APPENDIX 70

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

1. Nunez S, Leclere J. Diagnosis of hypothyroidism in the adult. Rev Prat. 1998; 48(18): 1993-8.

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

2. Nicoloff JT, Spencer CA. The use and misuse of the sensitive thyrotropin assay. J Clin Endocrinol Metab. 1990;71:553-8.
3. De Los Santos ET, Mazzaferri EL. Sensitive thyroid-stimulating hormone assays: Clinical applications and limitations. Compr Ther. 1988; 14(9): 26-33.
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 shoul be based on both clinical and laboratory findings and not solely on the results of a single laboratory test")
5. Rippere V. Biochemical victims: False negative diagnosis through overreliance on laboratory results—a personal report. Med Hypotheses. 1983; 10(2): 113.

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!)*
7. Dickey RA, Wartofsky L, Feld S. Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. Thyroid. 2005 Sep;15(9):1035-9
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

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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

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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

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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**

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

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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

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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

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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

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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
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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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129. De Nayer P, Dozin B, Vandeput Y, Bottazzo FC, Crabbe J. Altered interaction between triiodothyronine and its nuclear receptors in absence of cortisol: A proposed mechanism for increased thyrotropin secretion in corticoid deficiency states. Eur J Clin Invest. 1987 Apr;17(2):106-8
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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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***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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102. Libeer JC, Simonet L, Gillet R. Analytical evaluation of twenty assays for determination of thyrotropin (TSH). Ann Biol Clin Paris. 1989; 47(1): 1-11

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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
114. Spencer C, Eigen A, Shen D, Duda M, Quails S, Weiss S, Nicoloff J. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. Clin Chem. 1987;33(8):1391-6
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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
118. 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

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

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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