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- Selective review/update that is evidence-based, current, and practical.
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TITLE

A Comparison of Therapeutic Regimens in the Treatment of Hypothyroidism.

ABSTRACT

Hypothyroidism is a chronic medical condition that results in the inadequate production of thyroid hormones. Thyroid hormones are essential for the metabolism of almost every organ in the body. The prominent symptoms of hypothyroidism include lack of energy, weight gain, constipation, and intolerance to cold temperatures. Medical therapies aim to replenish thyroid hormones enough to meet the body's metabolic demands. Unfortunately, many individuals experience persistent symptoms despite stable thyroid hormone levels. Current treatment options for hypothyroidism include Levothyroxine, Liothyronine, and Desiccated Thyroid Extract (DTE). Levothyroxine contains synthetic T4 and is the current gold-standard medical therapy in hypothyroid patients. Liothyronine, synthetic T3, can be added to Levothyroxine to improve symptomatology. DTE is a natural form of T3 and T4 and the historical first-line medical treatment. Combination therapy with Liothyronine or DTE is an option for symptomatic euthyroid patients on Levothyroxine monotherapy. Unfortunately, most primary care providers do not feel comfortable managing alternative regimens. This article’s focus is to review hypothyroidism treatment modalities while discussing their efficacy and reviewing current practice guidelines.

Keywords: Hypothyroidism, thyroxine, triiodothyronine, T3, T4, desiccated thyroid extract, levothyroxine, and liothyronine.

LEARNING OBJECTIVES

- Review the pathophysiology and most common etiologies of hypothyroidism encountered in primary care.
- Compare the efficacy and patient preference of Levothyroxine, Liothyronine, and Desiccated Thyroid Extract in the treatment of hypothyroidism.
- Review the current primary care guidelines and dosing regimens for prescribing Levothyroxine, Liothyronine, and Desiccated Thyroid Extract.

INTRODUCTION

Hypothyroidism results when the thyroid gland produces inadequate amounts of the thyroid hormones thyroxine (T4) and triiodothyronine (T3).[1,2] Hypothyroidism is a prevalent chronic medical condition, affecting 3-7% of people in the United States.[1] Thyroxine is a prohormone that converts into bioactive triiodothyronine in the peripheral tissue.[2] Primary hypothyroidism often occurs when autoantibodies form against thyroid peroxidase and thyroglobulin.[3] When the anterior pituitary gland (APG) fails to release thyroid-stimulating hormone (TSH) in response, the resulting pathology is secondary hypothyroidism.[3,4] Tertiary hypothyroidism results when there is an impaired release of thyrotropin-releasing hormone (TRH) from the hypothalamus.[4] Hypothyroidism treatment begins with the initiation of Levothyroxine monotherapy.[1,5] Less traditional treatment regimens include combination therapy with Liothyronine or Desiccated Thyroid Extract (DTE).[1,5] Levothyroxine, synthetic T4, is the first-line medical treatment for hypothyroidism.[1,5] Liothyronine contains synthetic T3 and is used as add-on therapy to help manage symptoms.[1] DTE is a combination therapy that contains T3 and T4 thyroid hormones.[1] It is important to note that patients and medical professionals often use combination therapy with DTE to help improve symptoms and quality of life.[5] This article's

purpose is to discuss current practice guidelines and medical regimens used to treat hypothyroidism. Additionally, the efficacy of these regimens will be compared in terms of TSH stability, symptom management, and patient preference. This article hopes to provide primary care clinicians with the knowledge to manage combination therapy in symptomatic hypothyroid patients. Clinicians must feel comfortable managing alternative regimens, especially in rural communities with limited access to specialty care.

PATHOPHYSIOLOGY

Thyroid hormone release is self-regulated through a negative feedback mechanism containing the hypothalamus, anterior pituitary gland (APG), and thyroid gland.[4] These organs form the hypothalamus-pituitary-thyroid (HPT) axis, which controls the metabolism of nearly every organ in the body.[4] The hypothalamus produces and secretes thyrotropin-releasing hormone (TRH) in response to circulating T3 levels.[4] TRH reaches the APG, which leads to the formation and excretion of thyroid-stimulating hormone (TSH).[4] TSH is released from the APG into the bloodstream and travels to the thyroid gland.[4] Once TSH reaches the thyroid gland, it attaches to the TSH receptors on the follicular cells.[4] In response to TSH, the follicular cells produce the protein thyroglobulin.[4] Thyroid hormone (T3 and T4) production occurs when thyroid peroxidase (TPO) combines thyroglobulin with iodine.[4] Once produced, the thyroid hormones travel throughout the bloodstream interacting with the lungs, heart, and skeletal muscle.[4] The primary function of thyroid hormones is to provide thermoregulation while increasing the body's basal metabolic rate.[4] Reduced thyroid hormone levels lead to the characteristic symptoms of fatigue, weight gain, bradycardia, constipation, dry skin, and cold intolerance.[4]

Primary hypothyroidism often results from an autoimmune attack on the thyroid gland.[3,4,6] Autoantibodies develop against TPO, leading to decreased production of thyroid hormones.[3,4,6] Primary hypothyroidism can also lead to the formation of antibodies targeting the protein thyroglobulin.[3,4,6] This characteristic autoimmune attack on the thyroid gland is termed autoimmune thyroiditis or Hashimoto's thyroiditis.[3,4,6] Genetic and environmental factors play a role in the underlying etiology of autoimmune thyroiditis.[3,4,6] Primary hypothyroidism can result from thyroid gland removal, iodine deficiency, radioactive iodine treatment, and medication side effects (e.g., amiodarone, lithium, thalidomide, and many more).[3,6]

Secondary and tertiary hypothyroidism occurs when there is an impaired release of hormones from either the anterior pituitary gland (APG) or hypothalamus.[4] Secondary hypothyroidism is defined as an impaired release of TSH from the APG, while tertiary hypothyroidism is from the impaired release of TRH from the hypothalamus.[4] The most common etiology of secondary and tertiary hypothyroidism is a tumor of the APG or hypothalamus.[4] Most of these tumors impair the release of TRH or TSH, leading to reduced thyroid hormone production from the thyroid gland.[4] The end result is reduced thyroid hormone production leading to a diagnosis of hypothyroidism.

DIAGNOSIS

Diagnosing hypothyroidism is based on serum levels of TSH and thyroid hormones.[3,4] Primary hypothyroidism is diagnosed with an elevated TSH and reduced serum free-T4 level.[3,4,6] To confirm the diagnosis, clinicians may test for antibodies against TPO and thyroglobulin.[3,4,6] Etiologies related to thyroid gland removal/destruction will not show autoantibody development.[3,4,6] A diagnosis of secondary hypothyroidism results when both the TSH and thyroid hormone levels are low.[4] Low TSH and thyroid hormone levels occur when the APG

fails to release TSH in response to thyrotropin-releasing hormone (TRH) levels.[4] Finally, the diagnosis of tertiary hypothyroidism will lead to reduced TSH and thyroid hormone levels.[4] The inability of the hypothalamus to produce TRH results in decreased TSH release and thyroid hormone production.[4] Serum T3 levels may be helpful in some cases but are usually not necessary to diagnose hypothyroidism.[3,4]

MANAGEMENT

Three primary treatments are used to manage hypothyroidism: Levothyroxine, Liothyronine, and Desiccated Thyroid Extract. These medical regimens aim to supplement deficient hormones by using synthetically made hormones identical to T3 and T4 produced by the thyroid gland, most notably T4.

Desiccated Thyroid Extract (DTE) was first developed in the 1880s but became the treatment of choice for hypothyroidism in the early 1990s.[7] DTE is derived from pig thyroid gland tissue and contains the same T3 and T4 hormones found in humans.[1] Once produced, DTE contains mostly T4 with a concentration ratio of 4:1.[1] Concerns regarding DTE therapy include issues with batch potency, standardization of hormone concentration, and manufacturer oversight.[1] DTE remains outside of FDA approval as it predates the Food, Drug, and Cosmetic act of 1938.[1] Despite this, studies have concluded that DTE is a safe and effective treatment regimen for hypothyroidism.[1,5,7]

Levothyroxine is a form of synthetic T4 hormone identical to that produced by the thyroid gland.[7] Levothyroxine is the current gold-standard medical regimen when treating hypothyroidism.[7] In the 1970s, Levothyroxine became the treatment of choice due to its safety, effectiveness, affordability, predictable bioavailability, uniform potency, and absorption.[1,7] Also, Levothyroxine was found to provide stability in T4 levels while restoring T3 levels in the

body.[1,5] It is thought that normalization of TSH with Levothyroxine results in symptom resolution while reducing mortality associated with untreated hypothyroidism to that of the general population.[1,8] Concerns related to Levothyroxine include inadequate supplementation of T3, poorly controlled symptomatology, average weight gain (10 pounds), reduced metabolism, and higher cholesterol levels (total and LDL).[1,3]

Liothyronine, synthetic T3, is a medication used as add-on therapy with Levothyroxine monotherapy.[1] Combination therapy of Levothyroxine and Liothyronine aims to increase T3 levels in the body and improve symptoms.[1] Some international thyroid associations recommend a trial of T4 and T3 combination therapy for those who fail to benefit from Levothyroxine monotherapy.[1] Current concern about T3 combination therapy includes its rapid absorption, peak effect in 2-3 hours, and short half-life.[1,3] Additionally, excessive T3 treatment can lead to hypertriiodothyroninemia and symptoms of hyperthyroidism.[1] Having such quick absorption makes it challenging to assess serum T3 levels in the body.[1] For this reason, there is a need for strict guidelines and multiple serum measurements to determine serum T3 levels adequately.[1]

EFFICACY OF THYROID REPLACEMENT THERAPY

When comparing the efficacy of hypothyroid regimens, it is essential to consider TSH stability and normalization. Proper supplementation of thyroid hormones will result in a TSH level within the normal reference range of 0.320-5.500 μIU/mL.[5] Given this broad reference range, it is essential to consider whether higher or lower TSH levels impact an individual's quality of life and symptomatology. For instance, researchers have found that varying TSH levels, while managed on Levothyroxine, did not lead to changes in mood, quality of life, or cognitive function.[9] Regardless, participants preferred a higher dose of Levothyroxine despite measurable benefits.[9] Additionally, there is some concern that Levothyroxine does not

adequately supplement T3 to levels of the general population.[1] For example, researchers have found that Levothyroxine over supplements T4 by 12% while under-supplementing T3 by 10%.[1] Given initial concerns about DTE and batch-to-batch variability, it is essential to note that researchers have found equivocal TSH stability when compared to Levothyroxine.[5] Three-year stability for both medications is approximately 80%, meaning there are fewer fluctuations in thyroid hormone concentrations over time.[5] Having little TSH variability is essential to achieve therapeutic thyroid hormone levels for adequate basal metabolism and symptom management. Researchers have also found less variability in TSH values when managed on Levothyroxine monotherapy.[5] Of note, DTE therapy results in a one-unit lower TSH value, which might provide evidence for the perceived quality of life improvement seen on this regimen.[5]

Patient preference is also essential to consider when managing hypothyroid patients. Studies have revealed that symptomatic hypothyroid patients often prefer a regimen that supplements T3 because T3-containing regimens are associated with lower body weight and weight loss compared to Levothyroxine.[7,10] Additionally, combination therapy has been found to stabilize the TSH without any additional side effects.[1] Researchers have also found that combination therapy does not increase morbidity and mortality related to heart disease, cardiac arrhythmias, and fractures compared to monotherapy.[1] Unfortunately, the response to T3-containing regimens is variable and depends on genetics, environmental factors, and medical comorbidities.[7] Specifically, certain enzymes and transporter genes are associated with improved responses to T3-containing therapies.[9] Studies have also revealed no statistically significant difference in the quality of life on DTE compared to Levothyroxine.[10] Despite this, there is a perceived improvement in well-being, symptomatology, and preference for management with

DTE.[10,11] When listing patient preference combination therapy with DTE is first, Liothyronine second, and then Levothyroxine monotherapy.[1,5]

DISCUSSION

SUMMARY OF EFFICACY:

Levothyroxine, DTE, and Liothyronine are safe and effective therapies used to treat hypothyroidism.[7] Current guidelines suggest that symptomatic individuals trial combination therapy.[1] Combination therapy can be achieved by combining synthetic T4 and T3 or solely using DTE as monotherapy.[1] Combination therapy is recommended in these populations due to concerns regarding inadequate supplementation of T3 when managed on Levothyroxine monotherapy.[1] DTE is a combination therapy that can be used instead of Levothyroxine and Liothyronine.[1] It is essential to note that DTE stabilizes TSH without any increased side effects compared to other regimens.[1,5] DTE is a desirable alternative therapy because it provides a subjective improvement in quality of life and symptom management.[10] It is important to note that symptomatic individuals managed on monotherapy prefer treatment with DTE mainly due to its side effect of weight loss.[10]

REVIEW OF GUIDELINES:

Newly diagnosed hypothyroid individuals should follow current guidelines, which recommend synthetic T4 replacement with Levothyroxine monotherapy.[1,3] Daily dosing of Levothyroxine needed to achieve TSH stability is based on weight and is calculated at 1.5 to 1.8 μg/kg.[1,3] Patients with coronary artery disease should be initiated on 12.5-25 μg of Levothyroxine daily.[3] Levothyroxine is best absorbed when taken 30-60 minutes before the morning meal.[3] A medical provider should gradually increase or decrease the Levothyroxine dose as necessary to achieve TSH stability and normalization.[1,3] Whenever the Levothyroxine

dose changes, the TSH level should be re-measured in 4-12 weeks to determine if supplementation is adequate.[3] Providers choosing a tighter TSH goal should continue with Levothyroxine monotherapy as there is less TSH variability.[5] Combination therapy with T3 supplementation is an option for symptomatic individuals that are euthyroid on Levothyroxine monotherapy.[1] Before initiating combination therapy, evaluating individuals for other possible etiologies of their symptoms is essential.[1] When starting combination therapy, the daily dose of Levothyroxine is decreased by 25 μg, and Liothyronine is started at 2.5-7.5 μg once or twice daily.[1] This algorithm allows for adequate T3 and T4 levels within the reference range and minimal risk of side effects.[1] Appropriate measurement of serum T3 is essential and requires the individual to be fasting with a blood draw approximately three hours after dose administration.[1] DTE is another combination therapy used in managing symptomatic hypothyroid individuals.[1] Normal TSH levels typically occur when DTE supplements 11 μg of T3 daily.[1] When the TSH value is stable within the normal reference range, there are no increased side effects on DTE.[1]

CONCLUSION

Hypothyroidism is an incredibly prevalent medical condition that significantly impacts an individual's quality of life.[1,9] Slowed basal metabolism leads to symptoms of fatigue, cold intolerance, and weight gain.[4] Hypothyroidism management has grown dramatically since the creation of Desiccated Thyroid Extract (DTE) in the early 1800s.[7] The main focus of medical therapies is to supplement deficient thyroid hormones, most notably T4.[1] Levothyroxine, Liothyronine, and DTE are frequently used medical therapies in hypothyroidism. Levothyroxine contains synthetic T4 and is the current gold standard treatment regimen.[1,5] Unfortunately, not all individuals report improvement in symptom management on Levothyroxine monotherapy.[1,9] DTE and Liothyronine are alternative therapies that provide subjective improvement in quality of

life and symptom management.[5] Additionally, combination therapy is safe and effective in managing hypothyroidism without increased side effects.[1,5,7] For this reason, current clinical guidelines recommend a trial of Liothyronine or DTE combination therapy in symptomatic individuals.[1] Despite this, most clinicians do not feel comfortable treating hypothyroidism with alternative regimens. For this reason, clinicians must follow current clinical guidelines and recognize the benefit these regimens offer in terms of quality of life and symptom management.

Needs assessment:

This CME article is essential for publication as most family practice providers do not feel comfortable managing patients on alternative hypothyroid regimens. In addition, rural healthcare providers must be able to manage symptomatic hypothyroid patients when a referral to endocrinology is not feasible. For instance, providers must feel comfortable dosing, adjusting, and monitoring combination therapy with Liothyronine and Desiccated Thyroid Extract.

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TABLE 1: Outline of medical regimens used in the treatment of hypothyroidism.[1,3,5,7]

	Mechanism	Dosing	Benefits	Concerns
Levothyroxine (Gold Standard)	Synthetic T4 hormone.	Initiate Levothyroxine at a dose of 1.5 to 1.8 µg/kg/day.	Safe, effective, affordable, uniform potency, and predictable bioavailability.	Poor supplementation of T3, poorly controlled symptomatology, weight gain, reduced metabolism, and higher cholesterol levels.
Liothyronine	Synthetic T3 hormone.	Decrease Levothyroxine dose by 25 µg daily and initiate Liothyronine at 2.5-7.5 µg once or twice daily dosing.	Increased supplementation of T3 with subjective improvement in symptoms.	Rapid absorption, short half-life, potential for excess T3, and difficulty assessing serum T3 concentrations.
Desiccated Thyroid Extract (DTE)	Natural T4 and T3 hormones (T4:T3 ratio is 4:1).	Initiate DTE at a dose that will supplement 11 µg of T3 daily.	Natural form of thyroid hormones with subjective improvement in symptoms.	No formal FDA oversight, variable batch potency, and difficulty standardizing hormone concentrations.

FIGURE 1: Point of Care Ultrasound (POCUS) of a thyroid gland containing nodules.