

Monotherapy versus Combination Therapy in the Treatment of Hypothyroidism

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Background

disruption in the hypothalamic-pituitary-thyroid pathway but is most often caused by a disease of the thyroid gland.

- This leads to decreased serum levels of T4 and T3 and, due to compensatory mechanisms, increased levels of TSH.
- 5% to 10% of patients will continue to experience hypothyroid symptoms while on L-thyroxine (LT4) monotherapy despite normal TSH and free T4 levels.
- A question remains whether or not patients with persistent hypothyroid symptoms should be treated with a combination therapy, consisting of synthetic liothyronine in addition to

Case Report

- A 38-year-old, Caucasian, female presented with complaint of fatigue, dry skin, irregular periods, and difficulty losing weight.
- Physical exam was unremarkable with the exception of dry skin noted on arms. Pertinent negatives included normal heart rate and rhythm and no thyromegaly or thyroid nodules.
- Complete blood count, complete metabolic panel, TSH level and free T4 level were ordered. CBC, CMP and free T4 labs were unremarkable, TSH was elevated at 6.61 mIU/L.
- Diagnosed with hypothyroidism
- Prescribed levothyroxine 100mcg by mouth daily and recommended follow-up in 4-6 weeks to check TSH and free T4 levels and to evaluate symptoms.

Abstract

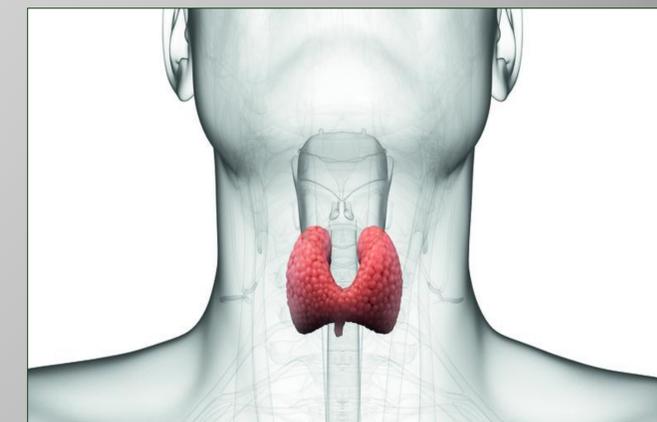
Hypothyroidism is a common disorder in the United States. Most patients will return to an euthyroid state with the use of L-thyroxine. Some, however, will continue to experience hypothyroid symptoms despite the use of L-thyroxine and normal thyroid hormone levels. The clinician may encounter a challenging situation if the patient presents with continued complaint of hypothyroid symptoms, but normal thyroid hormone levels. Controversy remains on whether to treat those who return with persistent hypothyroid symptoms with combination therapy (L-thyroxine plus liothyronine). The literature review discusses current recommendations on the use of monotherapy versus combination therapy for hypothyroidism, including the potential risks and benefits of combination therapy and suggestions for future research.

Literature Review

- The literature review of 11 articles indicates an overwhelming recommendation for the use of LT4 monotherapy for treating hypothyroidism, with the exception of two studies.
- American Association of Clinical Endocrinologists and the American Thyroid Association state those with hypothyroidism should be treated with LT4 monotherapy.
- Several articles noted adverse effects of LT3 which include hyperthyroidism, increase use in antipsychotic drugs, and risk for delayed intellectual development in fetuses when used during pregnancy.
- Potential alternative causes noted for persistent hypothyroid symptoms include diabetes mellitus, pernicious anemia, vitamin deficiencies, obesity, stressful life events, poor sleep habits, depression, and anxiety.
- Several articles stated polymorphisms in the deiodinase type 2 gene (DIO2) may indicate the need for the addition of LT3.
- Limitations in past studies included limited populations studied, small sample sizes, and dosages of LT4:LT3 that were not congruent with natural ratios produced by the thyroid.
- A common recommendation for future studies is to study the effects of extended release LT3 or dosages of three times a day.

Learning Points

- The practice guidelines supported by the American Association of Clinical Endocrinologists and the American Thyroid Association state to use LT4 monotherapy in the routine treatment of hypothyroidism.
- Educate patients about the possible adverse effects related to the use of other-the-counter thyroid supplements due to the potential for exceeding average T4 and T3 levels.
- Though combination therapy is not recommended, it has become more popular in recent years and clinicians may encounter more patients with hypothyroidism on a combination therapy. It is important to discuss the possible risks of combination therapy, especially in those who are pregnant or who are trying to conceive.
- Combination therapy may be considered for those with polymorphisms of DIO2.
- Future randomized controlled studies with the use of extended release LT3 or three times a day dosing is recommended.



References Attached

References

- Duntas, L. H., Wartofsky, L. (2016). There is no 'universal fit': Reflections on the use of L-triiodothyronine in the treatment of hypothyroidism. *Metabolism*, 65, 428-431.
- Escobar-Morreale, H. F., Botella-Carretero, J. I., Morreale de Escobar, G. (2015). Treatment of hypothyroidism with levothyroxine or a combination of levothyroxine plus L-triiodothyronine. *Best Practice & Research Clinical Endocrinology & Metabolism*, 29, 57–75. <http://dx.doi.org/10.1016/j.beem.2014.10.004>
- Foeller, M. E., & Silver, R. M. (2015). Combination levothyroxine + liothyronine treatment in pregnancy. *Obstetrical & Gynecological Survey*, 70(9), 584–586. <https://doi-org.ezproxylr.med.und.edu/10.1097/OGX.0000000000000217>
- Garber, J. R., Cobin, R. H., Gharib, H., Hennessey, J. V., Klein, I., Mechanick, J. I.,...Woeber, K. A. (2012). Clinical practice guidelines for hypothyroidism in adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocrine Practice*, 18(6), 988-1028. Retrieved from <https://www.aace.com/files/final-file-hypo-guidelines.pdf>
- Hennessey, J. V., & Espallat, R. (2018). Current evidence for the treatment of hypothyroidism with levothyroxine/levotriiodothyronine combination therapy versus levothyroxine monotherapy. *International Journal of Clinical Practice*, 72(2), 1. <https://doi-org.ezproxylr.med.und.edu/10.1111/ijcp.13062>
- Jonklaas, J. (2016). Update on the treatment of hypothyroidism. *Current Opinion in Oncology*, 28(1), 18–25. <https://doi-org.ezproxylr.med.und.edu/10.1097/CCO.0000000000000242>
- Jonklaas, J. (2017). Persistent hypothyroid symptoms in a patient with a normal thyroid stimulating hormone level. *Current Opinion in Endocrinology, Diabetes & Obesity*, 24(5), 356–363. <https://doi-org.ezproxylr.med.und.edu/10.1097/MED.0000000000000355>
- Jonklaas, J., Burman, K. D. (2016). Daily administration of short-acting liothyronine is associated with significant triiodothyronine excursions and fails to alter thyroid-responsive parameters. *Thyroid*, 26(6), 770-778.
- Kraut, E., & Farahani, P. (2015). A systematic review of clinical practice guidelines' recommendations on levothyroxine therapy alone versus combination therapy (LT4 plus LT3) for hypothyroidism. *Clinical and Investigative Medicine*, 38(6), E305–E313. Retrieved from <http://ezproxylr.med.und.edu/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=mdc&AN=26654514&site=ehost-live&custid=s9002706>
- Linder, L. M., & Clements, J. N. (2015). Is combination therapy appropriate for hypothyroidism? *Journal of the American Academy of Physician Assistants*, 28(9), 16–19. <https://doi-org.ezproxylr.med.und.edu/10.1097/01.JAA.0000470438.14941.98>
- McAninch, E. A., & Bianco, A. C. (2016). The history and future of treatment of hypothyroidism. *Annals of Internal Medicine*, 164(1), 50–56. <https://doi-org.ezproxylr.med.und.edu/10.7326/M15-1799>
- Ross, D. S. (2019). Disorders that cause hypothyroidism. UpToDate. Retrieved from https://www.uptodate.com/contents/disorders-that-cause-hypothyroidism?search=hypothyroidism%20etiology§ionRank=1&usage_type=default&anchor=H2&source=machineLearning&selectedTitle=1~150&display_rank=1#H2
- Surks, M. I. (2019). Clinical manifestations of hypothyroidism. UpToDate. Retrieved from https://www.uptodate.com/contents/clinical-manifestations-of-hypothyroidism?search=hypothyroidism%20clinical%20manifestations&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2
- Tariq, A., Wert, Y., Cheriya, P., & Joshi, R. (2018). Effects of long-term combination LT4 and LT3 therapy for improving hypothyroidism and overall quality of life. *Southern Medical Journal*, 111(6), 363–369. <https://doi-org.ezproxylr.med.und.edu/10.14423/SMJ.0000000000000823>