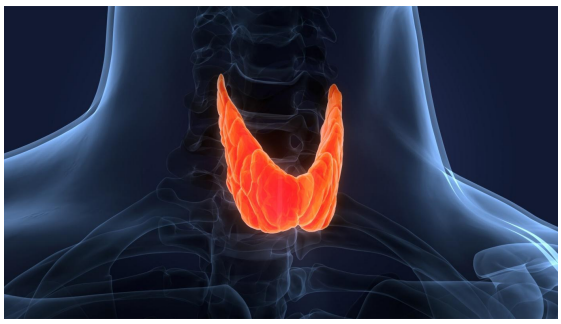
The Conundrum of Subclinical Hypothyroidism

By
Stuart M. Caplen MD
Updated 9/14/22



This article will discuss the entity of subclinical hypothyroidism, looking at some of the complex issues clinicians face with respect to making the diagnosis, deciding whether to initiate treatment, and how effective that treatment will be.

The thyroid gland located in the anterior neck produces three hormones: T4, thyroxine which contains four iodide atoms, T3, triiodothyronine containing three iodide atoms, and calcitonin which is involved in calcium regulation in the body.

T3 and T4 hormones are involved in the control of body metabolism. The release of thyroid hormones is in a feedback loop with the hypothalamus where thyrotropin releasing hormone (TRH) stimulates the pituitary gland to release thyroid stimulating hormone (TSH), also known as thyrotropin, which increases the production and release of T3 and T4 from the thyroid gland. In hypothyroidism when T3 and T4 levels are low more TRH and TSH is released and in hyperthyroidism when T3 and T4 are elevated, TRH and TSH release is reduced. About 20% of T3 is produced in the thyroid gland. T4 is metabolically inactive and is converted to T3 in a process called deiodination to produce the other 80% of needed T3.[1] The deiodination of T4 occurs mainly in the liver and kidneys but also can occur in the central nervous system, pituitary gland, brown adipose tissue and muscle.[2] A small decrease in serum T4 may result in a relatively large increase in serum TSH, which can elevate the serum TSH level while T4 levels are still within the normal range.[3] When people are floridly hypothyroid there is little debate about the need for treatment. **However, in subclinical hypothyroidism where TSH levels are elevated with normal T3 and T4 levels, the decision to treat or not treat is more complex.** The TSH elevation in subclinical hypothyroidism indicates a relative lack of thyroid hormone in the body which requires more TSH to be released which stimulates the thyroid gland to produce and release more hormones to maintain normal T3 and T4 levels. Even though the T3 and T4 levels may be normal, some patients with subclinical hypothyroidism will have adverse symptoms.

The prevalence of subclinical hypothyroidism varies among populations and ranges from 3% to 15%.[3] There is a higher prevalence of between 8% and 18% in adults over 65 years of age.[4] The conversion from subclinical hypothyroidism to overt hypothyroidism is about 2% to 6% per year, and is more likely in the elderly, women, people with higher TSH levels, the presence of thyroid antibodies, people with a low-normal T4 level,[3] high iodine intake or who have a goiter.[5] Up to 46% of patients

found to have an isolated elevated TSH level will revert back to normal within two years.[3] In asymptomatic patients with an elevated TSH, it is recommended to get a repeat TSH level in two to three months before making a diagnosis of subclinical hypothyroidism due to the high number of people who spontaneously revert back to normal.[3]

Causes of subclinical hypothyroidism in the adult include; chronic autoimmune thyroiditis (Hashimoto's disease), treated hyperthyroidism (Grave's disease), radiation to the neck, iodine deficiency, medications such as lithium, iodine, amiodarone or antithyroid drugs, infiltrative diseases, such as amyloidosis, sarcoidosis, or hemochromatosis,[5] idiopathic hypothyroidism, and hypopituitarism causing secondary hypothyroidism.[6] Hashimoto's disease is thought to be responsible for 60% to 80% of cases.[5]

Symptoms of Subclinical Hypothyroidism

Up to 70% of patients with subclinical hypothyroidism feel normal without any symptoms of hypothyroidism,[5] but some do present with mild symptoms, such as fatigue, muscle weakness, weight gain, cold intolerance, constipation, dry skin, puffy eyes or some reduction in cognitive function and memory.[3] Overt hypothyroidism can cause peripheral neuropathy, but the evidence for causation in subclinical hypothyroidism is mixed.[7,8] However, there are some studies that found symptoms of diabetic neuropathy are worsened in patients with subclinical hypothyroidism.[9,10]

A literature review of the cardiac effects of subclinical hypothyroidism found that as TSH levels increased so did the number of adverse cardiac events, although it did not increase mortality. Coronary events were highest in subclinical hypothyroidism patients with TSH levels between 10 and 19.9 mIU/L (milli-international units/liter).[11] In a literature review, patients with subclinical hypothyroidism were found to be at higher risk for congestive heart failure, especially those with levels over 10mIU/L.[12] Subclinical hypothyroidism is known to increase total cholesterol and low-density lipoprotein (LDL) levels.[3]

An analysis of subclinical hypothyroidism and stroke found no overall increase in events in the total group but there was an increased risk of stroke in adult patients with subclinical hypothyroidism under 65 years of age.[13]

Subclinical hypothyroidism may increase the risk of female infertility, spontaneous abortion, gestational hypertension and preeclampsia. Normal values for TSH and T4 are altered during pregnancy.[3]

Laboratory Testing

Subclinical hypothyroidism is defined as a serum TSH over the reference range with a normal T4 level. Over 99% of T3 and T4 are bound to protein in the body and inactive biologically.[14] The preferred test is free T4 to measure the biologically active levels of the hormone rather than total T4 which includes the inactive protein bound portion. Conversely, in pregnancy measurement of total T4 is recommended because alterations in serum proteins may yield lower values of free T4 based on reference ranges established with normal non-pregnant individuals.[15] There is a consensus recommendation that T3 levels are not needed for the diagnosis of hypothyroidism and do not need to be drawn.[15]

The normal values may vary slightly depending on the laboratory, but the reference range for free T4 (ages 20 and older) is 0.8-1.8 ng/dL (nanograms/deciliter) used by one national laboratory.[16] Total T4 normal values in females (over 20 years of age) are 5.1-11.9 mcg/dL (micrograms/deciliter).[17]

The TSH reference range for patients ages 20 and older is 0.40-4.50 mIU/L,[18] although one consensus guideline recommends 4.12 mIU/L as the upper limit of normal.[15] In pregnancy the TSH reference ranges are much lower than in nonpregnant women with the first trimester reference range being 0.26-2.66 mIU/L, second trimester 0.55-2.73 mIU/L, and third trimester 0.43-2.91 mIU/L.[18]

It should be noted that some authorities have recommended lowering the upper limit of normal of TSH to 3.0 mIU/L. The arguments for doing that is that the mean and median values of approximately 1.5 mIU/L are much closer to the lower limit of the reported normal reference range than the upper limit, and the distribution of TSH values used to establish the normal reference range is skewed to the right by values over 3.0. The arguments against lowering the upper limit of a normal TSH is that it would lead to more than 10 million additional diagnoses of hypothyroidism in the United States per year, without any clear-cut benefit, and many of those patients would not actually have subclinical hypothyroidism.[15]

Thyroid peroxidase antibodies are antibodies of an enzyme involved in the synthesis of thyroid hormones. Patients who have these antibodies are more likely to progress to overt hypothyroidism compared to those that don't; 4.3% per year in the antibody positive group versus 2.6% per year in subclinical hypothyroidism patients without antibodies.[15] Thyroid peroxidase antibodies may be seen in Hashimoto's thyroiditis as well as idiopathic myxedema and Graves' disease (hyperthyroidism).[3,19]

Thyroglobulin antibodies are antibodies to a thyroid protein used to make thyroid hormones, and a correlation between elevated levels of these antibodies and symptoms of hypothyroidism has been found.[20] This test is more commonly used in thyroid cancer screening as elevated thyroglobulin levels are used to screen for cancer

reoccurrences, and the presence of antibodies may make the test inaccurate.[21] Thyroglobulin antibodies are not as sensitive as thyroid peroxidase antibodies for subclinical hypothyroidism testing.[15]

High dose **biotin supplementation** has been found to interfere with some thyroid immunoassay testing and can falsely elevate T4 and T3 levels and falsely decrease TSH levels.[22,23] It is recommended that patients stop biotin at least two days before testing to prevent spurious values and misdiagnosis.[22,24] Biotin supplementation is not uncommon. In one study of emergency department patients, 7.7% of the subjects were taking biotin supplements and 7.4% had serum concentrations at or above the lowest known threshold for biotin interference with thyroid testing.[25]

Does Treatment Help?

What is the evidence that treatment will help patients with subclinical hypothyroidism?

There is strong evidence that early treatment will prevent onset of more severe symptoms if the patient progresses to overt hypothyroidism. There is strong evidence that treatment of subclinical hypothyroidism will improve symptoms of hypothyroidism especially with TSH levels over 10 mIU/L. There is moderate evidence that treatment will reduce total cholesterol and LDL levels but it is not certain whether this decreases the risk of a cardiovascular event. There is only weak evidence of a benefit to prevent strokes, CHF, cognitive decline, and coronary heart disease in TSH levels less than 10 mIU/L. The evidence for reduction of congestive heart failure and coronary artery disease is stronger for TSH levels above 10 mIU/L.[3] A Cochrane systematic review of the literature concluded that there was no survival benefit, reduced cardiovascular morbidity or improvement in health-related quality of life for subclinical hypothyroidism patients treated with levothyroxine. There was some evidence that treatment improved lipid profile parameters and left ventricular function.[26] A trial of elderly patients with subclinical hypothyroidism comparing levothyroxine versus placebo found no symptomatic benefits in the treatment group over placebo.[27]

Treatment recommendations

Most sources base treatment recommendations for subclinical hypothyroidism on the amount of TSH elevation, patient symptoms and age. The American Thyroid Association and the American Association of Clinical Endocrinologists guidelines for elevated TSH levels under 10mIU/L state that treatment should be individualized, and recommend treating subclinical hypothyroidism only if the patient has symptoms of hypothyroidism, is positive for thyroid peroxidase antibodies, or has evidence of atherosclerotic cardiovascular disease, heart failure, or major cardiac risk factors. The rest should be followed and treatment started as needed. For TSH levels over 10mIU/L the consensus is to start thyroid replacement treatment.[15]

There are slightly different recommendations from the European Thyroid Association (ETA) based on age. With TSH levels less than or equal to 10 mIU/L, they recommend that geriatric patients, especially those over 80 years of age without specific signs of hypothyroidism can be followed with careful follow-up with a wait-and-see strategy trying to avoid hormonal treatment if possible. The ETA also recommends lower treatment target TSH levels of 0.4 to 2.5 mIU/L for adult patients less than 70 years of age, and a higher TSH target range of 1 to 5 mIU/L for patients over 70 years old.[28]

In pregnancy, treatment for subclinical hypothyroidism is recommended at lower TSH levels. There are questions of whether subclinical hypothyroidism can impair intellectual and psychomotor development in the fetus and increase miscarriages.[15] A meta-analysis and systemic review of 18 studies concluded that subclinical hypothyroidism patients were at higher risk for pregnancy loss, placental abruption, premature rupture of membranes, and neonatal death compared with euthyroid pregnant women, but the effects of replacement therapy were uncertain in preventing these complications.[29]

Treatment Options

Levothyroxine (T4) is considered the drug of choice for subclinical hypothyroidism. Because of differences in the biologic availability of various levothyroxine products, switching between different levothyroxine products should be avoided in patients whose condition is stable. Levothyroxine should be taken on an empty stomach with water 30-60 minutes before breakfast or at bedtime at least 4 hours after the last meal.[3,15]

Liothyronine is a manufactured form of the triiodothyronine (T3) and is sold individually and in a combination pill with levothyroxine, and is not generally recommended for treating subclinical hypothyroidism, as there is no evidence supporting a benefit over using levothyroxine alone.[15,28]

Combination Therapy

Desiccated Thyroid is made from the thyroid gland of animals and contains both T3 and T4. It was in use before levothyroxine was available and is still available today. The ratio of T4 to T3 may vary in desiccated thyroid preparations by brand and whether it is of porcine or bovine origin,[15] and T3 levels vary substantially throughout the day in those taking desiccated thyroid.[30] The American Association of Clinical Endocrinologists and the American Thyroid Association guideline, based on expert opinion, states that “There is no evidence to support using desiccated thyroid hormone in preference to L-thyroxine monotherapy in the treatment of hypothyroidism and therefore desiccated thyroid hormone should not be used for the treatment of hypothyroidism”.[15]

However, a small study of 70 patients comparing desiccated thyroid to levothyroxine found 48.6% of patients preferred the desiccated preparation compared to 19% who preferred T4 monotherapy. Subjects reported subjective increases of concentration, memory, sleep, decision-making capability, happiness, and energy levels while on the desiccated preparation. While more study is needed, and there was no difference in thyroid blood levels, the paper presents the possibility that there may be subgroups of hypothyroid patients that may benefit from combined T4/T3 therapy in ways that may not be easily clinically discernable.[31]

While monotherapy with levothyroxine is currently recommended for most patients with hypothyroidism one study found that people with certain genetic variants in the deiodinase 2 gene (DIO2) which helps convert T4 to T3 in the body were found to have decreased psychological well-being while on T4 monotherapy which improved when combination T4/T3 therapy was used. In that study the DIO2 variant was present in 16% of the study population. This polymorphism (variant form of a DNA sequence) had no effect on circulating thyroid hormone levels.[32] Another small study with 45 subjects found that 63% patients with one variant gene, DIO2 or MCT10 (which may affect the transport of thyroid hormones into the brain) preferred thyroid combination therapy to T4 monotherapy. 100% of the patients that had both polymorphisms preferred the combined therapy.[33] A third study of 141 patients had different findings and concluded that any preference for combination T4/T3 therapy over T4 monotherapy could not be explained by DIO2 polymorphisms.[34]

While the data on combined T4/T3 therapy's advantage for certain individuals over monotherapy is subjective, based on small studies, and uses psychological profiles and patient preferences, some authors have suggested that in the future individualized hypothyroid replacement therapy based on genotype may become the standard.[35] However, much larger studies need to be done to confirm these findings, as no differences in thyroid hormone levels were found between groups.
The American Association of Clinical Endocrinologists and the American Thyroid Association guideline states that the evidence does not support using L-thyroxine and L-triiodothyronine combinations to treat hypothyroidism, but there are still unresolved issues raised by studies that report that some patients prefer and some patient subgroups may benefit from a combination of L-thyroxine and L-triiodothyronine.[15]

Dosage

In patients with subclinical hypothyroidism the initial levothyroxine dose is generally lower than required in the treatment of overt hypothyroidism. A daily dose of 25 to 75 μg should be considered, depending on the degree of TSH elevation. In patients with cardiac disease 12.5 μg might be considered as an initial dose.[36] Further adjustments should be guided by clinical response and follow up TSH and T4 values. It takes about six to eight weeks for TSH levels to equilibrate after a dosage change. Levothyroxine has a narrow therapeutic range, and a half-life of 7 days which means that

overtreatment can have a prolonged effect.[5] Small dosage increases of levothyroxine are recommended to avoid causing the patient to become hyperthyroid with possible complications such as atrial fibrillation.[3,15]

Conclusion

Subclinical hypothyroidism is a fairly common disease entity which increases in prevalence with age. Treatment with a TSH level over 10mIU/L is generally recommended. However, with TSH levels between 4.5 to 10 mIU/L therapy needs to be individualized for each patient, with recommendations to only treat symptomatic patients and those with cardiac risk factors, as the benefits for asymptomatic patients are uncertain. Levothyroxine is the recommended treatment and liothyronine is not recommended for most patients. Combination T4/T3 therapy is not recommended but there may be subgroups who might benefit and more research is needed. When treating subclinical hypothyroidism start with low doses of levothyroxine to avoid causing iatrogenic hyperthyroidism. There are different recommendations regarding testing and treatment of subclinical hypothyroidism in pregnancy to avoid potential complications.

Correction: The European Thyroid Association recommendation is that geriatric patients with TSH levels **less than or equal to 10 mIU/L**, especially those over 80 years of age without specific signs of hypothyroidism can be followed with careful follow-up with a wait-and-see strategy trying to avoid hormonal treatment if possible. It was incorrectly presented as "TSH levels > 10 mIU/L" in a previous version.

References

[1]Thyroid hormone, Cleveland Clinic. Last reviewed 02/15/2022. Retrieved from: https://my.clevelandclinic.org/health/articles/22391-thyroid-hormone

[2]Peeters RP, Visser TJ. Metabolism of Thyroid Hormone. [Updated 2017 Jan 1]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK285545/

[3]Peeters RP. Subclinical Hypothyroidism. NEJM. 2017;376:2556-65. Retrieved from: https://www.nejm.org/doi/10.1056/NEJMcp1611144

[4] Stott DJ et al. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. N Engl J Med 2017; 376:2534-2544. June 29, 2017. Retrieved from: https://www.nejm.org/doi/full/10.1056/NEJMoa1603825

[5]Azim S, Nasr C. MD Subclinical hypothyroidism: When to treat. Cleveland Clinic Journal of Medicine February 2019, 86 (2) 101-110. Retrieved from: https://www.ccjm.org/content/86/2/101

[6]Adlin V. Subclinical Hypothyroidism: Deciding When to Treat. Am Fam Physician. 1998 Feb 15;57(4):776-780. Retrieved from: https://www.aafp.org/afp/1998/0215/p776.html

[7]Misiunas A. Peripheral neuropathy in subclinical hypothyroidism. Thyroid. 1995 Aug;5(4):283-6. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/7488869/

[8]Penza P. Painful neuropathy in subclinical hypothyroidism: clinical and neuropathological recovery after hormone replacement therapy. Neurol Sci. 2009 Apr;30(2):149-51. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/19214379/

[9]Allam MA. Prevalence and Clinical Significance of Subclinical Hypothyroidism in Diabetic Peripheral Neuropathy. Int J Gen Med. 2021;14:7755-7761. Retrieved from: https://www.dovepress.com/getfile.php?fileID=75583

[10]Reshdat, Sara. Relationship between subclinical hypothyroidism and distal-symmetric diabetic polyneuropathy in type 2 diabetes mellitus referred to Kosar Hospital in Semnan and related indicators in 2019–2020, Journal of Family Medicine and Primary Care: April 2022 - Volume 11 - Issue 4 - p 1361-1368. Retrieved from: https://journals.lww.com/jfmpc/Fulltext/2022/04000/Relationship_between_subclinical_hypothyroidism.22.aspx

[11]Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA. 2010;304(12):1365-1374. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3923470/

[12]Gencer B, Collet TH, Virgini V, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation. 2012;126(9):1040-1049. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3884576/

[13]Chaker, Layal et al. “Subclinical Hypothyroidism and the Risk of Stroke Events and Fatal Stroke: An Individual Participant Data Analysis.” The Journal of clinical endocrinology and metabolism vol. 100,6 (2015): 2181-91. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4454799/

[14]Krassas GE, Rivkees SA, Kiess W (eds): Diseases of the Thyroid in Childhood and Adolescence. Pediatr Adolesc Med. Basel, Karger, 2007, vol 11, pp 80–103. Retrieved from: https://www.karger.com/WebMaterial/ShowFile/894088

[15]Garber JR et al. American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract. 2012 Nov-Dec;18(6):988-1028. Retrieved from: https://www.endocrinepractice.org/article/S1530-891X(20)43030-7/fulltext

[16]T4 Free. Quest Diagnostics. Retrieved from: https://testdirectory.questdiagnostics.com/test/test-detail/866/t4-free-ft4?cc=MASTER

[17]T4 (Thyroxine), Total. Quest Diagnostics. Retrieved from: https://testdirectory.questdiagnostics.com/test/test-detail/867/t4-thyroxine-total?cc=MASTER

[18]TSH. Quest Diagnostics. Retrieved from: https://testdirectory.questdiagnostics.com/test/test-detail/899/tsh?cc=MASTER

[19]Mayo clinic laboratories. Thyroperoxidase Antibodies, Serum. 2022. Retrieved from: https://neurology.testcatalog.org/show/TPO

[20]Barić A et al. Thyroglobulin Antibodies are Associated with Symptom Burden in Patients with Hashimoto's Thyroiditis: A Cross-Sectional Study. Immunological Investigations. Volume 48, 2019 - Issue 2. Retrieved from: https://www.tandfonline.com/doi/full/10.1080/08820139.2018.1529040

[21]Peiris AN, Medlock D, Gavin M. Thyroglobulin for Monitoring for Thyroid Cancer Recurrence. JAMA. 2019;321(12):1228. Retrieved from: https://jamanetwork.com/journals/jama/fullarticle/2728926

[22]Block-Galarza J. Biotin supplement use is common and can lead to the false measurement of thyroid hormone in commonly used assays. CLINICAL THYROIDOLOGY FOR THE PUBLIC A publication of the American Thyroid Association. December 2018. Vol 11 Issue 12 p.3-4. Retrieved from: https://www.thyroid.org/patient-thyroid-information/ct-for-patients/december-2018/vol-11-issue-12-p-3-4/

[23]Odhaib SA et al. How Biotin Induces Misleading Results in Thyroid Bioassays: Case Series. Cureus. 2019 May 23;11(5):e4727. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6663274/

[24]Ross DS et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. Volume 26, Number 10, 2016. Retrieved from: https://www.liebertpub.com/doi/pdf/10.1089/thy.2016.0229

[25]Katzman BM et al. Prevalence of biotin supplement usage in outpatients and plasma biotin concentrations in patients presenting to the emergency department. Clinical Biochemistry. Volume 60, 2018, Pages 11-16. Retrieved from: https://www.sciencedirect.com/science/article/abs/pii/S0009912018303151

[26]Cerqueira Cesar Esteves Villar H et al. Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Library. 18 July 2007. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6610974/

[27]Stott DJ et al. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. N Engl J Med 2017; 376:2534-2544. June 29, 2017. Retrieved from: https://www.nejm.org/doi/full/10.1056/NEJMoa1603825

[28]Pearce SHS et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J 2013;2:215–228. Retrieved from: https://www.eurothyroid.com/files/download/ETA-Guideline-Management-of-Subclinical-Hypothyroidism.pdf

[29]Maraka S et al. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid. 2016 Apr;26(4):580-90. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4827301/

[30]Jonklaas J et al. American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the American thyroid association task force on thyroid hormone replacement. Thyroid. 2014 Dec;24(12):1670-751. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4267409/

[31]Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. J Clin Endocrinol Metab. 2013 May;98(5):1982-90. Retrieved from: https://academic.oup.com/jcem/article/98/5/1982/2536971?login=false

[32]Panicker V et al. Common Variation in the DIO2 Gene Predicts Baseline Psychological Well-Being and Response to Combination Thyroxine Plus Triiodothyronine Therapy in Hypothyroid Patients, The Journal of Clinical Endocrinology & Metabolism, Volume 94, Issue 5, 1 May 2009, Pages 1623–1629. Retrieved from: https://academic.oup.com/jcem/article/94/5/1623/2598196?login=true

[33]Carlé A et al. Hypothyroid Patients Encoding Combined MCT10 and DIO2 Gene Polymorphisms May Prefer L-T3 + L-T4 Combination Treatment - Data Using a Blind, Randomized, Clinical Study. Eur Thyroid J. 2017 Jul;6(3):143-151. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5527224/

[34]Bente C et al. Polymorphisms in Type 2 Deiodinase Are Not Associated with Well-Being, Neurocognitive Functioning, and Preference for Combined Thyroxine/3,5,3′-Triiodothyronine Therapy, The Journal of Clinical Endocrinology & Metabolism, Volume 90, Issue 11, 1 November 2005, Pages 6296–6299. Retrieved from: https://academic.oup.com/jcem/article/90/11/6296/2838503?login=true

[35]McAninch EA, Bianco AC. The Swinging Pendulum in Treatment for Hypothyroidism: From (and Toward?) Combination Therapy. Front Endocrinol (Lausanne). 2019 Jul 9;10:446. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6629976/

[36]Synthroid Full Prescribing Information. AbbVie Inc. July 2020. Retrieved from: https://www.rxabbvie.com/pdf/synthroid.pdf