Thyroid Hormone References

This document contains a selection of references compiled by Dr Thierry Hertoghe. It features multiple scientific studies on thyroid hormones, deficiencies and therapies. The reference list contains the major references of the pro and con studies on thyroid hormone therapy use, as it is important that physicians should be aware of these when debating with colleagues or other representatives of medical institutions.

The reader should find the list particularly valuable in his/her researches. Whenever possible, the references regarding human studies are mentioned in preference to those utilising animal studies.

Senescence is associated with a decline of the thyroid axis

Senescence is associated with reductions of the serum levels of TSH, T3 and T4

Senescence is associated with a reduction of the metabolic clearance of thyroid hormones

Senescence is associated with a reduction of the amount of thyroid hormone (cellular) receptors

Senescence is associated with alterations of the circadian cycle of serum TSH:
lower amplitude and phase advance

Thyroid hormones may oppose and thyroid hormones deficiency may trigger several mechanisms of senescence

Excessive free radical formation: thyroid hormones stimulate antioxidant activity


Imbalanced apoptosis: TSH inhibits undesireable apoptosis

Malaborption of important nutrients: thyroid hormones improve macronutrient uptake

Failure of repair systems: thyroid hormones reduce damage and accelerate repair

Immune deficiency: thyroid hormones stimulate the immune system

Low thyroid hormone levels are associated with immune deficiency

Thyroid treatment improves the immune defences


34. Dorshkind K, Horseman ND. The roles of prolactin, growth hormone, insulin-like growth factor-I, and thyroid hormones in lymphocyte development and function: insights from genetic models of hormone and hormone receptor deficiency. Endocr Rev. 2000 Jun;21(3):292-312


Limits to healthy cell proliferation: thyroid hormones stimulate fibroblast proliferation and differentiation


Poor gene polymorphisms: poor thyroid gene polymorphisms may increase the risk of age-related diseases, and thyroid dysfunction may increase the risk of phenotypic expression of other unfavourable gene polymorphisms


Thyroid hormones and psychic well-being

Lower quality of life and fatigue: the association with lower thyroid hormone levels


41. Guimaraes V, DeGroot LJ. Moderate hypothyroidism in preparation for whole body 131I scintiscans and thyroglobulin testing. Thyroid. 1996 Apr;6(2):69-73


Lower quality of life and fatigue: the improvement with thyroid treatment


Depression: the association with lower thyroid hormone levels


59. Joffe RT, Marriott M. Thyroid hormone levels and recurrence of major depression. Am J Psychiatry. 2000 Oct;157(10):1689-91 ("the time to recurrence of major depression was inversely related to T3 levels but not to T4 levels")

Depression: the improvement with thyroid treatment

60. Bauer MS, Whybrow PC. Rapid cycling bipolar affective disorder. II. Treatment of refractory rapid cycling with high-dose levothyroxine: a preliminary study. Arch Gen Psychiatry. 1990 May;47(5):435-40


Anxiety: the association with lower thyroid hormone levels


75. Venero C, Guadano-Ferraz A, Herrero AI, Nordstrom K, Manzano J, de Escobar GM, Bernal J, Vennstrom B. Anxiety, memory impairment, and locomotor dysfunction caused by a mutant thyroid hormone receptor alpha1 can be ameliorated by T3 treatment. Genes Dev. 2005 Sep 15;19(18):2152-63

Anxiety: the improvement with thyroid treatment


75. Venero C, Guadano-Ferraz A, Herrero AI, Nordstrom K, Manzano J, de Escobar GM, Bernal J, Vennstrom B. Anxiety, memory impairment, and locomotor dysfunction caused by a mutant thyroid hormone receptor alpha1 can be ameliorated by T3 treatment. Genes Dev. 2005 Sep 15;19(18):2152-63

Memory loss and Alzheimer's disease: the association with lower thyroid hormone levels

76. Nakanishi T. Consideration on serum triiodothyronine (T3), thyroxine (T4) concentration and T3/T4 ratio in the patients of senile dementia - is it possible to prevent cerebro-vascular dementia? Igaku Kenkyu. 1990 Feb;60(1):18-25


Memory loss and Alzheimer's disease: the improvement with thyroid treatment


Sleep disorders: the improvement with thyroid treatment


Fertility:

Infertility: the association with lower thyroid hormone levels


Thyroid hormones and age-related diseases

Hypercholesterolemia: the association with lower thyroid hormone levels


Hypercholesterolemia: the improvement with thyroid treatment


Atherosclerosis: the association with lower thyroid hormone levels


Atherosclerosis: the improvement with thyroid treatment


Arterial hypertension: the association with lower thyroid hormone levels


Arterial hypertension: the improvement with thyroid treatment


Coronary heart disease: the association with lower thyroid hormone levels


Coronary heart disease and other cardiac diseases: the improvement with thyroid treatment

111. Barnes BO. Prophylaxis of ischaemic heart-disease by thyroid therapy. Lancet. 1959 Aug 22;2:149-52


Cardiovascular disease and mortality: increased in hypothyroidism (+ 70 % for both)

Stroke and other cerebrovascular disorders: the association with lower thyroid hormone levels
116. Hu R. Changes in serum thyroid hormones in acute cerebrovascular apoplexy and their clinical significance. Zhonghua Shen Jing Jing Shen Ke Za Zhi. 1990 Apr;23(2):87-9, 126

Obesity: the association with lower thyroid hormone levels

Obesity: the improvement with thyroid treatment

Diabetes: The association with lower thyroid hormone levels
Diabetes: the improvement with thyroid treatment
134. Houssay BA. The thyroid and diabetes. Vitam Horm. 1946;4:188

Rheumatism: the association with lower thyroid hormone levels

Rheumatism: the improvement with thyroid treatment

Osteoporosis: the improvement with thyroid treatment

Cancer: the association with lower thyroid hormone levels

Cancer: the improvement with thyroid treatment?
149. Lacka K. Treatment with L-thyroxine for differentiated thyroid carcinoma. Wiad Lek. 2001;54 Suppl 1:368-72

Longevity: the association with thyroid hormone
Thyroid Diagnosis:

Frequency of overt and subclinical hypothyroidism

Serum thyroid tests
156. Ladenson PW. Optimal laboratory testing for diagnosis and monitoring of thyroid nodules, goiter, and thyroid cancer. Clin Chem. 1996 Jan;42(1):183-7

Serum TSH
160. Beth Israel Hospital, Boston

Serum thyroxine and triiodothyronine

Serum thyroid antibodies
168. Aksoy DY, Kerimoglu U, Okur H, Canpinar H, Karaagaoglu E, Yetgin S, Kansu E, Gedik O. Effects of prophylactic thyroid hormone replacement in euthyroid Hashimoto's thyroiditis. Endocr J. 2005 Jun;52(3):337-43 (After 15 months of L-thyroxine treatment, there was a significant increase in free T4 and a significant decrease in TSH and anti-thyroglobulin antibody anti-thyroid peroxidase antibody levels, and a decrease in thyroid volume, whereas an increase was detected in patients who were followed without treatment)
### Serum TRH test


### 24-hour urine thyroid Hormones


175. Tal E, Sulman FG. Urinary thyroxine. Lancet. 1972, 1291


181. Ali Afrasiaki M, Dabir Vaziri N, Grant Gwinup, Mays M, Barton CH, Ness RL, Valenta LJ. Thyroid function in the nephrotic syndrome. Ann Int Med. 1979, 90, 335-8


Corrective Thyroid Therapy

Thyroid medications

Alley RA, Danowski TS, Robbins TJ, Weir TF, Sabeh G, Moses CL. Indices during administration of T4 and T3 to euthyroid adults. Metabolism. 1968 Feb;17(2):97-104 (equivalencies between T4, T3, T3 + T4, desiccated thyroid preparations)

Thyroxtene

194. Oppenheimer JH, Braverman LE, Toft A, Jackson, IM, Ladenson, PW. Thyroid hormone treatment when and what? J Clin Endocrinol Metab. 1995;80:2873-83
196. Roti E, Minelli R, Gardini E, Braverman LE. The use of misuse of thyroid hormone. Endocrine Rev. 1993;14:401-23
198. USP Dispensing Information: Volume 1 - Drug Information for Health Care Professionals. The United States Pharmacopeial Convention, Rockville, MD, 1997

Thyroxine-triiodothyronine associations

204. Hertoghe T. Many conditions related to age reduce the conversion of thyroxine to triiodothyronine - a rationale for prescribing preferentially a combined T3 + T4 preparation in hypothyroid adults. Anti-Aging Medical Therapeutics 2000; IV: 138-53

Frequency of use of thyroid hormone treatment

206. Sawin CT, Geller A, Hershman JM, Castelli W, Bacharach P. The aging thyroid: the use of thyroid hormone in older persons. JAMA 1989;261:2653-5
Thyroid treatment: dosage


Thyroid treatment: thyroid hormone absorption and malabsorption

218. Hays MT, Nielsen KRK. Human thyroxine absorption: age effects and methodological analyses. Thyroid. 1994;4:55-64


**Thyroid treatment: safety, special conditions to carefully watch for**


236. Bauer M, Priebe S, Berghof a, Bschor T, Kiesslinger U, Whybrow PC. Subjective response and tolerability of long-term supraphysiological doses of levothyroxine in refractory mood disorders. J Affect Disord. 2001 Apr;64(1):35-42 (“Subjective response and side-effect tolerability of long-term supraphysiological doses (mean dose 368 µg/day for a mean of 54 months) of T4 is favorable in patients with refractory mood and schizoaffective disorders who respond to the intervention”)


244. Magner J, Gerber P. Urticaria due to blue dye in synthroid tablets. Thyroid. 1994 Fall;4(3):341

**Thyroid treatment: interferences or associations**


Thyroid treatment: follow-up


251. Ain KB, Pucino F, Shiver TM, Banks SM. Thyroid hormone levels affected by time of blood sampling in thyroxine-treated patients. Thyroid. 1993;3:81-5
DISCUSSIONS ON THYROID DIAGNOSIS

SERUM TSH: IS THE TSH SERUM MEASUREMENT ALONE SUFFICIENT FOR DIAGNOSIS AND FOLLOW-UP OF THYROID DEFICIENCY?

Claim: TSH is the first line test to do. It is sufficient to diagnose all forms of eu-, hypo- and hyperthyroidism. No other test is necessary for the diagnosis.

Facts: TSH is often insufficient on its own to diagnose between eu-, hypo- and hyperthyroidism, particularly to diagnose milder, borderline states of hypothyroidism. Other tests are necessary, as is a complete clinical evaluation (medical history, actual complaints, physical examination) of the patient.

Article defending the serum TSH test as the first line approach to diagnose thyroid dysfunction

Doubts on the usefulness of the serum TSH test alone for diagnosis

Overreliance on laboratory tests without clinical evaluation may lead to considerable diagnostic errors
4. Becker DV, Bigos ST, Gaitan E, Morris JCrd, rallison ML, Spencer CA, Sugarawa M, Van Middlesworth L, Wartofsky L. Optimal use of blood tests for assessment of thyroid function. JAMA 1993 Jun 2; 269: 273 (“the decision to initiate therapy should be based on both clinical and laboratory findings and not solely on the results of a single laboratory test”)

Discussions and controversy in medical associations and journals on the TSH reference range
6. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291:228–38 (conclusions of a consensus panel of the Endocrine Society, the American Thyroid Association, and American Association of Clinical Endocrinology. Although the panel concluded that there was good data that patients with slight elevations of TSH above 4.5 may progress to overt hypothyroidism, and that levothyroxine therapy would prevent symptoms, they did not agree that early treatment provided any benefit!)
8. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005 Sep;90(9):5483-8 (remarkable article of which a lot of the following information is extracted)
11. Ringel MD, Mazzaferri EL. Editorial: subclinical thyroid dysfunction: can there be a consensus about the consensus? J Clin Endocrinol Metab. 2005;90:588–90
12. Pinchera A. Subclinical thyroid disease: to treat or not to treat? Thyroid. 2005;15:1–2
Studies that show that the serum TSH reference range of 0.1-5.1 mU/liter for a POPULATION is too large

Studies indicating a population mean value of 1.5 mU/liter for an iodine-sufficient population
15. Andersen S, Petersen KM, Brunn NH, Laurberg P. Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab. 2002;87:1068–72

A longitudinal study in diabetics where a baseline TSH levels above the 1.53 mU/liter predicted subsequent thyroid dysfunction, whereas no thyroid dysfunction if TSH levels < 1.53 mU/liter, the reference range for diabetics should then be 0.4-1.52 mU/liter

If the serum TSH reference range would be based upon a cohort of truly normal individuals with no personal or family history of thyroid dysfunction, no visible or palpable goiter, not taking any medication, who are seronegative for thyroid peroxidase antibodies, and whose blood samples are drawn fasting in the morning hours (06–10 h), the TSH reference range would become 0.4–2.5 mU/L (Demers & co, Baloch & co.)

When data for subjects with positive TPOAb or a family history of autoimmune thyroid disease are excluded, the normal reference interval becomes much tighter, i.e. 0.4–2.0 mU/liter. This tighter reference range may certainly be more applicable to African-Americans, who have a lower mean TSH
Publications with data to support a more narrow reference range for serum TSH that would be obtained when persons with diffuse hypoechochogenicity of the thyroid on ultrasound, a condition that precedes thyroid peroxidase antibody positivity in autoimmune thyroid disease, would be excluded.


For the American Association of Clinical Endocrinologists the revised reference TSH range is 0.3–3.0 mU/L


Ethnic differences: the mean TSH level in African-Americans is 1.18 mU/liter, in contrast to a mean of 1.40 mU/liter in Caucasians, due to the greater frequency of autoimmune thyroid disease in whites (12.3%) than in blacks (4.3%), which may have unjustifiably skewed the upper end of the TSH curve (NHANES data). For African-Americans, the TSH reference range should therefore be lower than in whites.


A study, which suggests that the serum TSH cut-off point between hypo- and euthyroidism is 2, not 4 or 5.5

27. Michalopoulou G, Alevizaki M, Piperingos G, Mitsibounas D, Mantzos E, Adampoulos P, Koutras DA. High serum cholesterol levels in persons with 'high-normal' TSH levels: Should one extend the definition of subclinical hypothyroidism? Eur J Endocrinol. 1998 Feb;138(2):141-5 (Treating TPO antibody-positive hypercholesterolemic patients with TSH levels between 2-4 mU/L with low dose levothyroxine normalizes TSH levels and improves the lipid profile)

In 2003, the National Academy of Clinical Biochemistry (NACB) has reduced the upper limit of the reference range from 5.5 to 4.1 mU/L, but stating also that "greater than 95% of healthy, euthyroid subjects have a serum TSH concentration between 0.4 - 2.5 mU/L". ".. patients with a serum TSH >2.5 mU/L, when confirmed by repeat TSH measurement made after 3 to 4 weeks, may be in the early stages of thyroid failure, especially if thyroid peroxidase antibodies are detected"


Supporters of the recommendations of the consensus panel (Endocrine Society, American Association of Clinical Endocrinologists, American Thyroid Association) promote a target TSH range of 1.0–1.5 mU/liter in patients already receiving T4 therapy.


The lower end of the normal or reference range for TSH lies between 0.2 and 0.4 mU/liter, as indicated by a number of clinical studies.

The TSH reference range for an INDIVIDUAL is narrower than the reference range for a population

The value of a population-based reference range is limited when the individual patient-based reference range (i.e. his personal reference range) is narrow


The individual TSH reference ranges are remarkably narrow within a relatively small segment of the population reference range, i.e. confined to only 25% of a range of 0.3–5.0 mU/liter.
A shift in the TSH value of the individual outside of his or her individual reference range, but still within the population reference range, would not be normal for that individual. For example, an individual (as in Anderson’s series) with a personal range of 0.5–1.0 mU/liter would be at subphysiological thyroid hormone levels at the population mean TSH of 1.5 mU/liter (as explained by Wartofsky 2005)

Studies of twins have data to support that each of us has a genetically determined optimal free T4 (FT4)-TSH set point or relationship

A measured TSH difference of 0.75 mU/liter can already be significant in a patient. The NACB guideline 8 states that “the magnitude of difference in ...TSH values that would be clinically significant when monitoring a patient’s response to therapy... is 0.75 mU/liter.” Greater TSH fluctuations in a specific patient may mean that s/he becomes hypothyroid or hyperthyroid.
A serum TSH that rises in a given individual from a set point of 1.0 to 3.5 is likely to be abnormally elevated and imply early thyroid failure. A minor change in serum free T4 results in an amplified change in TSH to outside of the usual population-based reference range, although the free T4 is still within its own population-based reference range, because of the log-linear relationship between TSH and free T4. In the case of subclinical hypothyroidism, for example, a slight drop in free T4 results in an amplified and inverse response in TSH secretion (as explained by Wartofsky 2005)


There is a 3-fold difference between the average daily maximal TSH (3) and minimal TSH (1 mIU/ml)


Conclusion: TSH reference range is too large => need for narrower ranges

47. Dickey RA, Wartofsky L, Feld S. Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. Thyroid. 2005 Sep;15(9):1035-9
48. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005 Sep;90(9):5483-8

Other arguments that may explain why the TSH test alone is not the only test

The TSH test is insufficient to diagnose all forms of hypothyroidism, including the borderline forms.

The frequency of abnormal TSH values


Longitudinal studies indicating a rate of progression of mild thyroid failure into overt hypothyroidism of about 5% per year (50% or more in 10 years!): they have to be treated

The pituitary 5'-deiodinase type 2 that converts thyroxine into triiodothyronine (T3), is different than the liver and kidney 5'-deiodinase type 1 that provides the T3 for the rest of the body. This difference may explain why TSH secretion and thus serum TSH secreted by the pituitary gland may be normal, while the rest of the body may be in a thyroid deficient state.


In fasting, hypothyroidism or selenium deficiency for example, the 5'-deiodinase of the pituitary gland increases or remains unchanged, while that of the liver decreases.


A normal or low serum TSH may reflect in elderly persons hypothyroidism in peripheral tissues, and not anymore eu- or hyperthyroidism, because the pituitary gland has aged. Progressively with increasing age, the serum TSH test becomes less reliable as a diagnostic test.


Necessity for other tests than the TSH to diagnosis thyroid dysfunction, e.g. the serum free T4

60. Ladenson PW. Diagnosis of hypothyroidism. In Werner and Ingbar's The Thyroid, 7th edition, Braverman LE and Utiger RE, Lippincott-Raven Publishers, Philadelphia. 1996; 878-82


Serum thyroid hormone levels may not reflect the cellular thyroid status

64. Escobar del Rey F, Ruiz de Ona C, Bernal J, Obregon MJ, Morreale de Escobar G. Generalized deficiency of 3, 5, 3'-triiodothyronine in tissues from rats on a low iodine intake, despite normal circulating T3 levels. Acta Endocrinol (Copenh) 1989; 120: 490-8

Need to analyse valuable indicators of peripheral activity such as the serum levels of plasma binding proteins SHBG, TBG, CBG, or of thyroid-dependent enzymes such as alkaline phosphatase, osteocalcin


Conditions or factors that DEPRESS the serum TSH

Aging

Fasting
69. Croxson MS, Hall TD, Kletzky OA, Jaramillo JE, Nicoloff OA. Decreased serum thyrotropin induced by fasting. J Clin Endocrinol Metab. 1977; 45: 560

Strenuous physical exercise
73. Scanlon MF, Toft AD. Regulation of thyrotropin secretion. In Werner and Ingbar's The Thyroid, 7th edition

Pregnancy (first trimester)

Depression and anxiety disorders

Non-thyroidal diseases: diabetes mellitus, Cushing’s syndrome, renal failure, cancer, myocardial infarction, AIDS, post-traumatic syndromes, chronic alcoholic liver disease, other illnesses

**Medications**: thyroid therapy, estroprogestative birth control pills, progestogens, anti-inflammatory agents (incl. glucocorticoids and aspirin), antidepressants, L-Dopa, bromocriptine, neuroleptica, anti-hypertensives, antiarrhythmics (amiodarone), hypolipemic agents, IGF-1, somatostatin, etc.
101. Chopra U, Carlson HE, Solomon DH. Comparison of inhibitory effects of 3,5,3'-triiodothyronine (T3), thyroxine (T4), 3,3',5'-triiodothyronine (rT3), and 3,3'-diiodothyronine (T2) on thyrotropin-releasing hormone-induced release of thyrotropin in the rat in vitro. Endocrinology. 1978; 103(2): 393-402


**Toxic foods:** MSG, alcohol


**Thyroid diseases:** hyperthyroidism, Graves-Basedow disease, nodular goiter, thyroiditis, secondary or tertiary hypothyroidism, congenital hypothyroidism


**FACTORS that ELEVATE the serum TSH**

**Neonatus, stress - emotional arousal, cold exposure, sleep deprivation, adrenal insufficiency, recovery from severe illness, congenital malformations**


**Medications:** iodine, antithyroida, , lithium, neuroleptica (haloperidol, chlorpromazine), cimetidine, sullapyridine, clomifen, antidepressants (sertraline), antihistaminic agents, cholestographic agents, etc.


**Auto-immune thyroiditis and hypothyroidism:** primary, iodine-deficient, thyroid hormone resistance


TSH-secreting tumors (rare)

FACTORS that ELEVATE or DEPRESS serum TSH

Physiological serum TSH fluctuations

Variations in the biological activity of TSH
90. Hiromoto M, Nishikawa M, Ishihara T, Yoshikawa N, Yoshimura M, Inada M. Bioactivity of thyrotropin (TSH) in patients with central hypothyroidism: Comparison between the in vivo 3,5,3'-triiodo-thyronine response to TSH and in vitro bioactivity of TSH. J Clin Endocrinol Metab. 1995 Apr;80(4):1124-8
TSH test kit imperfections


105. Laurberg P. Persistent problems with the specificity of immunometric TSH assays. Thyroid. 1993 Winter;3(4):279-83


115. Ealey PA, Marshall NJ, Ekins RP. Time-related thyroid stimulation by thyrotropin and thyroid-stimulating antibodies, as measured by the cytochemical section bioassay. J Clin Endocrinol Metab. 1981;52(3): 483-7
Doubts on the adequateness of measuring the serum TSH as a help to monitor a thyroid treatment (follow-up)

The serum TSH test for follow-up: The risk of misinterpretation increases when monitoring the treatment of hyper- or hypothyroidism


In 36-47 % of clinically euthyroid patients receiving adequate long-term thyroid therapy for hypothyroidism, an undetectable serum TSH is found


After intake of thyroid hormones, the serum TSH is transitorily depressed within 60 minutes and remains low for up to 9 hours after intake

119. Chopra U, Carlson HE, Solomon DH. Comparison of inhibitory effects of 3,5,3'-triiodothyronine (T3), thyroxine (T4), 3,3',5'-triiodothyronine (rT3), and 3,3'-diodothyronine (T2) on thyrotropin-releasing hormone-induced release of thyrotropin in the rat in vitro. Endocrinology. 1978;103(2):393-402

Some patients who exhibit reversion of an initially high TSH level back into the reference range, are found to subsequently develop mild thyroid failure


Supporters of the recommendations of the consensus panel promote a target TSH range of 1.0–1.5 mU/liter in patients already receiving T4 therapy, whereas they refuse to accept TSH levels of 3–10 mU/liter as abnormal in patients not receiving T4 therapy.


The lower end of the normal or reference range for TSH lies between 0.2 and 0.4 mU/liter, as indicated by a number of clinical studies


Other tests: urinary T3 as a complementary test
DISCUSSIONS ON THYROID TREATMENT

DOES THYROID TREATMENT DEFINITELY SUPPRESS THE THYROID GLAND?

No, after stopping thyroid medications, the thyroid axis recovers its initial condition in 2 to 3 weeks on the average

1. Krugman LG, Hershman JM, Chopra IJ, Levine GA, Pekary E, Geffner DL, Chua Teco GN. Patterns of recovery of the hypothalamic-pituitary-thyroid axis in patients taken of chronic thyroid therapy. J Clin Endocrinol Metab. 1975 Jul;41(1):70-80 (full recovery back to initial serum T3, T4, TSH levels is obtained after a mean of 16 to 22 days, even after 28 years of treatment)

2. Vagenakis AG, Braverman LE, Azizi F, Portinay GI, Ingbar SH. Recovery of pituitary thyrotropic function after withdrawal of prolonged thyroid-suppression therapy. N Engl J Med. 1975 Oct 2;293(14):681-4 (“During exogenous hormone administration, 131I uptake was suppressed, and serum thyrotropin concentrations before and after administration of thyrotropin-releasing hormone were undetectable. … After withdrawal of long-term thyroid hormone, decreased thyrotropin reserve persisted for two to five weeks. Detectable values of serum thyrotropin (less than 1.2 μU per milliliter) and a normal 131I uptake usually occurred concurrently in two to three weeks. Serum thyroxine concentration returned to normal at least four weeks after hormone withdrawal.”)

3. Greer MA. The effect on endogenous thyroid activity of feeding desiccated thyroid to normal human subjects. N Engl J Med. 1951 Mar 15;244(11):385-90 (“After withdrawal of thyroid therapy, thyroid function returned to normal in most subjects within 2 weeks, although a few were depressed for 6-11 weeks. Thyroid function returned as rapidly in those whose glands had been depressed by several years of thyroid medication as it did for those whose glands had been depressed for only a few days.”)

4. Mosier HD, DeGolia RC. Effect of prolonged administration of thyroid hormone on thyroid gland function of euthyroid children. J Clin Endocrinol Metab. 1960 Sep;20:1296-301. (“In all of the children and adolescents included in this study, thyroid function returned to normal (as judged by clinical signs ans by laboratory measurements) within four months after discontinuing thyroid hormone in spite of previous administration of suppressive doses for periods of 20 to 125 months during years of somatic growth”).

5. Farquharson RF, Squires AH. Inhibition of the secretion of the thyroid gland by continued ingestion of thyroid substance. Tr A Am Physicians. 1941;56:87


If the thyroid treatment is stopped because it is judged not necessary, recovery takes place

9. Rubinoff H, Fireman BH. Testing for recovery of thyroid function after withdrawal of long-term suppression therapy. J Clin Epidemiol. 1989;42(5):417-20 (At 8 weeks, 30 of the 45 patients whose chart reviews did not demonstrate a clear need for thyroid replacement., were normal)
MILD THYROID FAILURE: TO TREAT OR NOT TO TREAT

Arguments pro thyroid treatment of mild thyroid failure

Longitudinal studies indicating a rate of progression of mild thyroid failure into overt hypothyroidism of about 5% per year (50% or more in 10 years!): they have to be treated

Studies that show the efficacy of treating mild thyroid failure

Little benefit of T4 therapy if TSH reductions are put into only the range of 3–3.5 mU/IL. Mainly studies using dosage titration to TSH levels < 3.0 are associated with improvement in symptoms, lipid abnormalities, and cardiovascular function (except the study by Meier and colleagues that showed benefit with minimal TSH reductions in the 3-3.5 mIU/ml range)
9. McDermott MT, Ridgway EC. Clinical perspective: subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab. 2001; 86:4585–90 (shows benefit with minimal TSH reductions down to only the range of 3–3.5 mU/liter)

Studies with appropriate dosage titration to TSH levels under 3.0 are more often associated with improvement in symptoms, lipid abnormalities, and cardiovascular function


Other studies in defence of treatment of mild thyroid failure: it is important to treat mild thyroid failure to avoid adverse physical and psychological consequences


33. Beyer IW, Karmali R, DeMeester-Mirkine N, Cogan E, Fuss MJ. Serum creatine kinase levels in overt and subclinical hypothyroidism. Thyroid 1998;8:1029–31
35. Foundation for Blood Research, Scarborough, ME 04074, USA
41. Kahaly GJ 2000 Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid 10:665–79
42. Arem R, Rokey R, Kiefe C, Escalante DA, Rodriquez A. Cardiac systolic and diastolic function at rest and exercise in subclinical hypothyroidism: Effect of thyroid hormone therapy. Thyroid. 1996 ;6:397-402


57. Danese MD, Powe NR, Sawin CT, Ladenson PW. Screening for mild thyroid failure at the periodic health examination. JAMA. 1996;276:285–92

58. McDermott MT, Haugen BR, Leazotte DC, Seggelke S, Ridgway EC. Management practices among primary care physicians and thyroid specialists in the care of hypothyroid patients. Thyroid. 2001;11:757–76

59. Zoncu S, Pigliaru F, Putzu C, Pisano L, Vargiu S, Deidda M, Mariotti S, Mercuro G. Cardiac function in borderline hypothyroidism: a study by pulsed wave tissue Doppler imaging. Eur J Endocrinol. 2005 Apr;152(4):527-33 (“impairment of systolic ejection, a delay in diastolic relaxation and a decrease in the compliance to the ventricular filling… Several significant correlations were found between the parameters and serum-free T(3) and T(4) and TSH concentrations. Data strongly support the concept of a continuum spectrum of a slight thyroid failure in autoimmune thyroiditis.”)

Subclinical thyroid dysfunction is an abnormal serum thyroid-stimulating hormone level (reference range: 0.45 to 4.50 µU/mL) and free thyroxine and triiodothyronine levels within their reference ranges


Important frequency of subclinical hypothyroidism:

61. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG,


64. Hollowell J, Braverman LE, Spencer CA, Staehling N, Flanders D, Hannon H Serum TSH, T4, and thyroid antibodies in the United States population: NHANES III. 72nd Annual Meeting of the American Thyroid Association, Palm Beach, FL, 1999; Abstract 213


68. Sawin CT, Chopra D, Azizi F, Mannix JE, Bacharach P. The aging thyroid. Increased prevalence of elevated serum thyrotropin levels in the elderly. JAMA. 1979;242:247–50


72. Wilson GR, Curry RW Jr. Subclinical thyroid disease. Am Fam Physician. 2005 Oct 15;72(8):1517-24 ("The prevalence of subclinical hypothyroidism is about 4 to 8.5 percent, and may be as high as 20 percent in women older than 60 years")

**Important risk of progression into overt hypothyroidism**


**Importance of clinical evaluation of subclinical hypothyroidism**


**Studies showing that it is important to treat mild glandular failure that causes other diseases such as diabetes and hypertension**


Arguments contra thyroid treatment of mild thyroid failure


Initiation of levothyroxine therapy for mild thyroid failure would be inappropriate because it results in overtreatment with attendant risks of subclinical hyperthyroidism. (citic: this risk applies to a very small fraction of the population to be treated. An equivalent risk of undertreatment of such individuals applies as well. Both results could be minimized by education of our primary care physicians about the desirable TSH target in their patients)

86. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291:228–38

T4 treatment does not improve clinically hypothyroid patients who have normal tests (critic: but possibly T3-T4 does)


T4 treatment in subclinically hypothyroid patients but normal tests does not improve the patient (explanation: The absence of clinically relevant benefits of thyroid therapy for mild thyroid failure may be due to (1) a TSH normalization that was typically described as lowering of TSH to < 5 mU/liter, whereas levels between 3 - 5 mU are probably still elevated and request higher dosage; (2) the use of thyroxine without any addition of triiodothyronine)


Thyroxine treatment does improve cholesterol levels and clinical symptoms in subclinical hypothyroidism

90. Meier C, Staub J-J, Roth C-B, Gugliemetti M, Kunz M, Miserey AR, Drewe J, Huber P, Herzog M, Muller B. TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). J Clin Endocrinol Metab. 2001 Oct;86:4860–6 (An important risk reduction of cardiovascular mortality of 9-31% can be estimated from the observed improvement in LDL cholesterol)

Studies that show the importance of treating mild thyroid excess: Subclinical hyperthyroidism

There is an equal concern about correct diagnosis and treatment of patients with TSH levels that are slightly below the reference interval because of risks to both heart and bone

CONTROVERSY ON THE BEST THYROID TREATMENT: T4 OR T4-T3?

Arguments pro treatment with T4 alone:

Guidelines on T4 recommendation
4. Roti E, Braverman LE. Thyroid hormone therapy: when to use it, when to avoid it. Drug Therapy. 1994; 24(4):2-35.

Arguments pro treatment with either T4 alone, either T4 and T3

T3-T4 treatments work as good as T4 alone, but not better

Arguments pro treatment with T4 and T3 combinations

T3-T4 (and T3) treatments work better than T4

T3-T4 treatment: adding T3 to T4 results in greater improvement of clinical symptoms and signs in hypothyroid patients
When T3 and T4 are both supplemented to the food simultaneously with goitrogens, a much better prevention of goiter is obtained than when solely T4 is added, even if T4 is given at doses 7 times higher than those of T3-T4 treatments


In humans, T4-T3 treatments reduce serum cholesterol and increase the speed of the Achilles tendon reflexes better than T4 treatments alone


A study in rats rendered hypothyroid shows that cellular euthyroidism is only obtained in the target organs of hypothyroid rats if T3 is added to the classic T4 medication


Medications with T4 alone do not succeed in achieving complete cellular euthyroidism in the target organs, probably because T3 is really the active hormone


T3 is much more potent than T4


Conditions that reduce the conversion of T4 to T3 such as aging, obesity, disease, stress, exercise, malnutrition, etc., reducing thereby the efficacy of a T4 alone treatment

25. Katzzeff HI, Selgrad C. Impaired peripheral thyroid hormone metabolism in genetic obesity. Endocrinology. 1993; 132 (3): 989-95
26. Croxson MS and Ibbetson HK. Low serum triiodothyronine (T3) and hypothyroidism in anorexia nervosa. J Clin Endocrinol Metab. 1977; 44: 167-73
27. Harns ARC, Fang SH, Vagenakis AG, and Braverman LE. Effect of starvation, nutriment replacement, and hypothyroidism on in vitro hepatic T4 to T3 conversion in the rat. Metabolism. 1978;27(11):1680-90

**Toxic substances** such as phenols, cadmium, mercury, etc, and medications such as propranolol, amiodarone and several others may interfere by stimulating or inhibiting the T4 to T3 conversion


**Deficiencies in hormones** (T3 itself, TSH, growth hormone, insulin, melatonin, etc) and trace elements (selenium, iron, zinc, cupper, etc) **partially block this essential step for thyroid function**

37. Erickson VJ, Cavalieri RR, Rosenberg LL. Thyroxine-5’-diodinase of rat thyroid, but not that of liver, is dependent on thyrotropin. Endocrinology. 1982;111:434-40
On the other hand, excesses in hormones (glucocorticoids, ACTH, estrogens, ...) and trace elements (iodine, lithium, ...) may slow down this conversion.


The absorption of oral T4 can be variable (50 to 73%\(^{40,41}\)), contrasting with that of T3 that is more constant and efficient (95%)


Defects in the commercial T4 preparation\(^{43,44}\)
THYROID TREATMENT AND THE HEART

Claim: Thyroid hormone treatment is dangerous for the heart as it can cause side effects such as atrial fibrillation.

Facts: Euthyroidism (normal thyroid function) is essential for the heart; both hypothyroidism as well as hyperthyroidism impair the working of the heart and may facilitate atrial fibrillation.

Arguments contra thyroid treatment: because of possible cardiac side effects, especially in cardiac patients

Hyperthyroidism: causes tachycardia (critic: tachycardia is the result of hyperthyroidism, hypocorticism, or drinking of caffeinated beverages; avoiding these conditions by adequate treatment or abstention will prevent many cases of tachycardia)


Hyperthyroidism (high serum thyroid hormones) is associated with an increased risk of atrial fibrillation

3. Parmar MS. Thyrotoxic atrial fibrillation. Med Gen Med. 2005 Jan 4;7(1):74 (atrial fibrillation was seen in 15 % of hyperthyroid patients)


5. Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. Arch Intern Med. 2004 Aug 9-23;164(15):1675 (atrial fibrillation was observed in 8.3 % of hyperthyroid patients)

Hyperthyroidism is associated with an increased risk of angina pectoris


Possibility to administer a betablocker together with thyroid medication to hypothyroid patients with angina pectoris


Patients aged 40 years or older at emergency admission who present a high serum free and total T3, have an increased risk of of angina pectoris and myocardial infarct at admission and 3 years later (critic: possibly due to hypocorticism that increases (the conversion of T4 into)T3??)


A high serum T4 is found in patients with coronary heart disease (critic: possibly accompanied by a low serum T3, which reflects a clinical more hypothyroid state, because of the decrease in conversion of T4 to T3 that is generally observed in the disease state)

10. Selivonenko VG, Zaika IV. The function of the thyroid and thyrotropic function in patients with chronic ischemic heart disease and rhythm disorders. Lik Sprava. 1998 Jan-Feb;(1):81-3

**Arguments pro thyroid treatment:** the heart needs to have thyroid hormones or heart disease appears; also the case for cardiac patients (but they must be treated with great caution and should receive lower thyroid doses)

**Associations between thyroid hormone levels and heart health**

Thyroid hormone levels are positively correlated with the heart rhythm

A lower serum T3 (and higher serum T4) is found in heart patients with arrhythmia
14. Vanin LN, Smetnev AS, Sokolov SF, Kotova GA, Masenko VP. Thyroid function in patients with ventricular arrhythmia. Kardiologiia. 1989 Feb;29(2):64-7 (Hyperthyroidism was diagnosed in 4.8% of 21 patients with persistent ventricular arrhythmias, and latent hypothyroidism was diagnosed in 38.1%)

Low serum T3 and T4 levels are found in patients with coronary heart disease

A low serum free T3 in patients with coronary bypass increases the risk of postoperative atrial fibrillation (higher risk than that of not taking a beta-blocker)

Progressively lower serum T3 levels are found in patients with ischemic heart disease form coronary stenosis to myocardial infarct
Low serum free and total T3 (and low free T4 and high TSH) levels are found in patients suffering from acute myocardial infarct with poor outcome

Auto-immune thyroiditis is associated with poorer heart indices
24. Zoncu S, Pigliaru F, Putzu C, Pisano L, Vargiu S, Deidda M, Mariotti S, Mercuro G. Cardiac function in borderline hypothyroidism: a study by pulsed wave tissue Doppler imaging. Eur J Endocrinol. 2005 Apr;152(4):527-33 (namely “impairment of systolic ejection, a delay in diastolic relaxation and a decrease in the compliance to the ventricular filling. Several significant correlations were found between the parameters and serum-free T(3) and T(4) and TSH concentrations. Data strongly support the concept of a continuum spectrum of a slight thyroid failure in autoimmune thyroiditis”)

Increased incidence of auto-immune thyroiditis and overt hypothyroidism in men with acute myocardial infarct, which may have contributed to the development of the disease.

A low serum T3 or T4 (hypothyroidism) is found in cardiac failure:
28. Rays J, Wajngarten M, Gebara OC, Nussbacher A, Telles RM, Pierrer H, Rosano G, Serro-Azul JB. Long-term prognostic value of triiodothyronine concentration in elderly patients with heart failure. Am J Geriatr Cardiol. 2003 Sep-Oct;12(5):293-7 (“Lower serum T3 in cardiac failure: the odds ratio for events was 9.8 (95% confidence interval,2.2-43, p=0.004) for patients in the lowest tertile of triiodothyronine, that is, lower than 80 ng/dL, compared with patients with levels above 80 ng/dL.”)

A low serum free T3 index/reverse T3 ratio in chronic heart failure patients is a highly significant predictor of poor outcome

A low serum T3 or T4 in heart patients is associated with an increased risk of cardiac arrest/death
Cardiovascular disease and mortality is increased in hypothyroidism (+70% for both)

Thyroid therapy of cardiac patients

Corrective thyroid therapy is safe in hypothyroid patients with common benign cardiac arrhythmias at the condition that thyroid treatment is started at low doses and then gradually and prudently increased to the adequate dose. The treatment does not trigger an increase in arrhythmia frequency except in rare patients with baseline atrial premature beats. It is, however, associated with an increase in basal, average and maximal heart rates.

Thyroid therapy corrects the bradycardia of hypothyroidism

Thyroid therapy corrects the ventricular arrhythmia
39. Vanin LN, Smetnev AS, Sokolov SF, Kotova GA, Masenko VP. Thyroid function in patients with ventricular arrhythmia. Kardiologiia. 1989 Feb;29(2):64-7 (“Thyroid therapy for hypothyroidism led to the disappearance of paroxysms of ventricular tachycardia and reduced the total number and grades of ventricular extra-systoles in patients with ventricular arrhythmias; moreover, sensitivity to antiarrhythmic agents developed to replace an earlier resistance”)

Coronary heart disease in humans: the improvement with thyroid treatment
40. Barnes BO. Prophylaxis of ischaemic heart-disease by thyroid therapy. Lancet. 1959 Aug 22;2:149-52
42. Israel M. An effective therapeutic approach to the control of atherosclerosis illustrating harmlessness of prolonged use of thyroid hormone in coronary disease. Am J Dig Dis. 1955 June;161-8

Adequate thyroxine replacement in hypothyroidism prevents coronary artery disease progression

Desiccated thyroid therapy improves cardiac failure refractory to digitalis in humans

T3-therapy improves the outcome of open heart sugery, especially heart transplants

**Thyroid hormone therapy greatly reduces the lesions of experimental myocardial infarct in rats**


**Thyroid therapy reduces coronary artery disease and cardiac fibrosis in mice**


**Thyroid therapy reduced the lesions of experimental cardiac arrest in dogs**


**Thyroid therapy reduced the complications of hemorrhagic shock in dogs**

THYROID THERAPY AND BONE DENSITY

Studies with association between thyroid therapy and increased loss of bone density

Bone loss during thyroid treatment mainly occurs in HRT untreated postmenopausal women and who have a suppressed TSH, possibly being overtreated with thyroid hormones


Bone loss is mainly transitory only during the first year with no increased fracture incidence


Oestrogen therapy neutralizes, prevents bone loss induced by corrective thyroid therapy


Studies where thyroid therapy does not cause or increase loss of bone density


Studies where thyroid therapy improves bone formation

Studies with association between thyroid therapy and increased loss of bone density