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

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

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

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Senescence is associated with alterations of the circadian cycle of serum TSH:
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Imbalanced apoptosis*:* TSH inhibits undesirable apotosis

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Malaborption of important nutrients: thyroid hormones improve macronutrient uptake

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Thyroid hormones and psychic well-being

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

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

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

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Infertility: the association with lower thyroid hormone levels

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Thyroid hormones and age-related diseases

Hypercholesterolemia: the association with lower thyroid hormone levels

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Atherosclerosis: the association with lower thyroid hormone levels

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Atherosclerosis: the improvement with thyroid treatment

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Arterial hypertension: the improvement with thyroid treatment

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Obesity: the association with lower thyroid hormone levels

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Obesity: the improvement with thyroid treatment

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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

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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)*
9. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. J Clin Endocrinol Metab. 2005;90:581–5
10. Surks MI. Commentary: subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. J Clin Endocrinol Metab. 2005;90:586–7
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

13. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995;43:55–68
14. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002; 87:489–99
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
16. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003;58:138–40
17. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid. 2003 Jan;13(1):3-126

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**

18. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. Thyroid. 2004;14:853–7

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 preoxidase 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.)

19. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003;58:138–40
20. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002; 87:489–99
21. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126

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*

22. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002; 87:489–99
23. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003;58:138–40

Publications with data to support a more narrow reference range for serum TSH that would be obtained when persons with diffuse hypoechogenicity of the thyroid on ultrasound, a condition that precedes thyroid peroxidase antibody positivity in autoimmune thyroid disease, **would be excluded**

24. Pedersen OM, Aardal NP, Larssen TB, Varhaug JE, Myking O, Vik-Mo H. The value of ultrasonography in predicting autoimmune thyroid disease. Thyroid. 2000;10:251–9

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

25. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract. 2002;8:457–69

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 unjustifiedly skewed the upper end of the TSH curve (NHANES data).* **For African-Americans, the TSH reference range should therefore be lower than in whites**

26. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489–9

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 peroxidise antibodies are detected"**

28. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126

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

29. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126

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

30. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National

Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126
31. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf). 1991;34:77-83
32. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. Thyroid. 2004;14:853–7
33. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–34
34. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med. 1991;151:165–8
35. Hershman JM, Pekary AE, Berg L, Solomon DH, Sawin CT Serum thyrotropin and thyroid hormone levels in elderly and middle-aged euthyroid persons. J Am Geriatr Soc. 1993;41:823–8
36. Parle JV, Maisonneuve P, Sheppare MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet. 2001;358:861–5

<u>The TSH reference range for an INDIVIDUAL is narrower than the reference range for a population</u>

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**

37. Fraser CG, Harris EK. Generation and application of data on biological variation in clinical chemistry. Crit Rev Clin Lab Sci. 1989;27:409–37
38. Harris EK. Effects of intra- and interindividual variation on the appropriate use of normal ranges. Clin Chem. 1974;20:1535–42

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)

39. 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

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

40. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003;58:138–40
41. Meikle AW, Stringham JD, Woodward MG, Nelson JC. Hereditary and environmental influences on the variation of thyroid hormones in normal male twins. J Clin Endocrinol Metab. 1988 ; 66:588–92

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.

42. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National

Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126

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 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)

43. Cooper DS. Subclinical hypothyroidism. N Engl J Med. 2001;345:260–5
44. Ayala A, Wartofsky L. Minimally symptomatic (subclinical) hypothyroidism. Endocrinologist. 1997;7:44–50

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

89. Brabant G, Prank K, Ranft U, Schuermeyer T, Wagner TO, Hauser H, Kummer B,
45. Feistner H, Hesch RD, von zur Muhlen A. Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman. J Clin Endocrinol Metab. 1990 Feb;70(2):403-9

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

46. Pain RW. Simple modifications of three routine in vitro tests of thyroid function. Clin Chem. 1976; 22(10): 1715-8.
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

49. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–34
50. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. Thyroid. 2004;14:853–7

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*

51. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995; 43:55–68
52. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf). 1991;34:77–83
53. Huber G, Staub J-J, Meier C, Mitrache C, Guglielmetti M, Huber P, Braverman LE. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab. 2002;87:3221–6
54. Kabadi UM. 'Subclinical hypothyroidism:' natural course of the syndrome during a prolonged follow-up study. Arch Intern Med. 1993;153:957-61

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.

55. Koenig RJ, Leonard JL, Senator D, Rappaport N, Watson A, Larsen PR. Regulation of thyroxine 5'-deiodinase activity by 3,5,3'-triiodothyronine in cultured anterior pituitary cells. Endocrinology. 1984 Jul;115(1):324-9.

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.**

56. Suda AK, Pittman CS, Shimizu T, Cambers JB. The production and metabolism of 3,5,3'-triiodothyronine and 3,3',5'-triiodothyronine in normal and fasting subjects. J Clin Endocrinol Metab. 1978 Dec;47(6):1311-9
57. Larsen PR, Silva JE, Kaplan MM. Relationships between circulating and intracellular thyroid hormones: Physiological and clinical implications. Endocr Rev. 1981 Winter;2(1):87-102.
58. Chanoine JP, Safran M, Farwell AP, Tranter P, Ekenbarger DM, Dubord S, Arthur JR, Beckett GJ, Braverman LE Dubord S, Alex S, Arthur JR, Beckett GJ, Braverman LE, Leonard JLl. Selenium deficiency and type II 5'-deiodinase regulation in the euthyroid and hypothyroid rat: evidence of a direct effect of thyroxine. Endocrinology. 1992 Jul;131(1):479-84

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.**

59. Urban RJ. Neuroendocrinology of aging in the male and female. Endocrinol Metab Clin North Am. 1992;21(4): 921-31.

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
61. Pacchiarotti A, Martino E, Bartalena L, Aghini Lombardi F, Grasso L, Buratti L, Falcone M, Pinchera A. Serum free thyroid hormones in subclinical hypothyroidism. J Endocrinol Invest. 1986 Aug;9(4):315-9
62. Surks MI, Chopra IJ, Mariosh CN, Nicoloff JT, Salomon DH. American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. JAMA. 1990 Mar 16;263(11):1529-32
63. Davis JR, Black EG, Sheppard MC. Evaluation of a sensitive chemiluminescent assay for TSH in the follow-up of treated thyrotoxicosis. Clin Endocrinol Oxf. 1987; 27(5): 563-70

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

65. Smallridge RC. Metabolic, physiologic, and clinical indexes of thyroid function. In Werner and Ingbar's The Thyroid, 7th edition, Braverman LE and Utiger RP, Lippincott-Raven Publishers, Philadelphia, 1996
66. Foldes J, Tarjan G, Banos C, Nemeth J, Varga F, Buki B. Biologic markers in blood reflecting thyroid hormone effect at peripheral tissue level in patients receiving levothyroxine replacement for hypothyroidism. Exp Clin Endocrinol. 1992; 99(3): 129-33

Conditions or factors that DEPRESS the serum TSH

Aging

67. Urban RJ. Neuroendocrinology of aging in the male and female. Endocrinol Metab Clin North Am. 1992;21(4): 921-31
68. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med. 1991; 151(1): 165-8

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
70. Borst GC, Osburne RC, O'Brian JT, Georges LP, Burman KD. Fasting decreases thyrotropin responsiveness to thyrotropin-releasing hormone: A potential cause of misinterpretation of thyroid function tests in the critically ill. J Clin Endocrinol Metab. 1983 Aug;57(2):380-3
71. Campbell GA, Kurcz M, Marshall S, Meites J. Effects of starvation in rats on serum levels of follicle stimulating hormone, luteinizing hormone, thyrotropin, growth hormone and prolactin; response to LH-releasing hormone and thyrotropin-releasing hormone. Endocrinology. 1977; 100(2): 580-7
72. Opstad PK. The thyroid function in young men during prolonged physical stress and the effect of energy and sleep deprivation. Clin Endocrinol. 1984; 20: 657-69.

Strenuous physical exercise

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

Pregnancy (first trimester)

74. Braverman LE and Utiger RE, Lippincott-Raven Publisers, Philadelphia. 1996; 220-40.

Depression and anxiety disorders

75. Bartalena L, Placidi GF, Martino E, Falcone M, Pellegrini L, Dell'Osso L, Pacchiarotti A, Pinchera A. Nocturnal serum thyrotropin (TSH) surge and the TSH response to TSH-releasing hormone: dissociated behavior in untreated depressives. Clin Endocrinol Metab. 1990 Sep;71(3):650-5.
76. Rupprecht R, Rupprecht C, Rupprecht M, Noder M, Mahlstedt J. Triiodothyronine, thyroxine, and TSH response to dexamethasone in depressed patients and normal controls. Biol Psychiatry. 1989;25(1): 22-32.
77. Maeda K, Yoshimoto Y, Yamadori A. Blunted TSH and unaltered PRL responses to TRH following repeated administration of TRH in neurological patients: A replication of neuroendocrine features of major depression. Biol Psychiatry. 1993; 33(4): 277-83.
78. Duval F, Macher JP, Mokrani MC. Difference between evening and morning thyrotropin responses to protirelin in major depressive episode. Arch Gen Psychiatry. 1990; 47(5): 443-8.
79. Loosen PT, Prange AJ Jr. erum thyrotropin response to thyrotropin-releasing hormone in psychiatric patients: A review. Am J Psychiatry 1982; 139(4): 405-16.

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

80. Devos P. Rationele keuze van schildklierfunctie tests. Tijdschr Geneesk. 1990; 46(8): 591-9
81. Alexander CM, Kaptein EM, Lum SMC, Spencer CA, Kumar K, Nicoloff JT. Pattern of recovery of thyroid hormone indices associated with treatment of diabetes mellitus. J Clin Endocrinol Metab. 1982; 54: 362-366
82. Andrade SF, Kanitz-Ml, Povoa H Jr. Study of thyrotropic reserve in diabetics of adult type. Acta-Biol Mod Ger 1977; 36(10): 1479-81

83. Gonzalez C, Montoya-E, Jolin T. Effect of streptozotocin diabetes on the hypothalamic pituitary thyroid axis in the rat. Endocrinology 1980; 107(6): 2099-103
84. Rossi GL, Bestetti GE, Tontis DK, Varini M. Reverse hemolytic plaque assay study of luteinizing and follicle-stimulating hormone and thyrotropin secretion in diabetic rat pituitary glands. Diabetes 1989; 38(10): 1301-6
85. Adriaanse R, Brabant G, Endert E, Wiersinga W. Pulsatile thyrotropin secretion in patients with Cushing's syndrome. Metabolism. 1994 Jun;43(6):782-6
86. Beyer HK-, Schuster P, Pressler H. Studies on hypothalamic pituitary thyroid regulation in hemodialysis patients. Nuklearmedizin 1981;20(1):19-24
87. Kokei S, Inoue T, lino S. Serum free thyroid hormones and response of TSH to TRH in nonthyroidal illnesses. Nippon Naibunpi Gakkai Zasshi. 1986; 62(11): 1231-43
88. De Marinis L, Mancini A, Masala R, Torlontano M, Sandric S, Barbarino A. Evaluation of pituitary-thyroid axis response to acute myocardial infarct. J Endocrinol Invest. 1985; 8(6): 519-22
89. Rondanelli M, Solerte SG, Fioravanti M, Scevola K, et al. Circadian secretory pattern of growth hormone, insulin-like growth factor type I, cortisol, adrenocorticotropic hormone, thyroid-stimulating hormone, and prolactin during HIV infection. AIDS Res Hum Retroviruses. 1997; 13(14): 1243-9.
90. Wintemitz WW, Dzur JA. Pituitary failure secondary to head trauma. Case report. J Neurosurg. 1976; 44(4): 504-5
91. Dzur JA, Wintemitz WW. Posttraumatic hypopituitarism: Anterior pituitary insufficiency secondary to head trauma. South Med J. 1976; 69(10): 1377-9
92. Modigliani E, Periac P, Perret G, Hugues JN, Coste T. TRH response in 53 patients with chronic alcoholism. Ann Med Interne Paris. 1979; 130(5):297-302
93. Ekman AC, Vakkuri 0, Ekman M, Leppalusto J, Ruckonen A, Knip M. Ethanol decreases nocturnal plasma levels of thyrotropin and growth hormone but not those of thyroid hormones or protection in man. J Clin Endocrinol Metab. 1996; 81(7):2627-32
94. Bacci V, Schussler GC, Kaplan TB. The relationschip between serum triidothyronine and thyrotropin during systemic illness. J Clin Endocrinol Metab. 1982; 54:1229-35
95. Hamblin PS, Dyer SA, Mohr VS, Le Grand BA, Lim CF, Tuxen DV, Topliss DJ, Stockigt JR. Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. J Clin Endocrinol Metab. 1986 Apr;62(4):717-22
96. Bermudez F, Sucks MI, Opperheimer JH. High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. J Clin Endocrinol Metab. 1975; 41: 27-40.

Medications: *thyroid therapy, estroprogestative birth control pills, progestogens, anti-infammatory agents (incl. glucocorticoids and aspirin), antidepressants, L-Dopa, bromocriptine, neuroleptica, anti-hypertensives, antiarrhythmics (amiodarone), hypolipemic agents, IGF-1, somatostatin, etc.*

97. Franklyn JA, Black EG, Betteridge J, Sheppard MC. Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. J Clin Endocrinol Metab. 1994;78(6):1368-71
98. Gow SM, Caldwell G, Toft AD, Seth J, Hussey AJ, Sweeting VM, Beckett GJ. Relationship between pituitary and other target organ responsiveness in hypothyroid patients receiving thyroxine replacement. J Clin Endocrinol Metab. 1987;64(2):364-70
99. Custro N, Scafidi V Costanzo G, Corsello FP. Variations in the serum levels of thyroid hormones and TSH after intake of a dose of L-thyroxine in euthyroid subjects and in adequately treated hypothyroid patients. Bull Soc Ital Biol Sper. l989; 65(11):1045-52
100. England ML, Hershman JM. Serum TSH concentration as an aid to monitoring compliance with thyroid hormone therapy in hypothyroidism. Am J Med Sci. 1986 Nov;292(5):264-6
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

102. Fraser WD, Biggart EM, O'Reilly DS, Gray HW, McKillop JH, Thomson JA. Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine replacement? Br Med J (Clin Res Ed). 1986 Sep 27;293(6550): 293-808
103. Cooper DS, Walker H, Rodbard D, Maloof F. Peripheral responses to thyroid hormone before and after L-thyroxine therapy in patients with subclinical hypothyroidism. J Clin Endocrinol Metab. 1981 Dec;53(6):1238-42
104. Saberi M, Utiger RD. Serum thyroid hormone and thyrotropin concentrations during thyroxine and triiodothyronine therapy. J Clin Endocrinol Metabol. 1974;39:923-7
105. Rey Stocker I, Zufferey MM, Lemarchand MT, Rais M. The sensibility of the hypophysis, the gonads and the thyroid before and after the administration of oral contraceptives. A resume. Pediatr Ann. 1981;10(12):15-20.
106. Lemarchand-Beraud T. Influence of estrogens on pituitary responsiveness to LHRH and TRH in human. Reymond M, Berthier C. Ann Endocrinol Paris. 1977; 38(6): 379-82.
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114. Trainer PI, Holly 1, Medbak S, Rais LH, Besser GM. The effect of recombinant IGF-1 on anterior pituitary function in healthy volunteers. Clin Endocrinol (Chef) 1994; 41(6): 801-7.

Toxic foods: *MSG, alcohol*

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

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FACTORS that ELEVATE the serum TSH

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

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Medications: *iodine, antithyroidea, , lithium, neuroleptica (haloperidol, chlorpromazine), cimetidine, sulfapyridine, clomifen, antidepressants (sertraline), antihistaminic agents, cholestograhic agents, etc.*

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133. Mc Caven KC, Garber JR, Spark R. Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. N Engl J Med. 1997; 337(14):1010-1
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Auto-immune thyroiditis **and hypothyroidism:** *primary, iodine-deficient, thyroid hormone resistance*

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TSH-secreting tumors (rare)

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FACTORS that ELEVATE or DEPRESS serum TSH

Physiological serum TSH fluctuations

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95. Rose SR, Nisula BC. Circadian variation of thyrotropin in childhood. J Clin Endocrinol Metab. 1989; 68(6):1086-90
96. Scanlon MF, Weetman AP, Lewis M, Pourmand M, Rodriguez Arnao MD, Weightman DR, Hall R. Dopaminergic modulation of circadian thyrotropin rhythms and thyroid hormone levels in euthyroid subjects. J Clin Endocrinol Metab. 1980 Dec;51(6):1251-6
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Variations in the biological activity of TSH

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TSH test kit imperfections

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103. Spencer CA, Takeuchi M, Kazarosyan M, MacKenzie F, Beckett GJ, Wilkinson E. Interlaboratory/intermethod differences in functional sensitivity of immunometric assays of thyrotropin (TSH) and impact on reliability of measurement of subnormal concentrations of TSH. Clin Chem. 1995 Mar;41(3):367-74
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105. Laurberg P. Persistent problems with the specificity of immunometric TSH assays. Thyroid. 1993 Winter;3(4):279-83
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111. Bartlett WA, Browning MC, Jung RT. Artefactual increase in serum thyrotropin concentration caused by heterophilic antibodies with specificity for IgG of the family Bouidea. Clin Chem. 1986; 32(12): 22(4-9)
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113. Seghers J, Schruers F, De Nayer P, Beckers C. Interference in thyrotropin (TSH) determination: Falsely elevated TSH values in a transplanted patient. Eur J Nucl Med. 1989; 15(4): 194-6
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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

116. Talbot JN, Duron F, Feron R. Aubert P, Milhaud G. Thyroglobulin, thyrotropin and thyrotropin binding inhibiting immunoglobulins assayed at the withdrawal of antithyroid drug therapy as predictors of relapse of Graves' disease within one year. J Endocrinol Invest. 1989; 12(9): 589-95

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

117. Franklyn JA, Black EG, Betteridge J, Sheppard MC. Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. J Clin Endocrinol Metab 1994; 78(6): 1368-71
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After intake of thyroidhormones, 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'-diiodothyronine (T2) on thyrotropin-releasing hormone-induced release of thyrotropin in the rat in vitro. Endocrinology. 1978;103(2):393-402

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

120. Calaciura F, Motta RM, Miscio G, Fichera G, Leonardi D, Carta A, Trichitta V, Tassi V, Sava L, Vigneri R. Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. J Clin Endocrinol Metab. 2002;87:3209–14

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.*

121. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126

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

122. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126
123. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf). 1991;34:77-83
124. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. Thyroid. 2004;14:853–7

125. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–34
126. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med. 1991;151:165–8
127. Hershman JM, Pekary AE, Berg L, Solomon DH, Sawin CT Serum thyrotropin and thyroid hormone levels in elderly and middle-aged euthyroid persons. J Am Geriatr Soc. 1993;41:823–8
128. Parle JV, Maisonneuve P, Sheppare MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet. 2001;358:861–5

Other tests : urinary T3 as a complementary test

129. Baisier W, Hertoghe J, Eeckhaut W. Thyroid insufficiency Is TSH measurement the only diagnostic tool? J Nutr Environm Med. 2000; 10(3): 109-113

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 off 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 recoveryback 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 muU 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 ofr 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 echildren 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 too 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
6. Johnston MW, Squires AH, Farquharson RF. The effect of prolonged administration of thyroid. Ann Intern Med. 1951 Nov;35(5):1008-22
7. Riggs DS, Man EB, Winkler AW. Serum iodine of euthyroid subjects treated with desiccated thyroid. J Clin Invest. 1945;24:722-31
8. Stein RB, Nicoloff JT. Triiodothyronine withdrawal test -a test of thyroid-pituitary adequacy. J Clin Endocrinol Metab. 1971 Feb;32(2):127-9

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*

1. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995; 43:55–68
2. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf). 1991;34:77–83
3. Huber G, Staub J-J, Meier C, Mitrache C, Guglielmetti M, Huber P, Braverman LE. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab. 2002;87:3221–6
4. Kabadi UM. 'Subclinical hypothyroidism:' natural course of the syndrome during a prolonged follow-up study. Arch Intern Med. 1993;153:957-61

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/lL. 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)

5. Meier C, Staub J-J, Roth C-B, Guglielmetti M, Kunz M, Miserez AR, Drewe J, Huber P, Herzog M, Muller B. TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism. Am J Med. 2001;112:348–54
6. Meier C, Staub J-J, Roth C-B, Guglielmetti M, Kunz M, Miserez 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; 86:4860–6
7. Cooper DS 2001 Subclinical hypothyroidism. N Engl J Med 345:260–5
8. Ayala A, Wartofsky L. Minimally symptomatic (subclinical) hypothyroidism. Endocrinologist. 1997;7:44–50
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

10. 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;138:141–5
11. Ayala A, Wartofsky L 2002 The case for more aggressive screening and treatment of mild thyroid failure ("subclinical" hypothyroidism). Cleveland Clin J Med. 69:313–20
12. Faber J, Petersen L, Wiinberg N, Schifter S, Mehisen J. Hemodynamic changes after levothyroxine treatment in subclinical hypothyroidism. Thyroid. 2002; 12:319–24
13. Monzani F, DiBello V, Caraccio N, Bertini A, Giorgi D, Guisti C, Ferranni E. Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. J Clin Endocrinol Metab. 2001; 86:1110–5

14. Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A, Bone F, Lombardi G, Sacca L. Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. J Clin Endocrinol Metab. 1999; 84:2064–7
15. Di Bello V, Monzani F, Giorgi D, Bertini A, Caraccio N, Valenti G, Talini E, Paterni M, Ferrannini E, Giusti C. Ultrasonic myocardial textural analysis in subclinical hypothyroidism. J Am Soc Echocardiogr. 2000;13:832–40
16. Lekakis J, Papamichael C, Alevizaki M, Piperingos G, Marafelia P, Mantzos J, Stametelopoulos S, Koutras DA. Flow-mediated, endothelium-dependent vasodilatation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin values. Thyroid. 1997; 7:411-4
17. Taddei S, Caraccio N, Virdis A, Dardano A, Versari D, Ghiadoni L, Salvetti A, Ferrannini E, Monzani F. Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. J Clin Endocrinol Metab. 2003;88:3731–7
18. Bakker SJ, ter Maaten JC, Popp-Snijders C, Slaets JPJ, Heine RJ, Gans ROB. The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. J Clin Endocrinol Metab. 86:1206–11
19. Krausz Y, Freedman N, Lester H, Newman JP, Barkai G, Bocher M, Chisin R, Bonne O. Regional cerebral blood flow in patients with mild hypothyroidism. J Nucl Med. 2004; 45:1712–5
20. Imaizumi M, Akahoshi M, Ichimaru S, Nakashima E, Hida A, Soda M, Usa T, Ashizawa K, Yokayama N, Maeda R, Nagataki S, Eguchi K. Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. J Clin Endocrinol Metab. 2004;89:3365–70
21. Monzani F, Caraccio N, Kozakowa M, Dardano A, Vittone F, Virdis A, Taddei S, Palombo C, Ferrannini C. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2004;89:2099–106

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

22. Monzani F, Del Guerra P, Caraccio N, Pruneti CA, Pucci E, Luisi M, Baschieri L. Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. Clin Investig. 1993 May;71(5):367-71
23. Tappy L, Randin JP, Schwed P, Wertheimer J, Lemarchand-Beraud T. Prevalence of thyroid disorders in psychogeriatric inpatients. A possible relationship of hypothyroidism with neurotic depression but not dementia. J Am Geriatr Soc. 1987;35:526–31
24. Joffe RT, Levitt AJ 1992 Major depression and subclinical (grade 2) hypothyroidism. Psychoneuroendocrinology. 17:215–21
25. Haggerty Jr JJ, Stern RA, Mason GA, Beckwith J, Morey CE, Prange Jr AJ. Subclinical hypothyroidism: A modifiable risk factor for depression? Am J Psychiatry. 1993;150:508–10
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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

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Important frequency of subclinical hypothyroidism:

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Important risk of progression into overt hypothyrodism

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Importance of clinical evaluation of subclinical hypothyroidism

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

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Arguments contra thyroid treatment of mild thyroid failure

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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)

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

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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)

89. Kong WM, Sheikh MH, Lumb PJ, Naoumova RP, Freedman DB, Crook M, Dore CJ, Finer N. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. Am J Med. 2002;112:348–54

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

90. Meier C, Staub J-J, Roth C-B, Guglielmetti M, Kunz M, Miserez 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

91. Parle JV, Maisonneuve P, Sheppare MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet. 2001;358:861–5
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CONTROVERSY ON THE BEST THYROID TREATMENT: T4 OR T4-T3?

Arguments pro treatment with T4 alone*:*

Guidelines on T4 recommendation

1. Brent GA, Larsen PR. Treatment of hypothyroidism. In: Braverman LE, Utiger RD, ed. Werner and Ingbar's. The Thyroid: A Fundamental and Clinical Text. 7th ed., 1996, Philadelphia, Ravens-Lippincott Publishers
2. Utiger RD. Hypothyroidism. In DeGroot LJ et al, eds. Endocrinology, Vol 1. 2nd ed. Philadelphia, Pa: WB Saunders Co, 1989;702-21
3. Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. Ann Intern Med 1993;119:492-502
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

5. Rodriguez T, Lavis VR, Meininger JC, Kapadia AS, Stafford LF. Substitution of liothyronine at a 1:5 ratio for a portion of levothyroxine: effect on fatigue, symptoms of depression, and working memory versus treatment with levothyroxine alone. Endocr Pract. 2005 Jul-Aug;11(4):223-33
6. Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT. Does a combination regimen of thyroxine (T4) and 3,5,3'-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. J Clin Endocrinol Metab. 2003 Oct;88(10):4551-5

Arguments pro treatment with T4 and T3 combinations

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

7. Saravanan P, Simmons DJ, Greenwood R, Peters TJ, Dayan CM. Partial substitution of thyroxine (T4) with tri-iodothyronine in patients on T4 replacement therapy: results of a large community-based randomized controlled trial. Clin Endocrinol Metab. 2005 Feb;90(2):805-12
8. 1032. Kloppenburg M, Dijkmans BA, Rasker JJ. Effect of therapy for thyroid dysfunction on musculoskeletal symptoms. Clin Rheumatol. 1993 Sep;12(3):341-5
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11. Chernow B, Burman KD, Johnson DL, McGuire RA, O'Brian JT, Wartofsky L, Georges LP. T3 may be a better agent than T4 in the critically ill hypothyroid patient: evaluation of transport across the blood-brain barrier in a primate model. Crit Care Med. 1983 Feb;11(2):99-104
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T3-T4 treatment: adding T3 to T4 results in greater improvement of clinical symptoms and signs in hypothyroid patients

13. Benevicius R, Kazanavicius G, Zalinkovicius R, Prange AJ. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med.1999; 340: 424-9.

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 those of T3-T4 treatments

14. Devlin WF, Watanabe H. Thyroxin-triiodothyronine concentrations in thryoid powders. J Pharm Sci. 1966 Apr;55(4):390-3

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

15. Alley RA, Danowski TS, Robbins T JL, Weir TF, Sabeh G, and Moses CL. Indices during administration of T4 and T3 to euthyroid adults. Metabolism. 1968;17(2):97-104

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

16. Escobar-Morreale HF, del Rey FE, Obregon MJ, de Escobar GM. Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. Endocrinology. 1996 Jun;137(6):2490-502
17. Escobar-Morreale HF, Obregon MJ, Escobar del Rey F, Morreale de Escobar G. Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats. J Clin Invest. 1995 Dec;96(6):2828-38

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

18. Asper SP Jr, Selenkow HA, and Plamondon CA. A comparaison of the metabolic activities of 3,5,3'-triiodothyronine and l-thyroxine in myxedema. Bull John Hopkins Hosp. 1953; 93: 164
19. Blackburn CM, McConahey WM, Keating FR Jr, Albert A. Calorigenic effects of single intravenous doses of l-triiodothyronine and l-thyroxine in myxedematous persons. J Clin Invest. 1954 Jun;33(6):819-24

T3 is much more potent than T4

20. Gross J, Pitt-Rivers R. Physiological activity of 3:5:3'-L-triiodothyronine. Lancet. 1952 Mar 22;1(12):593-4
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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

22. Burroughs V, Shenkman L. Thyroid function in the elderly. Am J Med Sci. 1982, 283 (1): 8-17
23. Carter JN, Eastman CJ, Corcoran JM, and Lazarus L. Inhibition of conversion of thyroxine to triiodothyronine in patients with severe chronic illness. Clin Endocrinol. 1976; 5: 587-94
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26. Croxson MS and Ibbertson 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
28. Opstad PK, Falch D, Öktedalen O, Fonnum F, and Wergeland R. The thyroid function in young men during prolonged physical exercise and the effect of energy and sleep deprivation. Clin Endocrinol. 1984; 20: 657-69

29. Walfish PG. Triiodothyronine and thyroxine interrelationships in health and disease. Can Med Ass. J 1976, 115: 338-42

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

30. Feyes D, Hennemann G and Visser TJ. Inhibition of iodothyronine deiodinase by phenolphtalein dyes. Fed Eur Biomed Sci. 1982; 137(1):40-4
31. Bahn AK, Mills JL, Snyder PJ, Gann PH, Houten L, Bialik O, Hollmann L, and Utiger RD. Hypothyroidism in workers exposed to polybrominated biphenyls. N Engl J Med. 1980; 302: 31-3
32. Ikeda T, Ito Y, Murakami I, Mokuda O, Tominaga M and Mashiba H. Conversion of T4 to T3 in perfused liver of rats with carbontetrachloride-induced liver injury. Acta Endocrinol. 1986;112: 89-92
33. Paier B, Hagmüller K, Nolli Mi, Gonzalez Pondal M, Stiegler C and Zaninovich AA. Changes induced by cadmium administration on thyroxine deiodination and sulfhydryl groups in rat liver. J Endocrinol. 1993; 138: 219-24
34. Barregärd L, Lindstedt G, Schütz A, Sällsten G. Endocrine function in mercury exposed chloralkali workers. Occup Envir Med. 1994; 51: 536-40

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**

35. Burger AG, Lambert M, Cullen M. Interférence de substances médicamenteuses dans la conversion de T4 en T3 et rT3 chez l'homme. Ann Endocrinol (Paris). 1981,42:461-9
36. Grussendorf M, Hüfner M. Induction of the thyroxine to triiodothyronine converting enzyme in rat liver by thyroid hormones and analogs. Clin Chim Acta. 1977;80:61-6
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
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44. Beard J, Tobin B, and Green W. Evidence for thyroid hormone deficiency in iron-deficient anemic rats. J Nutr. 1989;772-8
45. Fujimoto S, Indo Y, Higashi A, Matsuda I, Kashiwabara N, and Nakashima I. Conversion of thyroxine into triiodothyronine in zinc deficient rat liver. J Pediatr Gastroenterol Nutr. 1986;5:799-805
46. Olin KI, Walter RM, and Keen CL. Copper deficiency affects selenoglutathione peroxidase and selenodeiodinase activities and antioxidant defense in weanling rats. Am J Clin Nutr 1994;59:654-8
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On the other hand, excesses in hormones *(glucocorticoids, ACTH, estrogens,…) and trace elements (iodine, lithium, …)* **may slow down this conversion.**

48. Heyma P, Larkins RG. Glucocorticoids decrease the conversion of thyroxine into 3,5,3'-triiodothyronine by isolated rat renal tubules. Clin Science. 1982; 62: 215-20
49. Scammell JG, Shiverick KT, Fregly MJ. Effect of chronic treatment with estrogen and thyroxine, alone and combined, on the rate of deiodination of l-thyroxine to 3,5,3'-triiodothyronine in vitro. Pharmacology. 1986;33: 52-7
50. Aizawa T, Yamada T. Effects of thyroid hormones, antithyroid drugs and iodide on in vitro conversion of thyroxine to triiodothyronine. Clin Exp Pharmacol Physiol. 1981; 8: 215-25
51. Voss C, Schrober HC, Hartmann N. Einfluss von Lithium auf die in vitro-Deioderung von l-Thyroxin in der Ratten leber. Acta Biol Med Germ. 1977; 36:1061-5

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%)

52. Hays MT. Absorption of oral thyroxine in man. J Clin Endocrinol Metab. 1968; 28 (6):749-56
53. Surks MI, Schodlow AR, Stock Jm, Oppenheimer JH. Determination of iodothyronine absorption and conversion of L-thyroxine using turnover rate techniques. J Clin Invest. 1973; 52:809-11
54. Hays MT. Absorption of triidothyronine in man. J Clin Endocrinol Metab. 1970; 30(5):675-6

Defects in the commercial T4 preparation[43,44]

55. Hubbard WK. FDA notice regarding levothyroxine sodium. Federal register. 1997; 62(157): 1-10
56. Peran S, Garriga MJ, Morreale de Escobar G, Asuncion M, Peran M. Increase in plasma thyrotropin levels in hypothyroid patients during treatment due to a defect in the commercial preparation . J Clin Endocrinol Metab. 1997;82(10):3192-5

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)*

1. Maciel BC, Gallo L Jr, Marin Neto JA, Maciel LM, Alves ML, Paccola GM, Iazigi N. The role of the autonomic nervous system in the resting tachycardia of human hyperthyroidism. Clin Sci (Lond). 1987 Feb;72(2):239-44
2. Abadie E, Leclercq JF, Fisch A, Babalis D, Blanche PM, Passa P, Coumel P. Pathogenesis of tachycardia in hyperthyroidism. Value of Holter monitoring and the use of a beta-blocker. Presse Med. 1985 Feb 2;14(4):197-9

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)*
4. Dorr M, Volzke H. Cardiovascular morbidity and mortality in thyroid dysfunction. Minerva Endocrinol. 2005 Dec;30(4):199-216 *(5.2 times more risk of atrial fibrillation in hyperthyroidism)*
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

6. Gitlin MJ. L-triiodothyronine-precipitated angina and clinical response. Biol Psychiatry. 1986 May;21(5-6):543-5

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

7. Ellyin F, Fuh CY, Singh SP, Kumar Y. Hypothyroidism with angina pectoris. A clinical dilemma. Postgrad Med. 1986 May 15;79(7):93-8

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 mycocardial infarct at admission and 3 years later *(critic: possibly due to hypocorticism that increases (the conversion of T4 into)T3??)*

8. Peters A, Ehlers M, Blank B, Exler D, Falk C, Kohlmann T, Fruehwald-Schultes B, Wellhoener P, Kerner W, Fehm HL. Excess triiodothyronine as a risk factor of coronary events. Arch Intern Med. 2000 Jul 10;160(13):1993-9

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)*

9. Sidorenko BA, Begliarov MI, Titov VN, Masenko VP, Parkhimovich RM. Blood thyroid hormones in ischemic heart disease (a comparison with coronary angiographic data, severity of stenocardia and blood lipid level)] Kardiologiia. 1981 Dec;21(12):96-101

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

<u>Arguments pro thyroid treatment</u>: 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)

<u>Associations between thyroid hormone levels and heart health</u>

Thyroid hormone levels are positively correlated with the heart rhythm

11. Tseng KH, Walfish PG, Persaud JA, Gilbert BW. Concurrent aortic and mitral valve echocardiography permits measurement of systolic time intervals as an index of peripheral tissue thyroid functional status. J Clin Endocrinol Metab. 1989 Sep;69(3):633-8

A lower serum T3 (and higher serum T4) is found in heart patients with arrhythmia

12. 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
13. Inama G, Furlanello F, Fiorentini F, Braito G, Vergara G, Casana P. Arrhythmogenic implications of non-iatrogenic thyroid dysfunction. G Ital Cardiol. 1989 Apr;19(4):303-10 *(Hypothyroidism in patients with hyperkinetic ventricular arrhythmias (25%), atrial fibrillation (37.5%) and atrio-ventricular block (37.5%))*
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%)*
15. Vanin LN, Smetnev AS, Sokolov SF, Kotova GA, Masenko VP. Study of thyroid function in patients with paroxysmal supraventricular tachycardia. Kardiologiia. 1989 Jan;29(1):71-4
16. Nesher G, Zion MM. Recurrent ventricular tachycardia in hypothyroidism--report of a case and review of the literature. Cardiology. 1988;75(4):301-6
17. Fredlund BO, Olsson SB. Long QT interval and ventricular tachycardia of "torsade de pointe" type in hypothyroidism. Acta Med Scand. 1983;213(3):231-5

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

18. Miura S, Iitaka M, Suzuki S, Fukasawa N, Kitahama S, Kawakami Y, Sakatsume Y, Yamanaka K, Kawasaki S, Kinoshita S, Katayama S, Shibosawa T, Ishii J. Decrease in serum levels of thyroid hormone in patients with coronary heart disease. Endocr J. 1996 Dec;43(6):657-63

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)

19. Cerillo AG, Bevilacqua S, Storti S, Mariani M, Kallushi E, Ripoli A, Clerico A, Glauber M. Free triiodothyronine: a novel predictor of postoperative atrial fibrillation. Eur J Cardiothorac Surg. 2003 Oct;24(4):487-92

Progressively lower serum T3 levels are found in patients with ischemic heart disease form coronary stenosis to mycocardial infarct

20. Telkova IL, Tepliakov AT. Changes of thyroid hormone levels in the progression of coronary artery disease. Arteriosclerosis. Klin Med (Mosk). 2004;82(4):29-34
21. Pavlou HN, Kliridis PA, Panagiotopoulos AA, Goritsas CP, Vassilakos PJ. Euthyroid sick syndrome in acute ischemic syndromes. Angiology. 2002 Nov-Dec;53(6):699-707
22. Pimenov LT, Leshchinskii LA. Thyroid hormone changes (iodothyroninemia) in patients with acute myocardial infarction, and their clinical significance. Kardiologiia. 1984 Oct;24(10):74-7

Low serum free and total T3 (and low free T4 and high TSH) levels are found in patients suffering from acute mycocardial infarct with poor outcome

23. Satar S, Seydaoglu G, Avci A, Sebe A, Karcioglu O, Topal M. Prognostic value of thyroid hormone levels in acute myocardial infarction: just an epiphenomenon? Am Heart Hosp J. 2005 Fall;3(4):227-33

Auto-immune thyroidiits 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 mycocardial infarct, *which may have contributed to the development of the disease.*

25. Cerillo AG, Bevilacqua S, Storti S, Mariani M, Kallushi E, Ripoli A, Clerico A, Glauber M. Free triiodothyronine: a novel predictor of postoperative atrial fibrillation. Eur J Cardiothorac Surg. 2003 Oct;24(4):487-92

A low serum T3 or T4 (hypothyroidism) is found in cardiac failure:

26. Khaleeli AA, Memon N. Factors affecting resolution of pericardial effusions in primary hypothyroidism: a clinical, biochemical and echocardiographic study. Postgrad Med J. 1982 Aug;58(682):473-6
27. Reza MJ, Abbasi AS. Congestive cardiomyopathy in hypothyroidism. West J Med. 1975 Sep;123(3):228-30
28. Rays J, Wajngarten M, Gebara OC, Nussbacher A, Telles RM, Pierri 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")*
29. Pingitore A, Landi P, Taddei MC, Ripoli A, L'Abbate A, Iervasi G. Triiodothyronine levels for risk stratification of patients with chronic heart failure. Am J Med. 2005 Feb;118(2):132-6
30. Klein I, Ojama K. In: Werner & Ingbar's The Thyroid, ed. Braverman LE & Utiger RD, Lippincott-Raven Publishers, Philadelphia, 1996, 62: 799-804

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

31. Cerillo AG, Bevilacqua S, Storti S, Mariani M, Kallushi E, Ripoli A, Clerico A, Glauber M. Free triiodothyronine: a novel predictor of postoperative atrial fibrillation. Eur J Cardiothorac Surg. 2003
32. Hamilton MA, Stevenson LW, Luu M, Walden JA. Altered thyroid hormone metabolism in advanced heart failure. J Am Coll Cardiol. 1990 Jul;16(1):91-5
33. Kozdag G, Ural D, Vural A, Agacdiken A, Kahraman G, Sahin T, Ural E, Komsuoglu B. Relation between free triiodothyronine/free thyroxine ratio, echocardiographic parameters and mortality in dilated cardiomyopathy. Eur J Heart Fail. 2005 Jan;7(1):113-8

A low serum T3 or T4 in heart patients is associated with an increased risk of cardiac arrest/death

34. Wortsman J, Premachandra BN, Chopra IJ, Murphy JE. Hypothyroxinemia in cardiac arrest. Arch Intern Med. 1987 Feb;147(2):245-8
35. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'Abbate A, Donato L. Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation. 2003 Feb 11;107(5):708-13

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

36. Dorr M, Volzke H. Cardiovascular morbidity and mortality in thyroid dysfunction. Minerva Endocrinol. 2005 Dec;30(4):199-216

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.*

37. Polikar R, Feld GK, Dittrich HC, Smith J, Nicod P. Effect of thyroid replacement therapy on the frequency of benign atrial and ventricular arrhythmias. J Am Coll Cardiol. 1989 Oct;14(4):999-1002

Thyroid therapy corrects the bradycardia of hypothyroidism

38. Yamauchi K, Takasu N, Ichikawa K, Yamada T, Aizawa T. Effects of long-term treatment with thyroxine on pituitary TSH secretion and heart action in patients with hypothyroidism. Acta Endocrinol (Copenh). 1984 Oct;107(2):218-24 *("T4 doses should be adjusted to maintain normal ET/PEP (systolic time intervals) rather than normal serum TSH levels")*

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
41. Holland FW 2nd, Brown PS Jr, Clark RE. Acute severe postischemic myocardial depression reversed by triiodothyronine. Ann Thorac Surg. 1992 Aug;54(2):301-5
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
43. Yokoyama Y, Novitzky D, Deal MT, Snow TR. Facilitated recovery of cardiac performance by triiodothyronine following a transient ischemic insult. Cardiology. 1992;81(1):34-45

Adequate thyroxine replacement in hypothyroidism prevents coronary artery disease progression

44. Perk M, O'Neill BJ; The effect of thyroid therapy on angiographic artery disease progression . Can J Card. 1997;13(3):273-6

Desiccated thyroid therapy improves cardiac failure refractory to digitalis in humans

45. Zondek H. Myxedema Heart. Munch Med Wochenschr. 1918, 65: 1180-3
46. Khaleeli AA, Memon N. Factors affecting resolution of pericardial effusions in primary hypothyroidism: a clinical, biochemical and echocardiographic study. Postgrad Med J. 1982 Aug;58(682):473-6

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

47. Novitzky D, Fontanet H, Snyder M, Coblio N, Smith D, Parsonnet V. Impact of triiodothyronine on the survival of high-risk patients undergoing open heart surgery. Cardiology. 1996 Nov-Dec;87(6):509-15.

48. Novitzky D, Cooper DK, Chaffin JS, Greer AE, DeBault LE, Zuhdi N. Improved cardiac allograft function following triiodothyronine therapy to both donor and recipient. Transplantation. 1990 Feb;49(2):311-6

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

49. Holland FW, Brown PS, Clark RE. Acute severe postischemic myocardial depression reversed by triiodothyronine**.** Ann Thorac Surg 1992 54: 301-305

Thyroid therapy reduces coronary artery disease and cardiac fibrosis in mice

50. Yao J, Eghbali M. Decreased collagen mRNA and regression of cardiac fibrosis in the ventricular myocardium of the tight skin mouse following thyroid hormone treatment. Cardiovasc Res. 1992 Jun;26(6):603-7

Thyroid therapy reduced the lesions of experimental cardiac arrest in dogs

51. Facktor MA, Mayor GH, Nachreiner RF, D'Alecy LG. Thyroid hormone loss and replacement during resuscitation from cardiac arrest in dogs. Resuscitation. 1993 Oct;26(2):141-62

Thyroid therapy reduced the complications of hemorrhagic shock in dogs

52. Shigematsu H, Shatney CH. The effect of triiodothyronine (T3) and reverse triiodothyronine (rT3) on canine hemorrhagic shock. Nippon Geka Gakkai Zasshi. 1988 Oct;89(10):1587-93.

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

4. Taelman P, Kaufman JM, Janssens X, Vandecauter H, Vermeulen A. Reduced forearm bone mineral content and biochemical evidence of increased bone turnover in women with euthyroid goitre treated with thyroid hormone. Clin Endocrinol (Oxf). 1990 Jul;33(1):107-17
5. Stall GM, Harris S, Sokoll LJ, Dawson-Hughes B. Accelerated bone loss in hypothyroid patients overtreated with L-thyroxine. Ann Intern Med. 1990 Aug 15;113(4):265-9
6. Adlin EV, Maurer AH, Marks AD, Channick BJ. Bone mineral density in postmenopausal women treated with L-thyroxine. Am J Med. 1991 Mar;90(3):360-6
7. Paul TL, Kerrigan J, Kelly AM, Braverman LE, Baran DT. Long-term L-thyroxine therapy is associated with decreased hip bone density in premenopausal women. JAMA. 1988;259:3137-41

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

8. Tremollieres F, Pouilles JM, Louvet JP, Ribot C. Transitory bone loss during substitution treatment for hypothyroidism. Results of a two year prospective study. Rev Rhum Mal Osteoartic. 1991 Dec;58(12):869-75
9. Ribot C, Tremollieres F, Pouilles JM, Louvet JP. Bone mineral density and thyroid hormone therapy. Clin Endocrinol (Oxf). 1990 Aug;33(2):143-53

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

10. Schneider DL, Barrett-Connor EL, Morton DJ. Thyroid hormone use and bone mineral density in elderly women. JAMA 1994;271:1245-9

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

11. Greenspan SL, Greenspan FS, Resnick NM, Block JE, Friedlander AL, Genant HK. Skeletal integrity in premenopausal and postmenopausal women receiving long-term L-thyroxine therapy Am J Med. 1991;91:5-14
12. Franklyn JA, Betteridge J, Daykin J, Holder R, Oates GD, Parle JV, Lilley J, Heath DA, Sheppard MC. Long-term thyroxine treatment and bone mineral density. Lancet. 1992 Jul 4;340(8810):9-13
13. Eulry F, Bauduceau B, Lechevalier D, Magnin J, Crozes P, Flageat J, Gautier D. Bone density in differentiated cancer of the thyroid gland treated by hormone-suppressive therapy. Study based on 51 cases. Rev Rhum Mal Osteoartic. 1992 Apr;59(4):247-52
14. Grant DJ, McMurdo ME, Mole PA, Paterson CR, Davies RR. Suppressed TSH levels secondary to thyroxine replacement therapy are not associated with osteoporosis. Clin Endocrinol (Oxf). 1993 Nov;39(5):529-33.

Studies where thyroid therapy improves bone formation

15. Svanberg E, Healey J, Mascarenhas D. Anabolic effects of rhIGF-I/IGFBP-3 in vivo are influenced by thyroid status. Eur J Clin Invest. 2001 Apr;31(4):329-36