic factors, age of blood transfusion initiation, annual blood transfusion volume, iron chelation therapy, and serum ferritin levels (7).

The pathophysiology of diabetes in thalassemia major (TM) is intricate and multifaceted. It encompasses several key factors, including uncontrolled iron overload and oxidative stress, which have the potential to inflict damage on pancreatic beta cells, thereby contributing to the development of diabetes. Genetic factors are also thought to be influential in the onset of diabetes in individuals with TM, with genetic predisposition potentially influenced by factors like genetic mutations, gene expression, and epigenetic modifications. Additionally, zinc deficiency and increased collagen deposition may further exacerbate the condition. Environmental factors, encompassing elements such as diet, physical activity, and stress, may likewise exert an influence on the development of diabetes in TM. Beyond these factors, other health indicators, including pancreatic microcirculation, may play a crucial role in the pathogenesis of diabetes in TM. Furthermore, patients with TM face an elevated risk of developing comorbidities, such as cardiovascular disease and endocrine dysfunction, which can also contribute to the emergence of diabetes (8-17).

The diagnostic criteria for glucose disorders in thalassemia patients are similar to those in non-thalassemic individuals. However, diagnosing diabetes in thalassemia patients is challenging, and the accurate method of diagnosing diabetes in these patients is a subject of debate. HbA1C has lower accuracy in screening for glucose disorders in thalassemia patients. Limited studies have been conducted on the use of continuous glucose monitoring (CGM) to identify early glucose disorders in these patients. The results of these studies indicate that CGM can be a useful and valid tool for identifying glucose disorders in thalassemia patients. However, this method is not universally accessible (8).

The general principles of diabetes management in thalassemia patients are similar to those in non-thalassemic individuals (9). Accurate monitoring of iron chelator therapy is essential in these patients (10). Many of these patients have a combination of endocrine, hepatic, and cardiac disorders. Furthermore, diabetes-related cardiac complications are more common in these patients (11-13). Considering the large number of thalassemia patients dependent on blood transfusion in the country and the burden of endocrine complications, especially diabetes, it is necessary to develop a national program

for early identification and timely treatment of glucose disorders in these patients. Therefore, an easy-to-use guide for diagnosing and treating glucose intolerance and diabetes in transfusion-dependent thalassemia patients has been developed. Due to the challenges involved in the diagnostic and control stages of glucose disorders in these patients, it is recommended that after identification and implementation of basic treatment measures, these patients be referred to endocrinologists and cardiologists for diabetes control and monitoring of cardiac complications (14).

The guideline for the diagnosis and treatment of diabetes in thalassemia patients with blood transfusion-dependent thalassemia is a comprehensive document that provides evidence-based recommendations for healthcare professionals managing this patient population based on a thorough review of the literature and expert consensus with aims to provide practical suggestions that can be implemented in clinical practice (15). Moreover, it covers a range of topics, including the diagnosis of diabetes in thalassemia patients, the management of diabetes in transfusion-dependent thalassemia patients, the prevention and management of diabetes-related complications, and the optimization of transfusion therapy to minimize the risk of developing diabetes.

Finally, the guideline for the diagnosis and treatment of diabetes in thalassemia patients with blood transfusion-dependent thalassemia is a valuable resource for healthcare professionals managing these patients' populations and will have a significant impact on diabetes management in thalassemia patients.

2. Methods

The development of the guideline for diagnosing and treating diabetes in thalassemia patients with blood transfusion-dependent thalassemia is based on a systematic and evidence-based approach. The process consisted of the literature review, expert opinion, synthesis of evidence, review and revision, and final review.

Literature review: A comprehensive literature review was conducted to identify studies, guidelines, and expert opinions on the diagnosis and management of diabetes in patients with thalassemia. Searches were performed using PubMed, Embase, and Cochrane Library databases. Search terms included diabetes, thalassemia, transfusion-dependent thalassemia, blood transfusion, diabetes management, and diabetes complications. The search was limited to studies published in English between January 2000 and August 2022.

Expert opinion: A panel of diabetes and thalassemia management experts convened to provide expert opinion on the diagnosis and treatment of diabetes in thalassemia patients with blood transfusion-dependent thalassemia. These experts are selected based on their experience and expertise in the field.

Synthesis of evidence: Combines data review and expert opinion to develop recommendations. These recommendations are based on the best available evidence and expert opinion.

Review and revision: Guideline recommendations are reviewed and revised by a group of external reviewers and experts in the field to ensure that the recommendations are evidence-based, effective, and relevant to the target audience.

Final review: The final report was approved by the Development Committee and published in a peer-reviewed journal.

Guidelines for the diagnosis and management of diabetes in patients with thalassemia with blood transfusion-dependent thalassemia is a comprehensive document that provides evidence-based recommendations for healthcare professionals managing these patients. The guideline is expected to significantly impact the management of diabetes in thalassemia patients and improve the overall health outcomes of this patient population.

3. Diabetes in Thalassemia Patients

3.1. General Overview

In the pathogenesis of glucose intolerance and diabetes in individuals with thalassemia, two mechanisms play a role: insulin resistance and impaired insulin secretion. Insulin resistance and hyperinsulinemia primarily occur due to iron deposition in the liver. The presence of concomitant liver diseases such as hepatitis C exacerbates insulin resistance further (16, 17). On the other hand, iron deposition in the pancreas and the resulting inflammatory reactions lead to progressive pancreatic destruction and decreased insulin secretion. The pathophysiological stages of diabetes in transfusion-dependent thalassemia patients progress as follows: Initially, there is the development of insulin resistance and hyperinsulinemia with normal glucose tolerance. This is followed by insulin resistance accompanied by glucose intolerance, along with the progressive deterioration and dysfunction of pancreatic beta cells, leading to decreased insulin secretion. Subsequently, patients transition to insulin-dependent diabetes. Additionally, individuals with thalassemia may also develop iron-dependent diabetes, which, in its early stages, can be reversible with proper and timely treatment (18, 19).

3.2. Important Diagnostic and Therapeutic Recommendations:

The presence of any of the following criteria indicates glucose intolerance (prediabetes)(20):

- Fasting blood glucose between 100-125 mg/dl
- Glucose tolerance test (GTT): Two-hour blood glucose level after consuming 75 grams of oral glucose between 140-199 mg/dl.

The presence of any of the following criteria indicates diabetes (21, 22):

- Fasting blood glucose of 126 mg/dl or higher (confirmed in two separate tests)
- Glucose tolerance test (GTT): Two-hour blood glucose level after consuming 75 grams of oral glucose of 200 mg/dl or higher (confirmed in two separate trials)
- Random blood glucose level of 200 mg/dl or higher, accompanied by symptoms of hyperglycemia such as excessive thirst, frequent urination, or unexplained weight loss.

Note: Fasting blood glucose is measured after an 8-hour fasting period.

To perform a glucose tolerance test in patients with weighing less than 43 kg, glucose is calculated and prescribed at a rate of 1.75 mg/kg, and for patients weighing 43 kg or more, 75 grams of glucose is prescribed (23, 24).

3.3. Screening

- FBS screening should start from age five and be repeated every six months until the end of life.
- Two-hour OGTT, ideally accompanied by measurements of insulin secretion at ages 10, 12, 14, and 16, followed by annual assessments thereafter.
- Whenever FBS ≥ 100 mg/dl, a GTT test should be performed for the patient.
- If one test is in the range of diabetes or prediabetes and the other test is normal, the abnormal test should be repeated, and based on the result of the second test, a decision should be made about continuing screening or treatment (25).

3.4. Therapeutic goals:

- The goal of treating patients in the prediabetes stage is to prevent prediabetes from turning into diabetes or at least delay the onset of diabetes (26).
- The goal of treating patients in the diabetes stage is to keep blood glucose in an acceptable range to prevent microvascular and macrovascular complications. The acceptable range of blood glucose in patients under treatment with oral medications or insulin is as follows:

• Fasting blood glucose is checked with a glucometer between 80-130 mg/dl.
• Two-hour postprandial blood glucose checked with a glucometer less than 180 mg/dl.
• One therapeutic goal is achieving HbA1c <7%, which is not a reliable indicator in patients with thalassemia. In situations where Fructosamine is accessible, Fructosamine should be checked to monitor blood glucose control in patients who do not have proper control. Fructosamine 322 µmol/L is equivalent to HbA1c 7% (0.322 mmol/L), and each 46 µmol/l of Fructosamine is equivalent to 1% of HbA1c (0.046 mmol/L) (27, 28).

3.5. Treatment and follow-up

3.5.1. If the patient's blood glucose is in the prediabetes range, the following is recommended:

For the management of prediabetes in transfusion-dependent thalassemia patients, the recommended approach includes adjusting the iron chelator dose and monitoring serum ferritin levels. It is advisable to refer the patient to a nutrition specialist who can provide guidance on adopting a suitable diet. Regular exercise, specifically brisk walking, for a minimum of 150 minutes per week is recommended, with at least one day of rest in between exercise sessions. If the patient is overweight, it is important to encourage weight loss of at least 3% of their initial weight through a combination of diet and exercise. After three months, the screening process should continue if both the fasting blood sugar (FBS) and glucose tolerance test (GTT) levels are within the normal range. However, if FBS and GTT results indicate prediabetes, lifestyle modifications should be implemented along with the potential prescription of metformin at a dosage of 500-2000 mg/day. Following three months of starting metformin, FBS levels should be checked to ensure that the patient's glucose remains within the normal range while regular metformin screening continues as usual. If blood glucose control is not achieved during the follow-up period and remains in the diabetes range, it is recommended to refer the patient to an endocrinologist for continued treatment.

3.5.2. If the patient's blood glucose is in the diabetes range, it is recommended:

In the management of diabetes in transfusion-dependent thalassemia patients, the recommended steps include increasing the iron chelator and serum ferritin dose. It is advisable to refer the patient to a nutrition specialist who can assist in implementing a suitable diet plan. Regular exercise, specifically brisk walking for a minimum of 150 minutes per week, is recommended. If the patient is overweight, it is important to encourage weight loss of at least 3% of their initial weight through a combination of diet and exercise.

For further treatment and follow-up, it is recommended to refer the patient to an endocrinologist. If the patient's blood sugar (BS) level is equal to or higher than 250 mg/dl, basal-bolus insulin treatment should be initiated after ruling out diabetic ketoacidosis (DKA). Consider basal-bolus insulin treatment if the patient exhibits symptoms such as polyuria, polydipsia, or weight loss. In asymptomatic patients with varying degrees of hyperglycemia, treatment with metformin (with or without a glitazone or basal insulin) may be considered.

Monitoring blood glucose levels is crucial in these patients, and a glucometer should be used until glucose control is achieved. After achieving control, fasting glucose should be measured every three months. Fructosamine levels should be checked every 1-5 months for blood glucose monitoring until control is achieved, and then every 3-5 months thereafter. The treatment goal is to achieve Fructosamine levels below 322 µmol/l, equivalent to an HbA1C level below 7%. It is important to tailor therapeutic goals based on the individual patient's

condition. Individuals on insulin therapy are advised to conduct blood glucose measurements a minimum of six times daily, encompassing preprandial readings and assessments two hours postprandial, utilizing a glucometer.

3.6. Medications

Insulin and oral medications whose safety and efficacy have been evaluated in patients with thalassemia include metformin and glipizide (29). There is insufficient data on newer-generation oral medications.

Notes:

- Checking normal kidney and heart function is essential before starting metformin (30).
- If GFR is 30-45 ml/min, metformin should be started at half dose (500 mg/daily).
- If GFR <30 ml/min, or the patient has uncorrected heart failure or advanced cirrhosis, metformin should not be started, and the patient should be referred to an internist or endocrinologist (31).
- In a patient using long-term metformin, vitamin B12 should be checked in case of neuropathy. If it is asymptomatic, vitamin B12 should be evaluated annually and treated if it is low (32, 33).

3.7. Evaluation of other metabolic markers (blood pressure - lipid profile):

In patients with diabetes, it is essential to check their blood pressure during each visit regularly. The target blood pressure should be maintained below 130/80 mmHg. If the patient's blood pressure is not within the acceptable range, it is recommended to refer them to a cardiologist for further control. For thalassemic patients with diabetes who are over two years of age, it is advised to conduct lipid profile tests at the initial diagnosis of diabetes. If the LDL (low-density lipoprotein) level is above 190 mg/dl, treatment with a statin medication such as atorvastatin (34-44 milligrams daily) or rosuvastatin (24-44 milligrams daily) should be initiated. If the reduction in LDL is less than 34%, it is recommended to refer the patient to specialists in endocrinology, internal medicine, pediatrics, or cardiology. Once drug treatment is initiated and the therapeutic goals are achieved, it is sufficient to check the lipid profile annually. However, in women who are planning to become pregnant, it is advisable to discontinue the use of statins (34-38).

3.8. Screening for complications

3.8.1. Retinopathy

In patients with diabetes who have had the condition for 3-5 years and are over 11 years old, it is recommended to assess them for retinopathy. If the evaluation shows no abnormalities, subsequent evaluations should be conducted every two years. However, if retinopathy is detected, it is crucial to follow the ophthalmologist's guidance and continue with regular screenings based on their advice. For females planning to conceive, it is advised to undergo a comprehensive eye examination either before or during the first trimester of pregnancy. Following that, regular eye exams should be continued throughout pregnancy and for one year postpartum, as per the ophthalmologist's recommendations (39-41).

3.8.2. Nephropathy

Patients who have had diabetes for three years or reach the age of 14 or puberty (whichever comes earlier) should undergo an evaluation for albuminuria and glomerular filtration rate (GFR). This evaluation involves checking the albumin/creatinine ratio in a morning spot urine sample. If the albumin/creatinine ratio is equal to or greater than 30 mg/gr, it should be repeated five times over a period of three months. If at least two out of three tests show a positive result, it is recommended to refer the patient to a nephrologist or internist for

further treatment. For patients with normal albumin/creatinine ratio (less than 30 mg/gr), the evaluation should be repeated annually. If the GFR is normal, annual evaluation should be continued. However, if the GFR is equal to or greater than 60 ml/min, it is advisable to refer the patient to a nephrologist or internist for ongoing treatment. (42-45).

3.8.3. Foot exam

Patients who have had diabetes for three years or reach the age of 14 or puberty (whichever comes earlier) should undergo an evaluation for foot vessels. This evaluation includes assessing the feet for wounds, fungal infections between the toes, and dry skin. Neuropathy can be evaluated by considering the patient's history of tingling sensations in a glove-sock pattern, numbness, or foot pain, and if available, performing simple tests such as using a monofilament and pinprick. Vascular evaluation involves checking pulses, examining the appearance of the skin (looking for signs like hair loss or shiny skin), and assessing for any symptoms of claudication. In the presence of any abnormalities detected during these evaluations, it is recommended to refer the patient to specialty foot care clinics for further management and treatment (46-48).

Figures 1 and **2** are a brief workflow for diagnosing and treating diabetes mellitus in transfusion-dependent thalassemia.

4. Characteristics of competent treating physicians for thalassemia endorsed and introduced by medical universities for prescribing and providing services

- Pediatric/Adult Hematology and Oncology Subspecialists
- Pediatric/Adult Endocrinology Subspecialist
- Pediatric Specialist
- Internal Medicine Specialist
- General Practitioner

5. Conclusion

Guidelines for diagnosing and managing diabetes in patients with transfusion-dependent thalassemia are crucial for providing evidence-based recommendations to healthcare professionals. These guidelines help ensure standardized and effective care for individuals with thalassemia who also have diabetes. By providing specific recommendations, these guidelines assist healthcare professionals in diagnosing diabetes in thalassemia patients, monitoring glucose metabolism, and managing the condition. They may include information on diagnostic criteria, target glucose levels, screening intervals, and treatment options, taking into consideration the unique challenges and complexities associated with thalassemia. Implementing guidelines for diagnosing and managing diabetes in thalassemia patients can have several benefits. It helps healthcare professionals stay up to date with the latest research and best practices, promotes consistency in care across different healthcare settings, and improves overall health outcomes for individuals with thalassemia and diabetes. Additionally, guidelines may address essential considerations such as the impact of iron overload, the role of iron chelation therapy, and the need for close collaboration between hematologists and endocrinologists to optimize patient care.

It is recommended that healthcare professionals involved in managing thalassemia patients with diabetes familiarize themselves with these guidelines and incorporate them into their clinical practice. Regular updates to the guidelines can also ensure they remain aligned with the most current evidence and best practices. Ultimately, the aim of these guidelines is to enhance the quality of care, improve diabetes management, and contribute to better health outcomes for individuals with transfusion-dependent thalassemia and comorbid diabetes.

In conclusion, in patients with Thalassemia Major, uncontrolled iron overload can have serious clinical

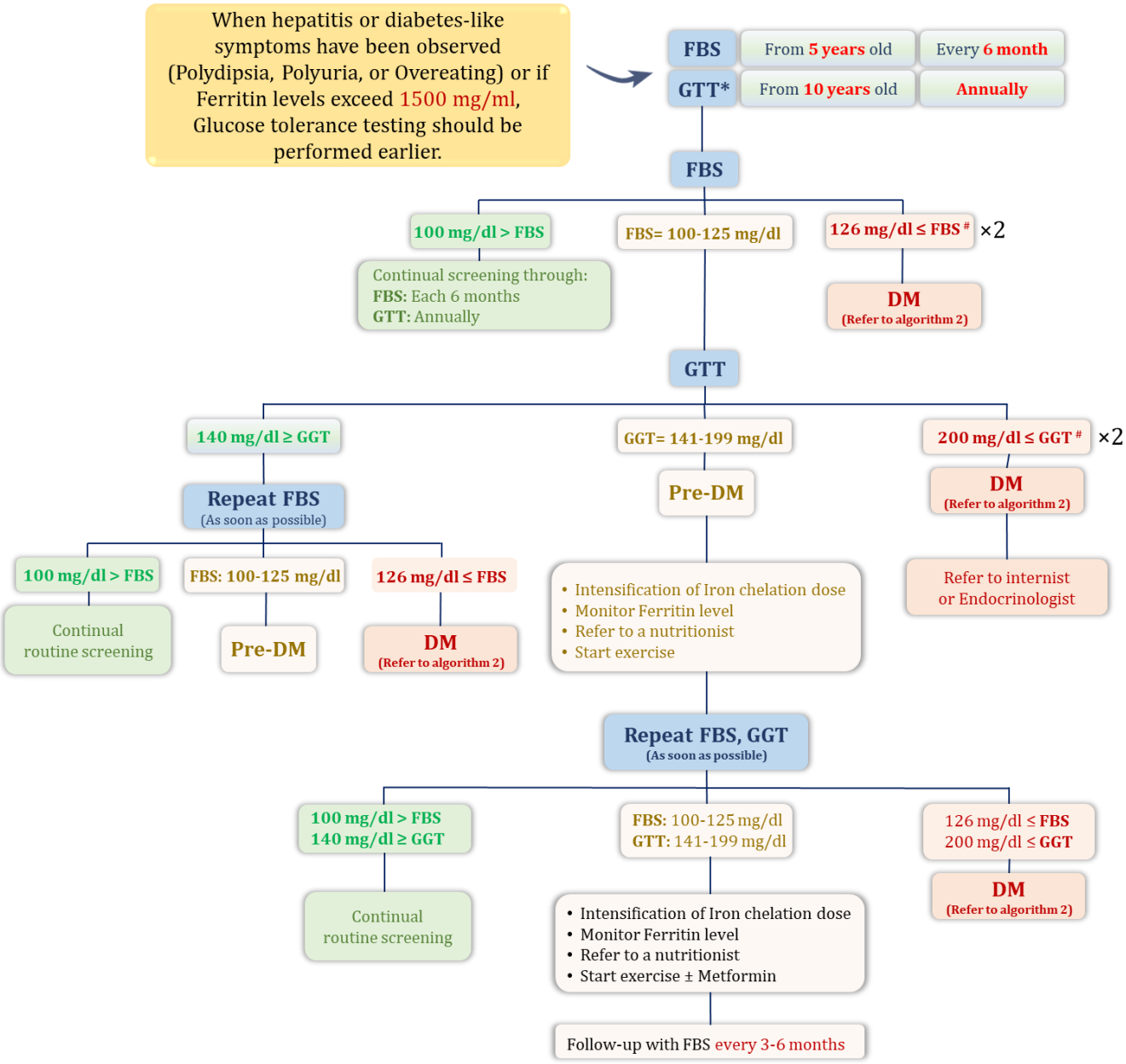

Figure 1. (Algorithm 1) Diagnosis and treatment of diabetes mellitus in transfusion-dependent thalassemia.
* 2 hours Plasma Glucose is considered in the GGT test.
# The diagnosis of diabetes is confirmed if FBS≥200 mg/dl is repeated.
GTT: Glucose Tolerance Test; **PG:** Plasma Glucose; **DM:** Diabetes Mellitus; **FBS:** Fasting Blood Sugar.

consequences, including liver damage, cardiac disease, endocrine dysfunction, and diabetes. Diabetes is a significant complication of TM, and the mechanisms of abnormal glucose homeostasis are complex and multifactorial. It is essential to manage iron overload effectively to prevent or minimize the development of these complications. This may involve regular blood transfusions, iron chelation therapy, and careful monitoring of glucose levels and other health indicators.

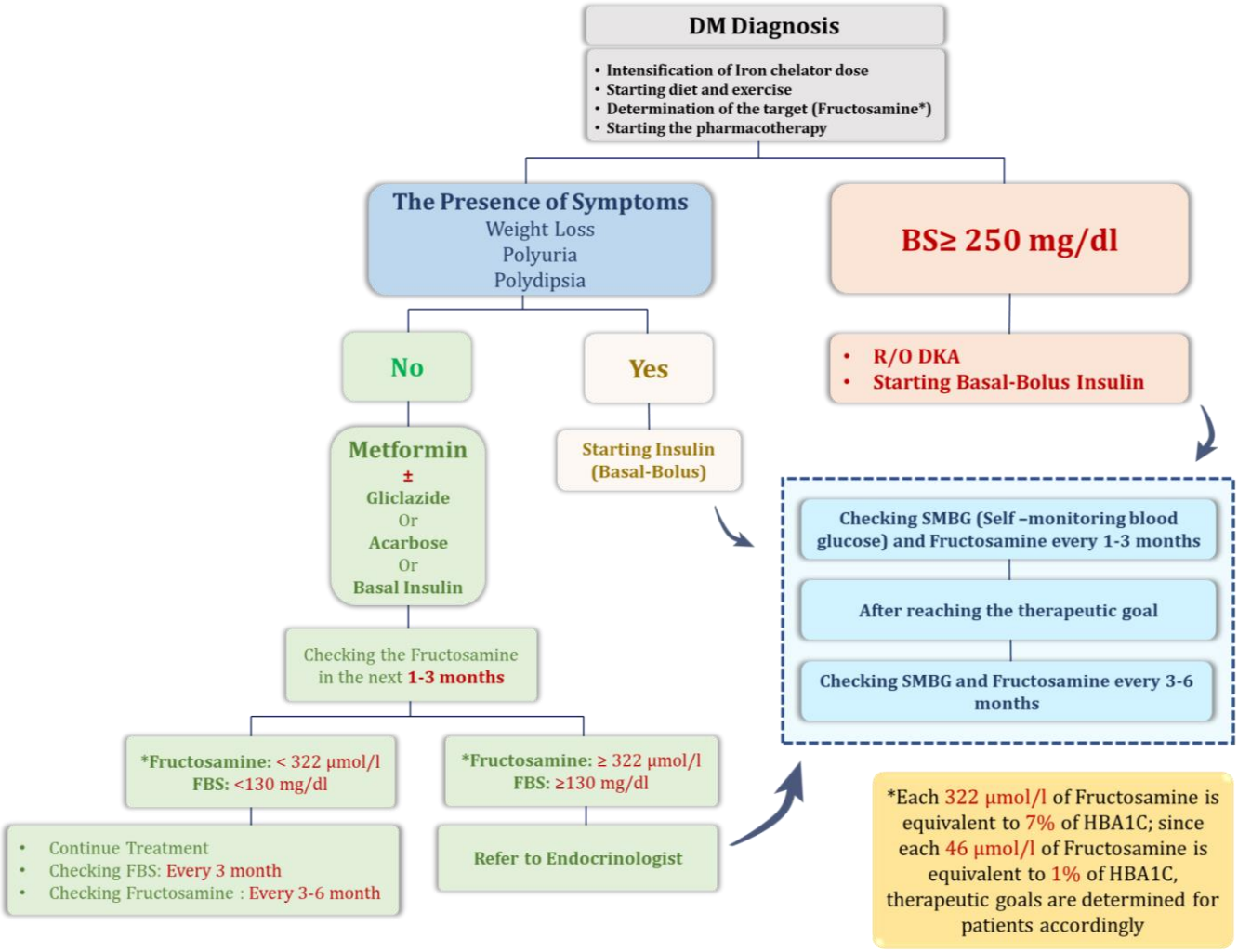

Figure 2. (Algorithm 2) Evaluation and monitoring of management in TDT and diabetes.

Conflict of interest

The Authors declare no conflict of interest for any financial or personal relationships that could potentially bias on work or influence the recommendations provided in the guidelines.

Acknowledgment

The authors would like to acknowledge the supportive assistance the Ministry of Health and Medical Education provided.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Ehsanipour F, Faranoush P, Foroughi-Gilvaee MR, Sadighnia N, Fallahpour M, Motamedi M, et al. Evaluation of immune system in patients with transfusion-dependent beta-thalassemia in Rasoul-e-Akram Hospital in 2021: A descriptive cross-sectional study. Health Science Reports. 2022;5(6):e871.

2. Faranoush P, Jahandideh A, Nekouian R, Mortazavi P. Evaluation of the in vitro and in vivo effect of liposomal doxorubicin along with oncolytic Newcastle disease virus on 4T1

cell line: Animal preclinical research. Veterinary Medicine and Science. 2023;9(3):1426-37.
3. Hashemi-madani N, Rahimian N, Khamseh ME, Faranoush P, Malek M, Ghasemi F, et al. Guideline for the diagnosis and treatment of hypothyroidism and hypoparathyroidism in patients with blood transfusion-dependent thalassemia. Iranian Journal of Blood and Cancer. 2023;15(2):89-96.
4. Jaruratanasirikul S, Chareonmuang R, Wongcharnchailert M, Laosombat V, Sangsupavanich P, Leetanaporn K. Prevalence of impaired glucose metabolism in beta-thalassemic children receiving hypertransfusions with a suboptimal dosage of iron-chelating therapy. Eur J Pediatr. 2008;167(8):873-6.
5. Kattamis C, Ladis V, Tsoussis D, Kaloumenou I, Theodoridis C. Evolution of glucose intolerance and diabetes in transfused patients with thalassemia. Pediatr Endocrinol Rev. 2004;2 Suppl 2:267-71.
6. Azami M, Sayehmiri K. Prevalence of Diabetes Mellitus in Iranian Patients with Thalassemia Major: A Systematic Review and Meta-Analysis. Journal of Mazandaran University of Medical Sciences. 2016;26(141):192-204.
7. Gamberini MR, Fortini M, De Sanctis V, Gilli G, Testa MR. Diabetes mellitus and impaired glucose tolerance in thalassaemia major: incidence, prevalence, risk factors and survival in patients followed in the Ferrara Center. Pediatr Endocrinol Rev. 2004;2 Suppl 2:285-91.
8. Martirosyan D, Jahanbakhshi F, Foroughi-Gilvaee MR, Mousavi F, Faranoush P, Ashoori MR, et al. Evaluation of the effect of electron beam therapy on oxidative stress and some minerals in patients with type 2 diabetes mellitus. Functional Food Science. 2022;2(5):124-35.
9. Olivatto GM, Teixeira CRS, Sisdelli MG, Zanetti ML, Silveira R, Gonçalves CV. Characterization of thalassemia major and diabetes mellitus patients at a reference center in Brazil. Hematol Transfus Cell Ther. 2019;41(2):139-44.
10. Mobarra N, Shanaki M, Ehteram H, Nasiri H, Sahmani M, Saeidi M, et al. A Review on Iron Chelators in Treatment of Iron Overload Syndromes. Int J Hematol Oncol Stem Cell Res. 2016;10(4):239-47.
11. De Sanctis V, Soliman AT, Canatan D, Tzoulis P, Daar S, Di Maio S, et al. An ICET-A survey on occult and emerging endocrine complications in patients with β-thalassemia major: Conclusions and recommendations. Acta Biomed. 2019;89(4):481-9.
12. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008;29(1):76-131.
13. Faranoush M, Faranoush P, Heydari I, Foroughi-Gilvaee MR, Azarkeivan A, Parsai Kia A, et al. Complications in patients with transfusion dependent thalassemia: A descriptive cross-sectional study. Health Science Reports. 2023;6(10):e1624.
14. Tzoulis P, Shah F, Jones R, Prescott E, Barnard M. Joint diabetes thalassaemia clinic: an effective new model of care. Hemoglobin. 2014;38(2):104-10.
15. Farmakis D, Porter J, Taher A, Domenica Cappellini M, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. Hemasphere. 2022;6(8):e732.
16. Dmochowski K, Finegood DT, Francombe W, Tyler B, Zinman B. Factors determining glucose tolerance in patients with thalassemia major. J Clin Endocrinol Metab. 1993;77(2):478-83.
17. Nouri-Vaskeh M, Khalili N, Khalaji A, Behnam P, Alizadeh L, Ebrahimi S, et al. Circulating glucagon-like peptide-1 level in patients with liver cirrhosis. Archives of Physiology and Biochemistry. 2023;129(2):373-8.
18. Bayanzay K, Alzoebie L. Reducing the iron burden and improving survival in transfusion-dependent thalassemia patients: current perspectives. J Blood Med. 2016;7:159-69.
19. Faranoush P, Elahinia A, Ziaee A, Faranoush M. Review of endocrine complications in transfusion-dependent thalassemia. Iranian Journal of Blood and Cancer. 2023;15(4):212-35.
20. Bansal N. Prediabetes diagnosis and treatment: A review. World J Diabetes. 2015;6(2):296-303.
21. Stuebe AM, Mantzoros C, Kleinman K, Gillman MW, Rifas-Shiman S, Seely E, et al. Gestational glucose tolerance and maternal metabolic profile at 3 years postpartum. Obstetrics and gynecology. 2011;118(5):1065.
22. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009;32 Suppl 1(Suppl 1):S62-7.
23. Ghosh S, Collier A. Section 1 - Diagnosis, classification, epidemiology and biochemistry. In: Ghosh S, Collier A, editors. Churchill's Pocketbook of Diabetes (Second Edition) (Second Edition). Oxford: Churchill Livingstone; 2012. p. 1-49.
24. Wile DB, Wilding JPH. CHAPTER 15 - Glucose metabolism and the pathophysiology of diabetes mellitus. In: Marshall WJ, Lapsley M, Day AP, Ayling RM, editors. Clinical Biochemistry: Metabolic and Clinical Aspects (Third Edition): Churchill Livingstone; 2014. p. 273-304.
25. Association AD. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2019;43(Supplement_1):S14-S31.
26. Khan RMM, Chua ZJY, Tan JC, Yang Y, Liao Z, Zhao Y. From Prediabetes to Diabetes: Diagnosis, Treatments and Translational Research. Medicina (Kaunas). 2019;55(9).
27. Danese E, Montagnana M, Nouvenne A, Lippi G. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. J Diabetes Sci Technol. 2015;9(2):169-76.
28. Zhang X, Xiao Y, Fan Y. Investigating the Reliability of HbA1c Monitoring for Blood Glucose Control During Late

Pregnancy in Patients with Gestational Diabetes Mellitus (GDM) with and without β-Thalassemia Minor. Diabetes Ther. 2018;9(6):2305-13.
29. De Sanctis V, Soliman A, Tzoulis P, Daar S, Kattamis A, Delaporta P, et al. The The use of oral glucose-lowering agents (GLAs) in β-thalassemia patients with diabetes: Preliminary data from a retrospective study of ICET-A Network. Acta Biomed. 2022;93(2):e2022162.
30. Hur KY, Kim MK, Ko SH, Han M, Lee DW, Kwon HS. Metformin Treatment for Patients with Diabetes and Chronic Kidney Disease: A Korean Diabetes Association and Korean Society of Nephrology Consensus Statement. Diabetes Metab J. 2020;44(1):3-10.
31. Heaf J. Metformin in chronic kidney disease: time for a rethink. Perit Dial Int. 2014;34(4):353-7.
32. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. World J Diabetes. 2021;12(7):916-31.
33. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, et al. Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2016;101(4):1754-61.
34. Al-Faris EA. Guidelines for the management of diabetic patients in the health centers of saudi arabia. J Family Community Med. 1997;4(1):12-23.
35. Saliba AN, Atoui A, Labban M, Hamade H, Bou-Fakhredin R, Mufarrij A, et al. Thalassemia in the emergency department: special considerations for a rare disease. Ann Hematol. 2020;99(9):1967-77.
36. Barnard M, Tzoulis P. Diabetes and thalassaemia. Thalassemia Reports. 2013;3(s1):e18.
37. Haghpanah S, Davani M, Samadi B, Ashrafi A, Karimi M. Serum lipid profiles in patients with beta-thalassemia major and intermedia in southern Iran. J Res Med Sci. 2010;15(3):150-4.
38. Bazi A, Sharifi-Rad J, Rostami D, Sargazi-Aval O, Safa A. Diabetes Mellitus in Thalassaemia Major Patients: A Report from the Southeast of Iran. J Clin Diagn Res. 2017;11(5):Bc01-bc4.
39. Wysocka-Mincewicz M, Gołębiewska J, Olechowski A, Szalecki M. Diabetic Retinopathy in Children with Type 1 Diabetes-Occurrence and Screening Using Optical Coherence Tomography. Life (Basel). 2021;11(6).
40. Solomon SD, Chew E, Duh EJ, Sobrin L, Sun JK, VanderBeek BL, et al. Diabetic Retinopathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017;40(3):412-8.
41. Mallika P, Tan A, S A, T A, Alwi SS, Intan G. Diabetic retinopathy and the effect of pregnancy. Malays Fam Physician. 2010;5(1):2-5.
42. Alleyn CR, Volkening LK, Wolfson J, Rodriguez-Ventura A, Wood JR, Laffel LM. Occurrence of microalbuminuria in young people with Type 1 diabetes: importance of age and diabetes duration. Diabet Med. 2010;27(5):532-7.
43. Muntean C, Starcea IM, Banescu C. Diabetic kidney disease in pediatric patients: A current review. World Journal of Diabetes. 2022;13(8):587.
44. Weckmann GF, Stracke S, Haase A, Spallek J, Ludwig F, Angelow A, et al. Diagnosis and management of non-dialysis chronic kidney disease in ambulatory care: a systematic review of clinical practice guidelines. BMC nephrology. 2018;19(1):1-18.
45. 11. Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S175-s84.
46. Risk Factors for Diabetic Peripheral Neuropathy in Adolescents and Young Adults With Type 2 Diabetes: Results From the TODAY Study. Diabetes Care. 2021;45(5):1065-72.
47. Herman W, Pop-Busui R, Braffett B, Martin C, Cleary P, Albers J, et al. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. Diabetic medicine. 2012;29(7):937-44.
48. Kumar S, Fernando D, Veves A, Knowles E, Young M, Boulton A. Semmes-Weinstein monofilaments: a simple, effective and inexpensive screening device for identifying diabetic patients at risk of foot ulceration. Diabetes research and clinical practice. 1991;13(1-2):63-7.