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Guideline

Guideline for the diagnosis and treatment of hypothyroidism and hypoparathyroidism in patients with blood transfusion-dependent thalassemia

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Abstract

Iron overload can adversely affect thyroid and parathyroid function in patients with transfusion-dependent thalassemia. Iron deposition in both glands or the pituitary gland, which controls thyroid function, can lead to their destruction and dysfunction. Hypothyroidism can cause symptoms such as fatigue, weight gain, and depression, while hypoparathyroidism can cause symptoms such as numbness and tingling in the hands and feet, muscle cramps, and seizures.

Regular thyroid and parathyroid function monitoring is essential in thalassemia patients to detect any dysfunction early and provide appropriate treatment. Treatment may include medications to replace thyroid hormone or calcium and vitamin D supplements to manage hypoparathyroidism. A comprehensive approach to managing endocrine complications in thalassemia patients can improve outcomes and quality of life for these individuals.

To provide professional healthcare members with clear and concise recommendations for diagnosing and treating hypothyroidism and hypoparathyroidism in transfusion dependent thalassemia patients, a practical national guideline should be developed.

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1. Introduction

Endocrine complications are common in thalassemia patients, especially those who are transfusion-dependent. Iron overload is a major risk factor for developing endocrine complications in thalassemia patients. Iron accumulation in the body increases labile iron and affects the Reactive Oxygen Species (ROS) system, causing oxidative stress and leading to cellular damage and dysfunction. This can affect the endocrine glands, including the thyroid and parathyroid glands, leading to complications such as hypothyroidism and hypoparathyroidism. ROS plays a significant role in developing endocrine complications in thalassemia patients. They are highly reactive molecules that can cause oxidative damage to cellular components, including DNA, proteins, and lipids.

Iron accumulation in the body can increase ROS production, leading to cell death and fibrosis, which can affect the endocrine glands and cause various complications(1-3).

Hypothyroidism in patients with thalassemia major has distinct causes compared to healthy individuals. The primary factor leading to this condition in thalassemia patients is blood transfusions containing high iron levels (1). Several risk factors contribute to hypothyroidism in these patients, including elevated serum ferritin levels, absence of regular iron chelation therapy, splenectomy, and using Amiodarone medication. Thyroid dysfunction in thalassemia major patients can be classified as either primary or secondary disorders. The primary type, more commonly observed, occurs due to iron accumulation in the thyroid tissue, leading to its destruction. Conversely, the secondary type arises from iron deposition in the pituitary gland, which destroys thyrotrophic cells and subsequent hypothyroidism (2-4).

The prevalence of primary hypothyroidism has been reported to range between 4% and 29%. However, it is essential to note that the prevalence varies significantly across different populations due to factors such as age, race, variations in blood transfusion protocols, and the consumption of iron chelators. Recent studies conducted in Iran have provided valuable insights, revealing a prevalence of 3.1% for clinical hypothyroidism and 6.7% for subclinical hypothyroidism. These findings highlight the significance of considering regional and population-specific factors when assessing the prevalence of hypothyroidism in different areas (5-7).

Hypoparathyroidism is one of the endocrine complications in transfusion-dependent thalassemia patients. The leading cause of this complication is iron deposition in the parathyroid gland, which results in its destruction and dysfunction. Studies have shown that hypoparathyroidism is related to increased blood iron levels in these patients (1, 8). This disorder has been reported in 3-20% of patients with thalassemia major (9, 10). In a study conducted in Iran in 2016, the prevalence of hypoparathyroidism in patients with thalassemia major was reported to be 10% (95% CI: 7-10). According to this study, the prevalence of hypoparathyroidism varies in different parts of the country, with 18% in the east, 14% in the west, 12% in the south, 10% in the north, and 3% in the central region (7, 11). Clinical manifestations of hypoparathyroidism vary from asymptomatic forms, mild symptoms such as numb fingers and around the lips, and severe and life-threatening symptoms such as seizures and cardiac arrhythmias. On the other hand, abnormal findings in brain CT scans have been reported in 40% of patients with thalassemia-related blood disorders, even in the absence of hypoparathyroidism symptoms and independently of the severity of the hormonal condition (12). Therefore, early identification and treatment of hypoparathyroidism in transfusion-dependent thalassemia patients require calcium-phosphate screening.

Given the substantial population of transfusion-dependent thalassemia patients in the country and the significant burden posed by endocrine complications associated with this disease, it is crucial to establish a national program aimed at early detection and timely treatment of these complications, including hypothyroidism and hypoparathyroidism. Some of these individuals are asymptomatic in the early stages, making a national program for their early identification and treatment essential. To address this need, a comprehensive guide for diagnosing and treating both complications in these patients has been developed, facilitating regular monitoring of thyroid and parathyroid function. This guide serves as a valuable resource, providing healthcare professionals with accessible and user-friendly information necessary for the accurate diagnosis of hypothyroidism and hypoparathyroidism in transfusion-dependent thalassemia patients. By implementing this guide within the national program, healthcare providers can effectively monitor thyroid and parathyroid function, enabling early intervention and appropriate treatment for affected individuals. This proactive approach to managing hypothyroidism and hypoparathyroidism in thalassemia patients will help alleviate the burden of endocrine complications and improve the overall quality of care provided to this vulnerable population (8, 9).

Given the relatively high prevalence of endocrine complications in transfusion-dependent thalassemia patients in the country, a practical guideline for diagnosing and treating these complications has been designed for general practitioners, internists, and pediatricians.

2. Method and Materials

The authors followed the steps below to develop national practice guidelines for the diagnosis and treatment of hypothyroidism and hypoparathyroidism in thalassemia patients:

A. Defined the scope and purpose of the guidelines:

The scope of the guidelines was defined to assist general practitioners, internists, and pediatricians in diagnosing and treating these complications in thalassemia patients.

B. Reviewed existing literature and guidelines: A comprehensive review of existing literature and guidelines was conducted to ensure that the guidelines were evidence-based and up-to-date.

C. Defined diagnostic criteria: The guidelines clearly defined the diagnostic criteria for each complication, including the tests to be performed, the frequency of testing, and the interpretation of test results.

D. Outlined treatment options: The guidelines provided practical treatment options for each complication, including medications, supplements, monitoring, and lifestyle modifications.

E. Developed algorithms and flowcharts: Algorithms and flowcharts were developed to provide a step-by-step approach to the diagnosis and treatment of these complications in thalassemia patients. These can help healthcare providers make informed decisions and ensure consistency in the management of these complications.

F. Developed practical recommendations: Practical recommendations were developed that can be easily implemented by healthcare providers. These may include dosing recommendations, guidance on patient education, and recommendations for referral to specialists.

By following these steps, the authors were able to develop comprehensive and practical guidelines for the diagnosis and treatment of hypothyroidism and hypoparathyroidism in thalassemia patients. These guidelines can improve the quality of care received by thalassemia patients and help prevent the development of long-term complications.

3. Hypothyroidism

3.1. Hypothyroidism Definition

Clinical indicators of hypothyroidism depend on the severity of the disease. In subclinical cases, the patient has no complaints, and thyroid dysfunction is observed only in laboratory tests performed during patient screening. More severe cases of the disease manifest as short stature, delayed puberty, fatigue, hypothermia, weight gain, constipation, dry skin, and heart failure (4, 5).

The classification of types of hypothyroidism according to the examinations:

1. Subclinical hypothyroidism: which is divided into two parts (6-9):

- Type A with normal FT4 and TSH: 5-10 mIU/ml
- Type B with normal FT4 and TSH > 10 mIU/ml

2. Apparent hypothyroidism(10): with FT4 < 0.8 ng/dL and TSH > 10 mIU/ml

3. Secondary hypothyroidism: with FT4 < 0.8 ng/dL and TSH < 5mIU/L

3.2 Essential recommendations on diagnosis and treatment

Principles of screening and diagnosis (9, 11-16):

1. It is recommended to start screening thalassemia patients for hypothyroidism from the age of 9 years old patients.

2. If disorders in development, growth, and puberty, heart failure, or clinical symptoms indicating hypothyroidism are observed, the screening should be initiated earlier in life.

3. The examination should be done at a younger age in patients whose ferritin level is higher than 1500 µg/L.

4. If the thyroid tests are normal, the examination should be continued annually.

5. Screening by conducting TSH, free T4 tests.

6. If the laboratory tests are in the sub-clinical range, they should be repeated in 1-2 months.

7. If free T4 standard and TSH is in the range of 5-10 mIU/ml, the patient should be evaluated regarding iron chelators and blood ferritin levels. Thyroid tests should be repeated in the next 4-6 months. If the thyroid disorder is corrected, screening continues, and if TSH is >10 mIU/ml, treatment with levothyroxine should be initiated.

8. In patients with sub-clinical hypothyroidism (recommendation in part 7) who do not meet the criteria to start treatment, screening continues every six months with TSH and free T4 levels examination.

9. If free T4 is normal and TSH is 5-10 mIU/ml, and the patient shows any of the following symptoms, treatment with levothyroxine should be initiated:

- Height growth disorder: In cases where the growth curve plateaus or the growth rate falls below 5-6 centimeters per year while initiating levothyroxine treatment, it is advisable to refer the patient to a pediatric or adult endocrinologist.
- Presence of goiter in clinical examination
- Positive Anti-TPO
- Pregnancy intention
- Infertility

10. Initiate treatment with levothyroxine if free T4 is normal and TSH > 10 mIU/ml.

11. If FT4 < 0.8 ng/dl and TSH > 10 mIU/ml, the patient has apparent hypothyroidism and treatment

with levothyroxine should be started.
12. If FT4 < 0.8 ng/dl and TSH < 5mIU/ml, the patient may have central hypothyroidism and should be referred to an endocrinologist.
13. Candidates for levothyroxine treatment must have normal echocardiography and no signs of adrenal insufficiency (such as significant weight loss); If there is any doubt about the existence of cardiac disorder or adrenal insufficiency, the patient should be referred to a cardiologist or endocrinologist before starting levothyroxine(17).
14. An endocrinologist should be consulted if a patient consumes drugs that interfere with thyroid function (such as amiodarone, lithium, and biotin) (refer to **Figure 1**).

3.3. Principles of treatment

3.3.1 Drug and Dosage

Levothyroxine dosage adjustment criteria:
✓ Levothyroxine is usually started with a daily dose of 12.5 micrograms.

✓ Dosage based on age:
- 1-3 years old: 4-6 µg/kg
- 3-10 years old: 3-5 µg/kg
- 10-16 years old: 2-4 µg/kg
- >16 years old: 1.6 µg/kg

✓ Essential factors in dose determination:
- Age
- Weight
- Cardiovascular health conditions
- Severity and time-duration of hypothyroidism

✓ Levothyroxine interactions include the following:
- Iron, aluminum, calcium, statin, pantoprazole.

✓ There should be at least 4-hour intervals between taking these drugs and levothyroxine.

3.3.2. Follow-up:

1. Dose adjustment is performed by regular monitoring of TSH. TSH levels should be monitored every 6-8 weeks.
2. TSH should be in the range of 0.5-2.5 mIU/ml.
3. Lack of control can lead to a change in dose to 12.5-25 micrograms.
4. After each dose change, the TSH level should be rechecked at an interval of 4-6 weeks.
5. When reaching the therapeutic target range and stabilization of TSH, the examination should be repeated every 6-12 months.

3.4 Thalassemia therapists with qualifications approved and introduced by universities of medical sciences to prescribe and provide services:

- Hematology and oncology specialist for children/ adults
- Pediatrician
- Internal specialist
- General Physician

4. Hypoparathyroidism

4.1. Hypoparathyroidism Definition

Hypoparathyroidism refers to cases where:
- The corrected calcium level is less than the standard range (normal range: 8.5-10.2 mg/dl), and the Parathyroid Hormone (PTH) level is low (PTH < 20 pg/ml)
- Phosphorus is high or within the upper limit of the normal range (normal range: 2.5-4.5 mg/dl). This criterion can aid in diagnosing hypoparathyroidism, but it is not a definitive diagnosis.

4.2 Critical diagnostic and treatment recommendations

Principals of screening and diagnosis:
1. It is recommended to initiate screening patients with thalassemia major for hypoparathyroidism from age ten.
2. Screening includes the following:
a. Evaluation of calcium levels every six months
b. Annual vitamin D evaluation
c. Annual PTH evaluation
3. Evaluating the total calcium and adjusting the measured calcium level with albumin is recommended.
4. Calculation of the effect of albumin on total calcium is done as follows: for every 1g/dl decrease in albumin from 4 g/dl, add 0.8 mg/dl to the measured calcium. For instance, if the calcium level is 7 mg/dl and the Albumin level is 3 g/dl, the corrected calcium will be 7.8 mg/dl.
5. PTH, phosphorus, vitamin D, and albumin should be evaluated in cases where calcium is low.
6. When calcium and PTH abnormalities are observed, examinations should be repeated two weeks later.
7. When the calcium level is below 7 mg/dl or severe hypocalcemia symptoms are present (such as numbness of the fingers and around the lips, carpopedal spasm, or seizures), the patient should be immediately treated with intravenous calcium.
8. Patients diagnosed with hypoparathyroidism should

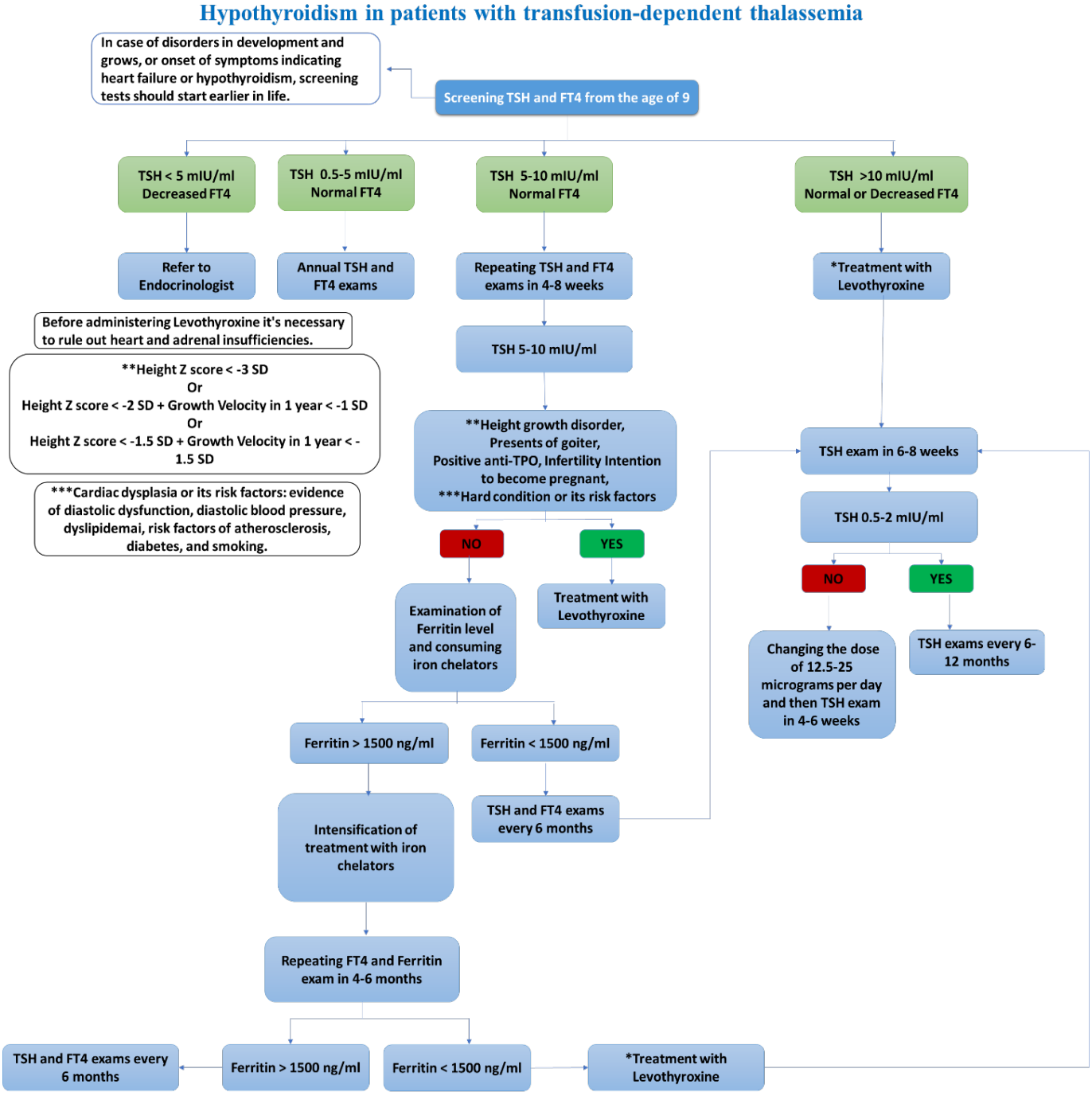

Figure 1. Diagnosis criteria and treatments of hypothyroidism in transfusion-dependent thalassemia

be referred to an endocrinologist, internal medicine specialist, or pediatrician (refer to **Figure 2**).

4.3. Treatment

4.3.1. Treatment objectives:

1. Management of hypocalcemia symptoms.
2. Prevention of acute and chronic complications of hypocalcemia.
3. Maintaining the plasma calcium levels within the lower normal to normal range (8-9 mg/dl).
4. Maintaining the phosphorus levels within the normal range.
5. Maintaining the calcium-phosphorus product below 55 mg/dl.
6. Maintaining 24-hour urine collection calcium levels below 300 mg to prevent nephrocalcinosis, nephrolithiasis, and tissue calcification.

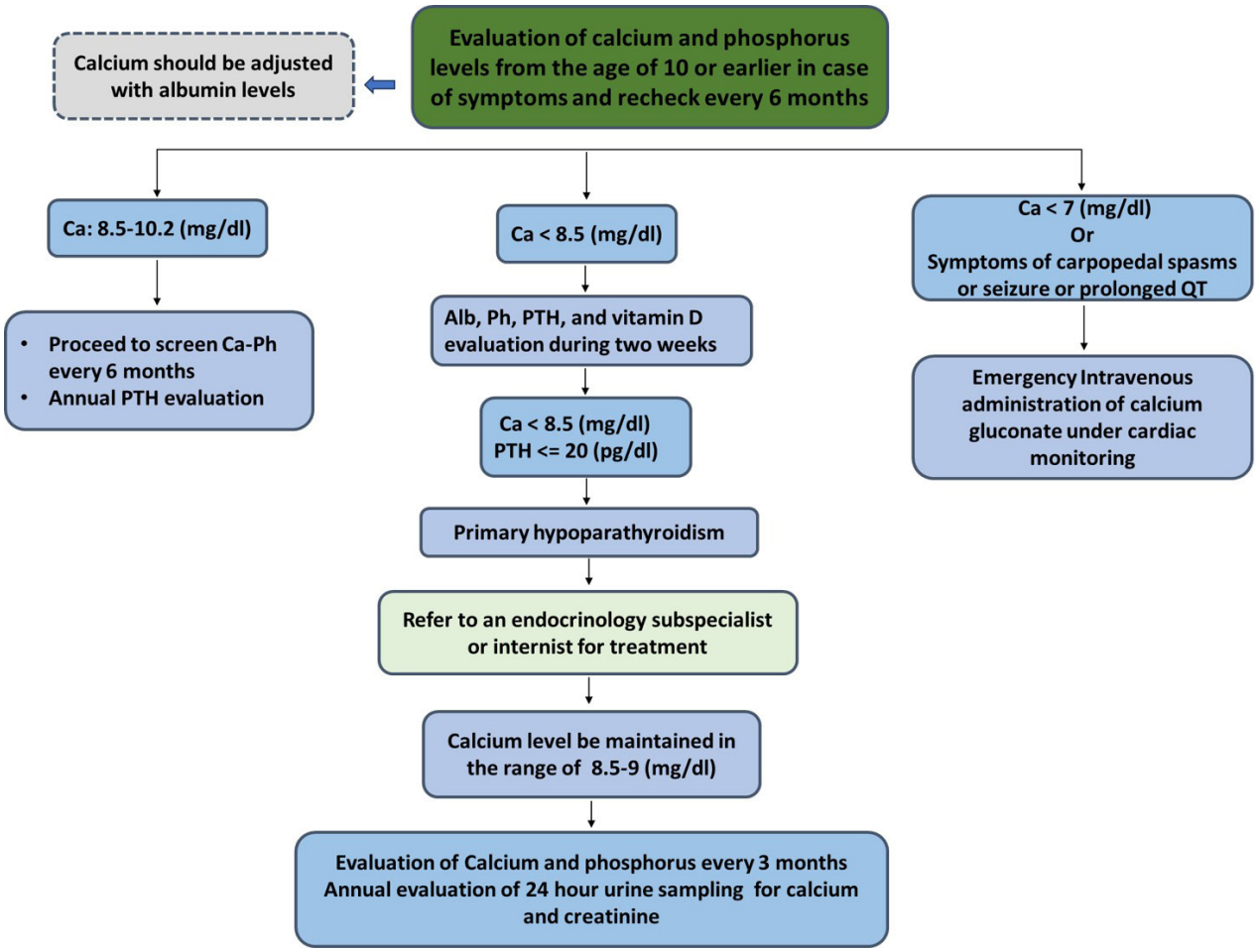

Figure 2. Diagnosis criteria and treatment of hypoparathyroidism in transfusion-dependent thalassemia

4.3.2. Principles of Treatment

1. When severe and acute hypocalcemia symptoms are present, one or two vials of 10% calcium gluconate, containing 90-180 mg elemental calcium, should be added to 50cc of 5% dextrose infusion and administered intravenously over 20 minutes. This treatment should be followed by a calcium infusion of 0.5-1.5 mg/kg/h over 8 hours. Consequently, the calcium level should be evaluated. It should be noted that the treatment of severe hypocalcemia should be performed under the supervision of an internal medicine specialist with cardiac monitoring.

2. Oral calcium carbonate should be prescribed at a dose of 1-6 grams daily based on the calcium level (In patients with achlorhydria or using proton pump inhibitors (PPIs) such as omeprazole or pantoprazole, calcium citrate should be prescribed).

3. Calcitriol (the active form of vitamin D) should be prescribed at a dose of 0.25-1 μ/day once or twice a day.

4. The patient should be referred for further evaluation if the plasma phosphorus level remains elevated (above 6mg/dl) despite a low phosphorus diet.

Note:

• The diet of patients with hypoparathyroidism should be rich in calcium (dairy products and vegetables) and low in phosphorus (eggs and meat).

• If the patient develops increased urine calcium excretion (more than 300 mg/day in adults and more than 4 mg/kg/day in children) during treatment, they should be referred to an endocrine specialist.

4.3.3. Principles of Follow-up

1. Calcium levels should be evaluated weekly or at shorter intervals as determined by the physician until the medication dosage is adjusted.

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2. After medication adjustment, calcium and phosphorus levels should be checked every three months.

3. 24-hour urine collection calcium and creatinine levels and GFR should be evaluated every six months.

4. When nephrocalcinosis or nephrolithiasis is suspected, the patient should be referred to an endocrine specialist, internal medicine specialist, or pediatrician

4.4. The characteristics of physicians who are qualified and recommended by medical universities to treat thalassemia are as follows:

- Pediatric and adult hematology and oncology subspecialists
- Pediatric and adult endocrinology subspecialists
- Pediatricians
- Internists
- General practitioners

5. Conclusion

In conclusion, hypothyroidism and hypoparathyroidism are common endocrine complications in thalassemia patients, particularly blood transfusion-dependent patients. These complications can result from iron accumulation in the thyroid and parathyroid glands, leading to dysfunction and a range of symptoms. Early detection and treatment of these complications are crucial to improving thalassemia patients' overall quality of life. A comprehensive approach, including regular monitoring of thyroid and parathyroid function, appropriate therapies, and iron chelators, can help alleviate the burden of these complications and improve outcomes for these patients. A practical guideline for the diagnosis and treatment of these complications can provide healthcare professionals with accessible and user-friendly information necessary for the accurate diagnosis of hypothyroidism and hypoparathyroidism in transfusion-dependent thalassemia patients. By implementing this guide within a national program, healthcare providers can effectively monitor thyroid and parathyroid function, enabling early intervention and appropriate treatment for affected individuals. This proactive approach to managing hypothyroidism and hypoparathyroidism in thalassemia patients will help alleviate the burden of endocrine complications and improve the overall quality of care provided to this vulnerable population.

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Conflict of Interest

The authors declare no conflicts of interest.

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