The Safe and Effective Prescribing of Thyroid Hormones: Guidelines for Doctors.

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INTRODUCTION

The British Thyroid Foundation (BTF News magazine - Issue no 67 Winter 2008/2009) and more recently the Royal College of Physicians http://www.rcplondon.ac.uk/specialties/Endocrinology-Diabetes/Documents/Hypothyroidism%20Statement.pdf have issued guidance for prescribing thyroid hormones for primary hypothyroidism which are entirely based on biochemical criteria. They also recommend solely synthetic thyroxine (T4) as the only acceptable replacement therapy.

These proscriptive guidelines have resulted in enormous patient dissatisfaction and uncertainty for clinicians. Many patients choose, often against medical advice, to increase their dose of thyroid hormones, or swap to biologically identical thyroid hormones because clinically they feel so much better. Our aim as clinicians is to give patients the best possible health and we should be working with them to ensure this while protecting against possible problems associated with overdosing.

The following is a clinical guide to the safe and effective prescribing of thyroid hormones as agreed by practicing physicians within the thyroid special interest group of the BSEM.

Underlying Principles

Patients vary in their biochemical and hormonal requirements as much as they vary in their requirement for food, micronutrients, characters and personalities. No one size fits all. The prescription of thyroid hormones is both a biochemical and a clinical decision – weight must be given to both of these issues. Conventional prescribing guidelines are almost entirely based on biochemical criteria. Problems arise because the individual person's normal range is not the same as the population normal range and most importantly not necessarily consistent with the laboratory reference ranges.

Reference ranges in individual laboratories will vary. The reason for this is that each new assay is tested against a large batch of stored sera, often obtained from blood donations. These will contain some undiagnosed thyroid disease and so the distribution (creating a bell curve of frequency) will have at its extreme ends people with both hypo and hyperthyroid abnormality but at the time of blood collection, undiscovered. This is one reason why reference ranges are wider than any normal range. Also the population normal ranges will fall well within the reference ranges of any laboratory. The dilemma is knowing clinically how to address someone who has a biochemical result within say 5 – 10% of the edge of the reported reference range. Furthermore individual normal ranges may be much narrower, running tightly within a few pmol/l – individuals have a genetically set free T4 status. As clinicians we see there is no doubt that some people feel much better running high normal levels of thyroid hormones rather than low normal levels, but remaining within, or just outside, reference ranges.

Who has Hypothyroidism?

Thyroid disease should be suspected clinically from the many clinical symptoms and signs listed in the literature. Any patient with a chronic fatigue syndrome *could* be hypothyroid. However, clinicians need to be mindful that there are a great many other causes of the symptoms in the literature and signs of allergy, poor nutritional status and toxic stress (from xenobiotics such as

heavy metals and pesticides), all need to be addressed as a separate issue. This is where biochemical tests are vital as part of the overall picture of thyroid disease.

Current biochemistry distinguishes the three common types of hypothyroidism we see in clinical practice namely:

1. Primary hypothyroidism – where the TSH is near to the limits or above the reference range. The free T4 may be low but often is not.
2. Secondary hypothyroidism – where the TSH is low. The free T4 may be low, but often is not.
3. Poor conversion of T4 to T3 – where the most active thyroid hormone, i.e. T3, is low. TSH may be high and the free T4 may be high.

Clinically we often see combinations of the above.

There are likely to be other, as yet undiscovered, biochemical indices related to other iodine containing compounds such as T1and T2. We know this because clinically many patients feel much better taking biologically identical thyroid hormones such as Armour thyroid. Currently the biochemical reasons for this are unclear.

So which patient do we start on thyroid hormones?
Those with symptoms suggestive of hypothyroidism that we cannot explain by nutritional, allergic, or toxic stress (chronic poisoning by heavy metals, pesticides, or other sych xenobiotics) who also have biochemistry which is either overtly abnormal, or results towards the limits of the reference ranges for whom there is scope to prescribe thyroid hormones, with little risk of straying outside the reference ranges..

So what are the reference ranges and how do they relate to normal ranges?
The reference range for the upper limit of TSH in UK is probably set too high. In the USA the threshold for prescribing thyroid hormones has recently been changed to a TSH of <3.0 mIU/L. A TSH at the upper limits of the reference range or low normal levels of free T4 and free T3 are associated with increased risk of many chronic degenerative diseases including cardiovascular disease, insulin resistance, lipid abnormalities, inflammation, obesity, cancer (breast, thyroid, prostate), poor survival in critical illness, poor cognitive function, depression, poor outcome of pregnancy and slow neurodevelopmental progress in babies.

Oddly in some UK laboratories, the target range after prescribing thyroid hormones is a TSH of less than 2.0 and sometimes less than 1.5. We do not see the logic for this. The target range is irrelevant when the patient is on replacement thyroid hormones. The aim is to achieve a good clinical status for the patient. This suggested target range illustrates the wide range of views in UK about thresholds and targets for prescribing thyroid hormones.

The population reference range for a Free T4 is very variable, with some labs stating a range of 7 – 17 pmol/L, others 12 – 22 pmol/L. The point here is that there is often a twofold difference between the lowest and the highest level of Free T4 within the stated reference range. Therefore there is scope to treat the patient with low levels of Free T4, but stay within or close to the reference range. Remember 5% of the "normal" population will lie outside the reference range.

All our clinical experince of patients presenting with the many symptoms and signs of hypothyroidism who improve with treatment, leads us to suspect that hypothyroidism is much more common than generally stated. Reference ranges are misunderstood because people who

could benefit from thyroid hormones are classed as normals even though they are at the limits or within 10% of the limits of the reference ranges.

The present serum biochemistry testing fails to indicate the rate of natural production and consumption of the hormones and has limited use as markers of status. The clinical picture is most important. We do need more sensitive biochemical indicators and some clinicans use urinary excretion indices as markers of sufficient hormone production. This needs further research.

How to start prescribing thyroid hormones

Firstly, the patient must satisfy the clinical criteria for a diagnosis of hypothyroidism, or be clinically euthyroid, but certainly not thyrotoxic. Secondly, there must be biochemical scope for a trial of thyroid hormones. It is important to recognise that this is a trial because in most cases we do not know if we are dealing with a patient whose genetically determined personal normal range is at the bottom or the top end of the population laboratory reference ranges.

The starting dose of thyroid hormones depends on the size and the state of unwellness of the patient. Small unwell patients should be started on just 12.5mcg daily, then increase their dose in 12.5mcg increments every two weeks until they get to 50mcg daily, at which point recheck the biochemistry. If the patient has a low T3 then some will find some benefit from a very small dose of T3 in the morning or twice daily as well as T4 replacement. Presently T3 is provided as a tiny 20 mcgm tablet and a quarter with food twice daily can dramatically improve well being. Later the T3 may not be needed and as it has a short half life, stopping this after the T4 has stabilised will quickly enable a check to be made to ensure that T4 to T3 conversion continues normally on just T4 therapy

Large and more robust individuals could be started on 50mcg daily and increase in 25mcg every two weeks until they get to 100mcg daily, wait four weeks for blood levels to stabilise and then recheck the biochemistry.

Many patients will fall between the two patients described.

So long as the patient does not develop any symptoms or signs of hyperthyroidism and the patients can be taught to self monitor, then the trial should be continued until they get to their target dose. If signs of thyrotoxicosis develop, this may be due to receptor hypersensitivity (in which case they settle down in a few days), or due to biochemical toxicosis despite the biochemistry being within reference ranges. In these cases the patient's genetically determined normal range is probably set low and is being exceeded by therapy. In either event, reduce the dose by 12.5 - 25mcg to relieve symptoms and assess the patient clinically and biochemically at the next convenient appointment.

Once up to the target dose, which may be anything between 25 and 200mcgms of thyroxine (or its equivalent), wait four weeks for blood levels of thyroid hormones to stabilise and then re-check for a free T4, free T3 and TSH, assess things clinically and continue to adjust according to the above parameters.

Monitoring

Once stable on the above regimes, so long as no new symptoms arise, patients should be rechecked clinically and biochemically on an annual basis. Once stable for two to three years, again so long as no new symptoms arise, rechecking can be safely done every two to three years.

However, some patients lose the ability to convert T4 to active T3 and monitoring should always check both these hormones.

Swapping the patient to bio-identical thyroid replacement hormones.

One obvious biochemical reason for swapping to bio-identical hormones is if the patient has high levels of T4, but low levels of T3, i.e. they have poor conversion. This is because the biologically identical hormones contain T3. However, some patients just feel much better on biologically identical hormones – the reason why is not clear, but there are other compounds in biologically identical hormones such as T1 and T2, which may well have biological activity, which then translates into clinical well being.

There are many biologically identical thyroid hormone preparations on the market, but they all amount to the same thing – standardised, dried, whole thyroid extract (from pig thyroid). The stability and keeping qualities are excellent. They have many names such as Armour thyroid, generic thyroid, natural thyroid, Thyroid S, Westhroid and so on. They are classified as Unlicensed Medicines but can legally be prescribed by NHS prescription or private prescription.

60mg of biologically identical hormone is the same thing as 1 grain, which contains 36mcg of T4 and 9mcg of T3. Since T3 is four times more active than T4, the T3 equivalent is 36mcg. Therefore one grain of natural thyroid is "equivalent" to 72mcg of T4.

Therefore a patient stabilised on 75mcg of synthetic T4 could easily be swapped to one grain of biologically identical hormone. Because T3 has a short half life, this is given in two doses daily.

Monitoring biologically identical hormones

The principles are exactly the same as synthetic thyroid hormones. However, the ratio of T3 to T4 is high for human requirements and so expect the blood tests to show high T3 compared to T4. Because T3 is short acting, levels fluctuate quite markedly over the 24 hours so the time at which the blood test is taken also needs to be taken into account in interpreting the results.

Monitoring the patient who only feels well on high doses of thyroid hormones with a suppressed TSH

Some patients fall into this category and it is this which prevents many doctors from prescribing thyroid hormones in the necessary doses to allow their patients to feel well.

Our experience is that many patients suffering from a chronic fatigue syndrome have secondary hypothyroidism. In CFS/ME there is a general suppression of the hypothalamic pituitary adrenal axis. Furthermore it is likely that a decline in the activity of the HPA axis is part of the normal ageing process and therefore we believe the incidence of secondary hypothyroidism in the elderly is likely to be increasing with age. Many doctors are nervous of prescribing thyroid hormones when the TSH is low. However, our view is that so long as levels of Free T4 and Free T3 are adjusted as we describe, and the patient feels well, complications need not arise.

Possible long term complications of thyroid hormones

The two complications most often cited are osteoporosis and heart disease. Three points here. The first is that *hypo*thyroidism is also a major risk factor for both osteoporosis and heart disease. Secondly there are excellent nutritional interventions which are highly protective against the development of both osteoporosis and heart disease and the good doctor may wish to consider these in the longer term for the perceived vulnerable patient . The third point, of course, is that unless the patient is feeling well, he/she will be unable to exercise. Exercise is vitally important to protect sufferers from heart disease and osteoporosis.

Properly done, the environmental approach combined with thyroid hormones is an essential tool to protect against chronic degenerative disease.

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We are grateful to the International Hormone Society **www.intlhormonesociety.org** for supplying the following references which underpin the above prescribing guidelines.

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97. Liel Y, Harman-Boehm I, Shany S. Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult hypothyroid patients. J Clin Endocrinol Metab. 1996:80:857-9

Thyroid treatment: side effects, complications

98. 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
99. Stall GM, Harris S, Sokoll LJ, Dawson-Hughes B. Accelerated bone loss in hypothyroid patients over treated with contemporary preparations. Ann Intern Med 1990; 105:11-5
100. 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
101. Franklyn JA, Betteridge J, Daykin J, Holder R, Oates GD, Parle JV, et al. Long-term thyroxine treatment and bone mineral density. Lancet. 1992;340:9-13

102. Schneider DL, Barrett-Connor EL, Morton DJ. Thyroid hormone use and bone mineral density in elderly women. JAMA. 1994;271:1245-9
103. Sawin CT, Geller A, Wolk PA, et al. Low serum thyrotropin concentration as a risk factor for atrial fibrillation in older persons. N Engi J Med. 1994;331:1249-52
104. Shibata H, Hayakawa H, Hirukawa M, Tadokoro K, Ogata E. Hypersensitivity caused by synthetic thyroid hormones in a hypothyroid patient with Hashimoto's thyroiditis. Arch Intern Med. 1986; 146:1624-5
105. Magner J, Gerber P. Urticaria due to blue dye in synthroid tablets. Thyroid. 1994 Fall;4(3):341

Some patients with low or borderline low cortisol levels may poorly tolerate any type of thyroid medication, and in particular thyroxin-triiodothyronine combinations

Studies that show that the conversion of T4 into T3 and serum T3 is increased in cortisol deficiency, reducing the serum level of T4 while increasing that of T3

106. Comtois R, Hebert J, Soucy JP. Increased in Ts levels during hypocorticism in patients with chronic secondary adrenocorticaal deficiency Insufficiency. Acta Endocrinol. (Copenh). 1992; 126(4):319-24

Studies that show that glucocorticoids reduce the conversion of T4 to T3

107. Westgren U, Ahren B, Burger A, Ingemansson S, Melander A. Effects of dexamethasone, desoxycorticosterone, and ACTH on serum concentrations ot thyroxine, 3,5,3'-triiodothyronine and 3,3',5'-triiodothyronine. Acta Med Scand. 1977;202 (1-2): 89-92
108. 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

Studies that show reduced T3 nuclear receptors in adrenal deficiency

De Nayer P et al. Altered interaction between triiodothyroinine and its nuclear receptors in absence of cortisol: a proposed mechanism for increased TSH secretion in corticossteroid deficiency states. J Clin Invest 1987; 17(2): 106-10

Diagnosis of hypothyroidism

Publications that stress the importance of both clinical and biochemical assessments in the evaluation of thyroid function

1. (No author listed). Optimal use of blood tests for assessment of thyroid function. JAMA 1993;269:2736; Thyroid. 1993;3(4):353-354
2. Larsen PR, Davies TF, Hay ID. Symptoms of hypothyroidism. In Williams' Textbook of endocrinology. 9th ed., WB Saunders: p. 461, table 11-22 (data from Ateans JH. The thyroid and its diseases. 2nd ed. JB Lippincott, Philadelphia 1948: 233)
3. Wiersinga WM. Hypothyroidism and myxedema coma. 105: 1491 In Endocrinology, 4th ed., Degroot LJ, Jameson JL. Ed., 2:
4. Zulewski H, Muller B, Exer P, Miserez AR, Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J Clin Endocrinol Metab. 1997;82:771–6

II. The reference ranges of normality for the thyroid tests are too wide and do not take into account specific individual reference ranges

A. Studies that show association of disease (markers) with serum T3 levels within the reference range

These associations are evidence suggesting that not all T3 levels within the reference ranges are healthy; some may be indicative of mild thyroid failure, and thus require correction with thyroid replacement

Serum free T3 (fT3)	2.8-5.7 pmol/L			
	1.8-3.7 pg/ml	Highest tertile	≥ 3.1 pg/ml	Auer J, et al.. Clin Cardiol. 2003 Dec;26(12):569-73
		Middle tertile	2.8 to 3.09	
		Lowest tertile	< 2.79	

Studies with data that indicate that

1) <u>The healthiest serum T3 levels may be found in the upper tertile (33%) of the reference range</u>

Study with suggestion that a healthy serum freeT3 should be in the upper two tertiles (upper 67%) of the reference range, and preferably in the upper tertile, in hemodialysis patients, otherwise, in particular in case of serum T3 in the lower tertile, there may be a higher risk of abnormal inflammatory markers (such as increases in serum interleukin-6 and C-reactive protein) markers of endothelial activation (intercellular adhesion molecule-1 [ICAM-1] and vascular cellular adhesion molecule-1 [VCAM-1]) (strong and inverse associations between free T3 and IL-6, C-reactive protein, ICAM-1, and VCAM-1)

5. Zoccali C, Tripepi G, Cutrupi S, Pizzini P, Mallamaci F. Low triiodothyronine: a new facet of inflammation in end-stage renal disease. J Am Soc Nephrol. 2005 Sep;16(9):2789-95. CNR-IBIM, Clinical Epidemiology and Pathosphysiology of Renal Diseases and Hypertension, Ospedali Riuniti, Calabria, Italy. carmine.zoccali@tin.it

Study with suggestion that a safe serum free T3 in elderly patients with heart failure should be above 80 ng/dL (upper limit of the lower tertile of the reference range), and preferably in the upper tertile (33%), otherwise the risk of adverse cardiovascular event may be significantly higher

6. 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. Division of Geriatric Cardiology, Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paolo, Brazil.

Study with suggestion that a healthy serum free T3 should be above the lower tertile (33%), and preferably in the upper tertile (33%) of the reference range in postmenopausal women, otherwise the risk of breast cancer may be highly increased

7. Strain JJ, Bokje E, van't Veer P, Coulter J, Stewart C, Logan H, Odling-Smee W, Spence RA, Steele K. Thyroid hormones and selenium status in breast cancer. Nutr Cancer. 1997;27(1):48-52. Human Nutrition Research Group, University of Ulster, Coleraine, Northern Ireland.

Study with suggestion that a healthy serum free T3 should be equal to or above 2.8 pg/ml (just above the lower tertile in patients who undergo coronary angiography, otherwise the risk is higher for having an increased severity of coronary artery atherosclerosis

8. Auer J, Berent R, Weber T, Lassnig E, Eber B. Thyroid function is associated with presence and severity of coronary atherosclerosis. Clin Cardiol. 2003 Dec;26(12):569-73. Second Medical Department, Division of Cardiology and Intensive Care, General Hospital Wels, Wels, Austria. johann.auer@khwels.at

Study with suggestion that a healthy serum TSH should be below 1.98 imU/L in patients with coronary artery disease, otherwise the risk of aggravation of coronary heart disease may be higher

9. Auer J, Berent R, Weber T, Lassnig E, Eber B. Thyroid function is associated with presence and severity of coronary atherosclerosis. Clin Cardiol. 2003 Dec;26(12):569-73. Second Medical Department, Division of Cardiology and Intensive Care, General Hospital Wels, Wels, Austria. johann.auer@khwels.at

2) <u>The healthiest serum free T3 and ratio of serum free T3/reverse T3 may be found in the upper three quartiles (75%) of the reference range</u>

Study with suggestion that a healthy serum free T3 should be above the lower quartile (25%) of the reference range in patients with end-stage renal disease, otherwise the risk of left ventricular dysfunction and left ventricular hypertrophy may be significantly increased

10. Zoccali C, Benedetto F, Mallamaci F, Tripepi G, Cutrupi S, Pizzini P, Malatino LS, Bonanno G, Seminara G. Low triiodothyronine and cardiomyopathy in patients with end-stage renal disease. J Hypertens. 2006 Oct;24(10):2039-46. CNR-IBIM, Institute of Biomedicine, Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension & Division of Nephrology, Reggio Calabria, Italy. carmine.zoccali@tin.it

Study with suggestion that a safe ratio of serum free T3/reverse T3 should be in the upper three quartiles (upper 75%)of the reference range in critically ill patients, and preferably in the upper quartile, otherwise the risk of dying may be higher

11. Peeters RP, Wouters PJ, van Toor H, Kaptein E, Visser TJ, Van den Berghe G. Serum 3,3',5'-triiodothyronine (rT3) and 3,5,3'-triiodothyronine/rT3 are prognostic markers in critically ill patients and are associated with post-mortem tissue deiodinase activities. J Clin Endocrinol Metab. 2005 Aug;90(8):4559-65 Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands.

3) <u>The healthiest serum free T3 may be found at a level of above 2.3 pg/ml (approximately the upper 4 quintiles) of the reference range</u>

12. Evrengul H, Tanriverdi H, Enli Y, Kuru O, Seleci D, Bastemir M, Kilic A, Kaftan A, Kilic M. Interaction of Plasma Homocysteine and Thyroid Hormone Concentrations in the Pathogenesis of the Slow Coronary Flow Phenomenon. Cardiology. 2006 Nov 3;108(3):186-192 Department of Cardiology, Pamukkale University Faculty of Medicine, Denizli, Turkey

4) <u>Associations between a low serum free T3 within the reference range and pathological parameters</u>

Study with suggestion that lower serum free T3 levels within the reference range may be associated in overweight and obese women with a higher risk of intra-abdominal adipose tissue, a risk factor for many diseases

13. Kunesova M, Hainer V, Obenberger J, Mikulova R, Parizkova J, Slaba S, Bezdickova D, Seidl Z. Adipose tissue distribution in obese females. Relationship to androgens,cortisol, growth hormone and leptin. Sb Lek. 2002;103(4):477-85. Obesity Management Centre of the 3rd Department of Internal Medicine, 1st Medical Faculty of Charles University, U nemocnice 1, 128 08 Prague 2, Czech Republic. mkune@lf1.cuni.cz

Study with suggestion that lower ratios of free T3/reverse T3 levels within the reference range in patients undergoing elective cardiac surgery may be associated with a higher risk of delirium after surgery

14. van der Mast RC, van den Broek WW, Fekkes D, Pepplinkhuizen L, Habbema JD. Is delirium after cardiac surgery related to plasma amino acids and physical condition? J Neuropsychiatry Clin Neurosci. 2000 Winter;12(1):57-63. Department of Psychiatry, Dijkzigt University Hospital Rotterdam, The Netherlands.

Study with suggestion that lower serum free T3 levels within the reference range in women may be associated with a higher risk of breast cancer

15. Takatani O, Okumoto T, Kosano H, Nishida M, Hiraide H, Tamakuma S. Relationship between the levels of serum thyroid hormones or estrogen status and the risk of breast cancer genesis in Japanese women. Cancer Res. 1989 Jun 1;49(11):3109-12. Third Department of Internal Medicine, National Defense Medical College, Saitama, Japan.

Study with suggestion that lower serum total T3 and free T3 index levels within the reference range in critically ill patients may be associated with a higher risk of dying

16. Maldonado LS, Murata GH, Hershman JM, Braunstein GD. Do thyroid function tests independently predict survival in the critically ill? Thyroid. 1992 Summer;2(2):119-23. Department of Medicine, Cedars-Sinai Medical Center, UCLA School of Medicine.

B. <u>Studies that show association of disease (markers) with serum T4 levels within the reference range</u>

Evidence suggests that not all serum T4 levels within the reference ranges are healthy; some may be indicative of mild thyroid failure, and thus require correction with thyroid replacement.

Free T4 (fT4)	0.8-1.8 ng/dl 10.3-27.7 pmol/L			
Total T4 (TT4)	4.5-12.5 µg/dl	Highest tertile	8.1 to 12.5 µg/dL	Volpato S, et al.. Neurology. 2002;:1055-61
		medium tertile	6.6 to 8.0 µg/dl)	
		lowest tertile	4.5 to 6.5 µg/dL	

Studies with data that indicate that

1) <u>The healthiest serum T4 levels may be found in the upper quartile of the reference range</u>

A study where it is suggested that a healthy serum free T4 in adults should be above the lower quartile (25%) of the reference range, preferably in the upper quartile, otherwise the risk of having metabolic syndrome and clinically features of it such as a high fasting glucose, a high blood pressure, a high serum total triglyceride, 8% had low high-density lipoprotein cholesterol, and obesity significantly increases

17. Lin SY, Wang YY, Liu PH, Lai WA, Sheu WH. Lower serum free thyroxine levels are associated with metabolic syndrome in a Chinese population. Metabolism. 2005 Nov;54(11):1524-8. Division of Endocrinology and Metabolism, Department of Medicine, Taichung Veterans General Hospital, Taichung 407, Taiwan. sylin@vghtc.gov.tw

Study with suggestion that a healthy serum free T3 should be in the upper half of the reference range in patients with Alzheimer's disease, otherwise the rish of depression may slightly increase

18. Stuerenburg HJ, Arlt S, Mueller-Thomsen T. Free thyroxine, cognitive decline and depression in Alzheimer's disease. Neuro Endocrinol Lett. 2006 Aug;27(4):535-7. Neurological Department, Median-Klinik Bad Suelze, Bad Suelze, Germany. stuerenburg@uke.uni-hamburg.de

2) <u>The healthiest serum T4 levels may be found in the upper tertile of the reference range</u>

Studies that suggest that the healthy range for serum T4 should be equal to or above 8 µg/dl (that's in the upper tertile of the T4 reference range) during thyroid treatment in children with infantile hypothyroidism, otherwise, at levels less than 8 µg/dl (that's approximately in the lower two tertiles of the T4 reference range), the risk significantly increases of lower intellectual development with lower intelligence quotient (IQ): eman 18 points less) and the treatment may be considered inadequate

19. [No authors listed] Characteristics of infantile hypothyroidism discovered on neonatal screening. J Pediatr. 1984 Apr;104(4):539-44.

Study with suggestion that a healthy serum free T4 should be situated in the upper two tertiles (66%° of the reference range, and preferably in the upper tertile (33%), in "biochemically euthyroid" older women, otherwise, at lower serum free T4 levels within the reference range, the risk of memory impairment may be increased (lowest tertile (4.5 to 6.5 µg/dL vs medium tertile (6.6 to 8.0 µg/dl) vs highest (best) T4 tertile (8.1 to 12.5 µg/dL))

20. Volpato S, Guralnik JM, Fried LP, Remaley AT, Cappola AR, Launer LJ. Serum thyroxine level and cognitive decline in euthyroid older women. Neurology. 2002 Apr 9;58(7):1055-61. Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA. vlt@unife.it

Study with suggestion that a healthy serum free T4 should be situated in the upper two tertiles (66%° of the reference range, and preferably in the upper tertile (33%), in "biochemiccally euthyroid" patients, otherwise, at lower serum free T4 levels within the reference range, the irsk may be increased of dyslipidemia (lower total & LDL cholesterol, lower triglycerides, higher HDL cholesterol) and metabolic X syndrome).

21. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab. 2007

Feb;92(2):491-6. Epub 2006 Nov 7. Department of Endocrinology, University Medical Center Groningen and University of Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands.

Study with suggestion that a healthy serum free T4 should be situated in the upper two tertiles (66%° of the reference range, and preferably in the upper tertile (33%), in "biochemiccally euthyroid" in patients with hyperlipidemia, otherwise, at lower serum free T4 levels within the reference range, the risk may be higher of having abnormal cardiovascular bio-markers

22. Jublanc C, Bruckert E, Giral P, Chapman MJ, Leenhardt L, Carreau V, Turpin G. Relationship of circulating C-reactive protein levels to thyroid status and cardiovascular risk in hyperlipidemic euthyroid subjects: low free thyroxine is associated with elevated hsCRP. Atherosclerosis. 2004 Jan;172(1):7-11. Department of Endocrinology, Group Hospitalier la Pitie-Salpetriere, Hopital Pitie-Salpetriere, AP-HP, 47-83 Boulevard de l'Hopital 75651, Paris Cedex 13, France. christel.jublanc@psl.ap-hop-paris.fr

3**) <u>The healthiest serum T4 levels may be found in the upper three quartiles of the reference range</u>**

Study with suggestion that a healthy serum free T4 should be in the upper three quartiles (upper75 %) of the reference range in infants born before 30 weeks of gestation, otherwise, at levels of serum free T4 in the lower quartile (25%), the risk of worse neurodevelopmental outcome at 2 and 5 years significantly increases

23. van Wassenaer AG, Briet JM, van Baar A, Smit BJ, Tamminga P, de Vijlder JJ, Kok JH. Free thyroxine levels during the first weeks of life and neurodevelopmental outcome until the age of 5 years in very preterm infants. Pediatrics. 2002 Sep;110(3):534-9. Department of Neonatology, Academic Medical Center, Emma Children's Hospital, Amsterdam, The Netherlands. a.vanwassenaer@amc.uva.nl

Study with suggestion that a healthy serum free T4 during the first 4 weeks after birth should be in the upper three quartiles (upper75 %) of the reference range (that's equal to or above 67.8 nmol/L (5.3 µg/dL)) in premature born infants (weighing 500 to 1500 g at birth), otherwise, at levels of serum free T4 in the lower quartile (25%), the risk of white matter damage (reflected as echolucency in the cerebral white matter) significantly increases

24. Leviton A, Paneth N, Reuss ML, Susser M, Allred EN, Dammann O, Kuban K, Van Marter LJ, Pagano M. Hypothyroxinemia of prematurity and the risk of cerebral white matter damage. J Pediatr. 1999 Jun;134(6):706-11. Children's Hospital, Boston, Massachusetts, USA.

4) <u>The healthiest serum T4 levels may be found in the 3rd to 6th deciles of the reference range</u>

25. Study with suggestion that the healthy range for serum T4 should be between the 3rd to 6th decile (11.9-14.6 pmol/l) within the reference range in patients with chronic heart failure, otherwise, at levels higher or lower, there an increased probability of more severe degree of heart failure

Optimal free T4 = 3rd-6th decile (11.9-14.6 pmol/l); vs (low-normal, bottom two deciles) (with fT4 < or = 11.8) or [high-normal, top four deciles] fT4 (>r 14.6 pmol/l)

26. Mayer O Jr, Cech J, Rosolova H, Pikner R, Simon J. [Association between free thyroxin concentration and degree of heart failure in patients with chronic heart insufficiency] Cas Lek Cesk. 2005;144(11):742-6. Centrum preventivni kardiologie, II. interni klinika LF UK, Plzen. mayerjr@lfp.cuni.cz

5) <u>The healthiest serumT levels may be found in the upper 90 % of the reference range (above the 10th percentile)</u>

A study with suggestion that a healthy serum free T4 in the mother during the pregnancy of healthy 10-month old children (born after uncomplicated pregnancies and deliveries) should be above the lower 10 % of the reference range, otherwise the risk of impaired psychomotor development for the child significantly increases

27. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf). 1999 Feb;50(2):149-55. Department of Social and Behavioural Sciences, University of Tilburg, The Netherlands.

A study with suggestion that a healthy serum T4 should be in the higher part of the reference range, and certainly above the lower 10 % of the reference range, in infants on the fifth day of life, otherwise the risk of needing intensive rescue interventions, mechanical ventilation or continuous positive airway pressure and/or treatment of neonatal seizures significantly increases for the child (inverse correlation of serum T4 on the fifth day of life with score for neonatal acute physiology)

28. Lim DJ, Herring MK, Leef KH, Getchell J, Bartoshesky LE, Paul DA. Hypothyroxinemia in mechanically ventilated term infants is associated with increased use of rescue therapies. Pediatrics. 2005 Feb;115(2):406-10. Department of Pediatrics Thomas Jefferson University, Philadelphia, Pennsylvania, USA.

A study where it is suggested that a safe serum T4 should be above the 5.4 µg/dl (which is within the reference range of 4.5-12.5 µg/dl) in premature infants weighing less than 1500 grams at birth, otherwise the risk of intraventricular hemorrhage increases

29. Paul DA, Leef KH, Stefano JL, Bartoshesky L. Low serum thyroxine on initial newborn screening is associated with intraventricular hemorrhage and death in very low birth weight infants. Pediatrics. 1998 May;101(5):903-7.Section of Neonatology, Department of Pediatrics, Christiana Care Health System, Newark, Delaware 19718, USA.

6) <u>Low serum T4 levels within the reference range may be associated with disease (associations between lower serum t4 levels within the reference range and pathological parameters)</u>

Study with suggestion that lower serum free T4 levels within the reference range may be associated in patients low in risk of developing coronary heart disease (because they have no or few established risk factors) with a higher risk of developing coronary heart disease in the next 5 to 6 years

30. Heller RF, Miller NE, Wheeler MJ, Kind PR. Coronary heart disease in 'low risk' men. Atherosclerosis. 1983 Nov;49(2):187-93.

Study with suggestion that lower serum free T4 levels within the reference range may be associated in women with a higher risk of breast cancer (high inverse correlation between serum free T4 and risk of breast cancer)

31. Thomas BS, Bulbrook RD, Goodman MJ, Russell MJ, Quinlan M, Hayward JL, Takatani O. Thyroid function and the incidence of breast cancer in Hawaiian, British and Japanese women. nt J Cancer. 1986 Sep 15;38(3):325-9.

Study with suggestion that lower serum free T4 levels within the reference range in women may be associated with a higher risk of breast cancer

32. Takatani O, Okumoto T, Kosano H, Nishida M, Hiraide H, Tamakuma S. Relationship between the levels of serum thyroid hormones or estrogen status and the risk of breast cancer genesis in Japanese women. Cancer Res. 1989 Jun 1;49(11):3109-12. Third Department of Internal Medicine, National Defense Medical College, Saitama, Japan.

Study with suggestion that lower serum total and free T4 levels within the reference range may be associated in pregnant women with a higher risk of spontaneous abortion occurring between 8 and 20 weeks of gestation

33. Ross HA, Exalto N, Kloppenborg PW, Benraad TJ. Thyroid hormone binding in early pregnancy and the risk of spontaneous abortion. Eur J Obstet Gynecol Reprod Biol. 1989 Aug;32(2):129-36. Department of Medicine, St. Radboud University Hospital, Nijmegen, The Netherlands.

Study with suggestion that lower serum T4 levels within the reference range may be associated in persons admitted to permanent institutional care with a higher risk of dying in the next two years

34. Tilvis RS, Visapaa J, Sorva A. Survival prognosis in geriatric patients admitted to permanent institutional care. Aging (Milano). 1992 Mar;4(1):77-84. Second Department of Medicine, University of Helsinki, Finland.

Study with suggestion that safe serum free & total T4 levels should be in the upper part of the reference range in burned patients, otherwise the risk of dying significantly increases

35. Vaughan GM, Mason AD Jr, McManus WF, Pruitt BA Jr. Alterations of mental status and thyroid hormones after thermal injury. J Clin Endocrinol Metab. 1985 Jun;60(6):1221-5

Studies with suggestion that safe serum total & free T4 levels should be in the upper part of the reference range in patients with acute myocardial infarction, otherwise, at decreasing levels of serum total & free T4, the risk of dying significantly increases

36. De Marinis L, Mancini A, Masala R, Torlontano M, Sandric S, Barbarino A. Evaluation of pituitary-thyroid axis response to acute myocardial infarction. J Endocrinol Invest. 1985 Dec;8(6):507-11
37. Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome". Endocr Rev. 1982 Spring;3(2):164-217.

C. <u>References of studies that show association of disease (markers) with serum TSH levels within the reference range</u>

Evidence suggests that not all TSH levels within the reference ranges are healthy; some may be indicative of mild thyroid failure, and thus require correction with thyroid replacement.

Serum TSH in primary hypothyroidism	Traditional Reference Range =	0.2-4.5 mU/ml

Studies with data that indicate that

1) The healthiest serum TSH levels may be found in the lower three quartiles of the reference range

Study with suggestion that a healthy serum TSH should be in the lower three quartiles (lower 75%) of the reference range in patients with major depression, as serum TSH levels in the upper 25th percentile of the normal reference range may be associated with characteristics of a more severe form of depression such as recurrent depression (with severe major depressive episodes), presence of somatic disease condition, suicide attempts, etc.

38. Berlin I, Payan C, Corruble E, Puech AJ. Serum thyroid-stimulating-hormone concentration as an index of severity of major depression. Int J Neuropsychopharmacol. 1999 Jun;2(2):105-110 Department of Pharmacology, Hopital Pitie-Salpetriere, Paris, France.

Study with suggestion that a healthy serum TSH should be in the lower three quartiles (lower 75%) of the reference range in depressed hospitalized patients, otherwise, in case of a serum TSH level in the upper quartile (25%) of the reference range, there may be an increased risk of more severe form of depression and slower or impaired response to antidepressant therapy

39. Nyrnes A, 2006Berlin I, Lemoine A, Hardy P. Should major depression with 'high normal' thyroid-stimulating hormone be treated preferentially with tricyclics? Neuropsychobiology. 2004;50(2):144-6. Psychiatry Department, Bicetre Hospital, Assistance Publique-Hopitaux de Paris, PSIGIM, Paris XI University, Kremlin Bicetre, France. emmanuelle.corruble@bct.ap-hop-paris.fr

2) The <u>healthiest serum TSH levels may be found below the 3 mU/L</u>

Study with suggestion that a healthy serum TSH should be below 3 mU/l in patients with auto-immune thyroiditis, otherwise cardiac abnormalities may be found found at Doppler imaging

40. 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. Department of Cardiovascular Sciences, University of Cagliari, Sardinia, Italy.

Study with suggestion that a healthy serum TSH should be below 3 mU/l in post-partum women, otherwise the risk of having had post-partum hypothyroidism and development of recurrent hypothyroidism after treatment withdrawal in the future is high

41. Azizi F. Age as a predictor of recurrent hypothyroidism in patients with post-partum thyroid dysfunction. J Endocrinol Invest. 2004 Dec;27(11):996-1002. Endocrine Research Center, Shaheed Beheshti University of Medical Sciences, Tehran, IR Iran.

3) <u>The healthiest serum TSH levels may be found in the lower half of the reference range</u>

Study with suggestion that a healthy serum TSH should be equal to or below 2.5 mIU/l in pregnant women, or otherwise there may be a significantly increased risk of auto-immune thyroid disease (positive for anti-thyroid peroxidase antibodies), which itself is associated with an increased risk of overt hypothyroidism. The risk increased with age.

42. Quinn FA, Gridasov GN, Vdovenko SA, Krasnova NA, Vodopianova NV, Epiphanova MA, Schulten M. Prevalence of abnormal thyroid stimulating hormone and thyroid peroxidase antibody-positive results in a population of pregnant women in the Samara region of the Russian Federation. Clin Chem Lab Med. 2005;43(11):1223-6. Abbott Laboratories, Abbott Park, IL, USA. frank.quinn@abbott.com

Study with suggestion that a healthy serum TSH should be equal to or below 2.5 mIU/l in women undergoing in vitro fertilization, or otherwise there may be an increased risk of a lower gestational age at delivery and lower birth weight of the baby

43. Baker VL, Rone HM, Pasta DJ, Nelson HP, Gvakharia M, Adamson GD. Correlation of thyroid stimulating hormone (TSH) level with pregnancy outcome in women undergoing in vitro fertilization. Am J Obstet Gynecol. 2006 Jun;194(6):1668-74; discussion 1674-5 Fertility Physicians of Northern California, San Jose, CA, USA. vbaker@fpnc.com

Study with suggestion that a healthy serum TSH should be equal to or below 2 for pregnant women, otherwise, in case their serum TSH is above 2, the risk to deliver a low birth weight (< 2.5 kg) baby may double

44. Idris I, Srinivasan R, Simm A, Page RC. Maternal hypothyroidism in early and late gestation: effects on neonatal and obstetric outcome. Clin Endocrinol (Oxf). 2005 Nov;63(5):560-5 Department of Diabetes and Endocrinology, Nottingham City Hospital, UK. iidris@aol.com

Study with suggestion that a healthy serum TSH should be equal to or below 1.9 for pregnant women, otherwise there may be an increased risk of auto-immune thyroiditis

45. Sieiro Netto L, Medina Coeli C, Micmacher E, Mamede Da Costa S, Nazar L, Galvao D, Buescu A, Vaisman M. Influence of thyroid autoimmunity and maternal age on the risk of miscarriage. Am J Reprod Immunol. 2004 Nov;52(5):312-6. Faculdade de Medicina/Servicos de Endocrinologia, HUCFF, UFRJ, Rio de Janeiro, Brazil. sieirorj@bol.com.br

Study with suggestion that a healthy serum TSH should be below 2.1 mU/l in angina patients, or otherwise serum creatinine, Gensini's score (assigns a severity score for a stenosed vessel depending on the degree of luminal narrowing and the importance of its location), and the incidence of multiple vessel disease, may be higher

46. Yun KH, Jeong MH, Oh SK, Lee EM, Lee J, Rhee SJ, Yoo NJ, Kim NH, Ahn YK, Jeong JW. Relationship of thyroid stimulating hormone with coronary atherosclerosis in angina patients. Int J Cardiol. 2007 Jan 11; [Epub ahead of print] Department of Cardiovascular Medicine, Wonkwang University Hospital, Iksan, South Korea.

Study with suggestion that a healthy serum TSH should be equal or below 2 mU/l in patients taking L-thyroxine-replacement therapy, or otherwise higher serum homocysteine and CRP levels may be found

47. Gursoy A, Ozduman Cin M, Kamel N, Gullu S. Which thyroid-stimulating hormone level should be sought in hypothyroid patients under L-thyroxine replacement therapy? Int J Clin Pract. 2006

Jun;60(6):655-9. Department of Endocrinology and Metabolic Diseases, Ankara University, School of Medicine, Ankara, Turkey. alptekingursoy@hotmail.com

Study with suggestion that a healthy serum TSH should be below 2.01 in normal individuals, or otherwise mild increases of arterial stiffness may occur

48. Dagre AG, Lekakis JP, Papaioannou TG, Papamichael CM, Koutras DA, Stamatelopoulos SF, Alevizaki M. Arterial stiffness is increased in subjects with hypothyroidism. Int J Cardiol. 2005 Aug 3;103(1):1-6 Vascular Laboratory, Department of Clinical Therapeutics, Alexandra University Hospital, Athens, Greece.

Study with suggestion that a healthy serum TSH should be below 2 mU/l in normotensives, otherwise the risk of familial predisposition to hypertension and thus the risk of hypertension may be increased

49. Gumieniak O, Hurwitz S, Perlstein TS, Ngumezi UC, Hopkins PN, Jeunemaitre X, Williams GH. Aggregation of high-normal thyroid-stimulating hormone in hypertensive families. J Clin Endocrinol Metab. 2005 Nov;90(11):5985-90. Epub 2005 Aug 9. Endocrinology, Diabetes, and Hypertension Division, 221 Longwood Avenue, RFB-2, Boston, Massachusetts 02115, USA.

Study with suggestion that a healthy serum TSH should be below 2 mU/l in patients with auto-immune thyroid antibodies, otherwise the patients may develop hypercholesterolemia (high total cholesterol >7.5 mmol/l and a high LDL cholesterol) that can be significantly reduced by two months of a small dose of 50 µg/day thyroxine

50. Michalopoulou G, Alevizaki M, Piperingos G, Mitsibounas D, Mantzos E, Adamopoulos 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. Department of Medical Therapeutics and Evgenidion Hospital, Athens University School of Medicine, Greece.

Study with suggestion that a healthy serum TSH should be below 1.98 mU/L in patients with coronary artery disease, otherwise the risk of aggravation of coronary heart disease may be higher

51. Auer J, Berent R, Weber T, Lassnig E, Eber B. Thyroid function is associated with presence and severity of coronary atherosclerosis. Clin Cardiol. 2003 Dec;26(12):569-73. Second Medical Department, Division of Cardiology and Intensive Care, General Hospital Wels, Wels, Austria. johann.auer@khwels.at

Study with suggestion that a healthy serum TSH should be below 2 mU/l in patients with auto-immune thyroiditis, or otherwise there is an increased risk of upcoming overt hypothyroidism

52. Geul KW, van Sluisveld IL, Grobbee DE, Docter R, de Bruyn AM, Hooykaas H, van der Merwe JP, van Hemert AM, Krenning EP, Hennemann G, et al. The importance of thyroid microsomal antibodies in the development of elevated serum TSH in middle-aged women: associations with serum lipids. Clin Endocrinol (Oxf). 1993 Sep;39(3):275-80. Department of Internal Medicine III, Erasmus University, Medical SchoolRotterdam, The Netherlands.

4) <u>The healthiest serum TSH levels may be found in the lower tertile (33%) of the reference range</u>

Study with suggestion that a healthy serum TSH should be /equal to or below 1.53 mU/L diabetic patients, otherwise, if the TSH is higher, the risk may highly increase of developing overt hypothyrodism in the next years

53. 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 Oct;14(10):853-7. Department of Diabetes, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom.

5) <u>The healthiest serum TSH levels may be found in the lower quartile (lower 25%) of the reference range</u>

Study with suggestion that a healthy serum TSH should be /in the lower quartile of the reference range in normal individuals, otherwise, if the TSH is higher, and in particular if the TSH in the upper 25% of the reference range, the risk may increase of undergoing a greater increase in body mass index over 7 years

54. Nyrnes A, Jorde R, Sundsfjord J. Serum TSH is positively associated with BMI. Int J Obes (Lond). 2006 Jan;30(1):100-5 Department of Geriatric Medicine, University Hospital of North Norway, Tromso. audhild.nyrnes@unn.no

Study with suggestion that a healthy serum TSH should be in the lower quartile ((25%) of the reference range in adult women, otherwise if the TSH is higher, and in particular if the TSH in the upper 25% of the reference range, the risk may increase of having cardiovascular abnormalities such as increased waist circumference, body mass index (BMI), glucose, triglyceride, and systolic blood pressure.

55. Waterhouse DF, McLaughlin AM, Walsh CD, Sheehan F, O'shea D. An examination of the relationship between normal range thyrotropin and cardiovascular risk parameters: a study in healthy women. Thyroid. 2007 Mar;17(3):243-8. Department of Endocrinology and Metabolism, St. Vincent's University Hospital, Dublin, Ireland.

Study with suggestion that a healthy serum TSH should be in the lower quartile of the reference range in normal individuals, otherwise, if the TSH is higher, and in particular if the TSH is in the upper 25% of the reference range, the risk may increase of having higher systolic and diastolic blood pressures. Optimally, is to have a serum TSH below the 1.88 in males and 1.79 in females

56. Iqbal A, Figenschau Y, Jorde R. Blood pressure in relation to serum thyrotropin: The Tromso study. J Hum Hypertens. 2006 Dec;20(12):932-6. Department of Cardiology, University Hospital of North Norway, Tromso, Norway. amjid.iqbal@unn.no Epub 2006 Oct 5.

Study with suggestion that a healthy serum TSH should be should be below 0.9 mU/L, and even below 0.4 mU/L in patients with palpable thyroid enlargement, otherwise the risk of thyroid malignancy may increase in parallel with the serum TSH level

57. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab. 2006 Nov;91(11):4295-301 Division of Medical Sciences, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, United Kingdom. k.boelaert@bham.ac.uk

Study with suggestion that a healthy serum TSH should be below 0.4 mU/L in patients with palpable thyroid enlargement, otherwise, at levels of serum TSH above the 0.4 mU/L, the risk of thyroid malignancy may increase

58. Kumar H, Daykin J, Holder R, Watkinson JC, Sheppard MC, Franklyn JA. Gender, clinical findings, and serum thyrotropin measurements in the prediction of thyroid neoplasia in 1005 patients presenting with thyroid enlargement and investigated by fine-needle aspiration cytology. Thyroid. 1999 Nov;9(11):1105-9. Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, United Kingdom.

6) <u>Adverse associations between serum TSH within the reference range & pathological parameters</u>

Study with suggestion that a higher serum TSH levels within the reference range may be associated with increased dyslipidemia in normal individuals without known thyroid disease: increases in total serum cholesterol, LDL cholesterol, non-HDL cholesterol & and in particular triglycerides, and a (linear) decrease in HDL cholesterol (with increasing TSH) (significant association of serum TSH with lipid parameters) The risk further increases in men over age 50 and overweight individuals.

59. Asvold BO, Vatten LJ, Nilsen TI, Bjoro T. The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. Eur J Endocrinol. 2007 Feb;156(2):181-6 Department of Public Health, Faculty of Medicine, Norwegian University of Science and Technology, N-7489 Trondheim, Norway.

Study with suggestion that higher serum TSH levels within the reference range in patients with insulin resistance may be associated with linear increases in LDL cholesterol and reductions in HDL cholesterol (with increasing serum TSH levels above 1.5 MU/l)

60. Bakker SJ, ter Maaten JC, Popp-Snijders C, Slaets JP, Heine RJ, Gans RO. The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. J Clin Endocrinol Metab. 2001 Mar;86(3):1206-11. Department of Internal Medicine, University Hospital Groningen, 9700 RB Groningen. s.j.l.bakker@int.azg.nl

Study with suggestion that higher serum TSH levels within the reference range in men may be associated with increased prostate cancer risk

61. Lehrer S, Diamond EJ, Stone NN, Stock RG. Serum thyroid-stimulating hormone is elevated in men with Gleason 8 prostate cancer. BJU Int. 2005 Aug;96(3):328-9. Department of Radiation Oncology, Mount Sinai Medical Center, Bronx, New York, NY 10029, USA. stevenlehrer@hotmail.com

Study with suggestion that higher serum TSH levels within the reference range in women may be associated with increased breast cancer risk (positive association of serum TSH with breast cancer risk)

62. Thomas BS, Bulbrook RD, Goodman MJ, Russell MJ, Quinlan M, Hayward JL, Takatani O. Thyroid function and the incidence of breast cancer in Hawaiian, British and Japanese women. nt J Cancer. 1986 Sep 15;38(3):325-9.

D. <u>Studies that show for each individual the reference range for thyroid tests, is different in particular for serum TSH, and constitutes a smaller part of the population reference range presented by the laboratory</u>

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

63. 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
64. Fraser CG, Harris EK. Generation and application of data on biological variation in clinical chemistry. Crit Rev Clin Lab Sci. 1989;27:409–37
65. 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)

66. 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

67. 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
68. 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.

69. 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)

70. Cooper DS. Subclinical hypothyroidism. N Engl J Med. 2001;345:260–5
71. 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)

72. Brabant G, Prank K, Ranft U, Schuermeyer T, Wagner TO, Hauser H, Kummer B, 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

E. <u>Publications on the need for more narrow reference ranges for the thyroid tests</u>:

73. Pain RW. Simple modifications of three routine in vitro tests of thyroid function. Clin Chem. 1976; 22(10): 1715-8.
74. Dickey RA, Wartofsky L, Feld S. Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. Thyroid. 2005 Sep;15(9):1035-9
75. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005 Sep;90(9):5483-8

Adaptation of the reference ranges for serum T3 and serum T4 may be indicated in certain conditions such as pregnancy

76. Soldin OP, Hilakivi-Clarke L, Weiderpass E, Soldin SJ. Trimester-specific reference intervals for thyroxine and triiodothyronine in pregnancy in iodine-sufficient women using isotope dilution tandem mass spectrometry and immunoassays. Clin Chim Acta. 2004 Nov;349(1-2):181-9

F. <u>Excessive fluctuations of serum levels of T3, T4 and TSH</u>:

Physiological serum TSH fluctuations

77. Brabant G, Prank K, Ranft U, Schuermeyer T, Wagner TO, Hauser H, Kummer B, 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 (There is a 3-fold difference between the average daily maximal TSH (3) and minimal TSH (1 mIU/ml))
78. Brabant G, Prank K, Ranft U, Bergmann P, Schuermeyer T, Hesch RD, von zur Muhlen A. Circadian and pulsatile TSH secretion under physiological and pathophysiological conditions. Horm Metab Res Suppl. 1990;23:12-7
79. Goichot B, Brandenberger G, Schlienger JL. Secretion of thyrotropin during states of wakefulness and sleep. Physiological data and clinical applications. Presse Med. 1996;25(21):980-4
80. Rao ML, Gross G, Strebel B, Halaris A, Huber G, Braunig P, Marler M. Circadian rhythm of tryptophan, serotonin, melatonin, and pituitary hormones in schizophrenia. Biol Psychiatry. 1994;1:35(3): 151-63
81. Rose SR, Nisula BC. Circadian variation of thyrotropin in childhood. J Clin Endocrinol Metab. 1989; 68(6):1086-90
82. 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
83. Rom Bugoslavskaia ES, Shcherbakova VS. Seasonal characteristics of the effect of melatonin on thyroid function. Bull Eksp Biol Med. 1986;101(3):268-9

Variations in the biological activity of TSH

84. Beck-Peccoz P, Persani L. Variable biological activity of thyroid stimulating hormone. Eur J Endocrinol. 1994 Oct;131(4):331-40
85. Maes M, Mommen K, Hendrickx D, Peeters D, D'Hondt P, Ranjan R, De Meyer F, Scharpe S. Components of biological variation of TSH, TT3, FT4, PRL, cortisol and testosterone in healthy volunteers. Clin Endocrinol (Oxf). 1997 May;46(5):587-98
86. Hiromoto M, Nishikawa M, Ishihara T, Yoshikawa N, Yoshimura M, Inada M. Bioactivity of thyrotropin (TSH) in patients with central hypothyroidism: Comparison between the in vivo 3,5,3'- triiodo-thyronine response to TSH and in vitro bioactivity of TSH. J Clin Endocrinol Metab. 1995 Apr;80(4):1124-8

Variations in serumT3 and T4

87. Azukizawa M, Pekary AE, Hershman JM, Parker DC. Plasma thyrotropin, thyroxine, and triiodothyronine relationships in man. J Clin Endocrinol Metab. 1976 Sep;43(3):533-42.
88. Sawin CT, Hershman JM, Chopra IJ. The comparative effect of T4 and T3 on the TSH response to TRH in young adult men. J Clin Endocrinol Metab. 1977 Feb;44(2):273-8.
89. Weeke J, Gundersen HJ. Circadian and 30 minutes variations in serum TSH and thyroid hormones in normal subjects. Acta Endocrinol (Copenh). 1978 Dec;89(4):659-72.

III. <u>Thyroid dysfunction at cellular level, undetectable by classical laboratory tests</u>

90. Tjørve E,. Tjørve K, Olsen JO, Senum R, Oftebro H. On the commonness and rarity of thyroid hormone resistance: A discussion based on mechanisms of reduced sensitivity in peripheral tissues. Med Hypotheses. 2007 Mar 23; *(PDF, ahead of print; It is argued that the acquired form of RTH, caused by endogenous and exogenous sources, may indeed be more common than the congenital, as in insulin resistance. If acquired resistance to thyroid hormone exists, then it may not be picked up by blood assays of thyroid hormone and TSH. An appropriate test to assess thyroid hormone action in peripheral tissues is therefore greatly desired.)*

Studies that show that the maximal nuclear binding capacity for T3 declines already at middle age (31-60 years) persons and for T4 at older age (61-90years) compared to young persons (16-30 years) in mononuclear blood cells

91. Kvetny J. Nuclear thyroxine and triiodothyronine binding in mononucear cells and dependence of age. Horm Metabol Res. 1985; 17 (1): 35-8)

Study that shows that in abrupt adrenal failure (by stopping glucocorticoid medication) the affinity of T3 nuclear receptors declines by more than 50 % after two days

92. De Nayer P, Dozin B, Vandeput Y, Bottazzo FC, Crabbe J. Altered interaction between triiodothyroinine and its nuclear receptors in absence of cortisol: a proposed mechanism for increased TSH secretion in corticossteroid deficiency states. J Clin Invest 1987; 17(2): 106-10

Study that shows that in obesity the affinity of T4 nuclear receptors I slower than in normal weight persons

93. Kvetny J. Nuclear thyroxine receptors and cellular metabolism of thyroxine in obese subjects before and after fasting Horm. Res. 1985;21(1):60-5.*(The maximal specific binding capacity for T4 was decreased in fed obese subjects compared to normal weight persons)*

Studies that show that in the cells there may be lower thyroid activity in older persons, despite apparently adequate serum T3 levels, because the level of reverse T3, a cellular antagonist of the active thyroid hormone T3, is increased in older persons

94. <u>Szabolcs I, Weber M, Kovacs Z, Irsy G, Goth M, Halasz T, Szilagyi G.</u> The possible reason for serum 3,3'5'-(reverse) triiodothyronine increase in old people. Acta Med Acad Sci Hung. 1982;39(1-2):11-7

95. Smeulers J, Visser TJ, Burger AK, Docter R, Hennemann G. Decreased triiodothyronine (T3) production in constant reverse T3 production in advanced age. Ned Tijdschr Geneeskd. 1979 Jan 6;123(1):12-5.

IV. Thyroid treatment of biochemical "euthyroid" patients.

Studies with no effect of thyroid treatment on clinically hypothyroid, but biochemically euthyroid patients

100 µg/day of Thyroxine was no more effective than placebo in improving cognitive function and psychological wellbeing in patients with symptoms of hypothyroidism although serum free T3 increased in patients taking thyroxine. Thyroid function tests remained within the reference range

96. Pollock MA, Sturrock A, Marshall K, Davidson KM, Kelly CJ, McMahon AD, McLaren EH. Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial. Br Med J. 2001;323: 91-5 Department of Biochemistry, Stobhill Hospital, Glasgow G21 3UW. anne.pollock@northglasgow.scot.nhs.uk

Successively increasing the dose of thyroxine with 25, 50 and 75 µg/day in women with primary hypothyroidism treated with thyroxine brought the serum TSH from a baseline serum TSH 0.1-4.8 mU/liter down to a mean of 2.8, 1.0, and 0.3 mU/liter respectively, but had **no significant effects** on well-being, symptoms, quality of life, or cognitive function and provided no significant treatment preference.

These data do not support the suggestion that the target TSH range for the treatment of primary hypothyroidism should differ from the general laboratory range.

97. Walsh JP, Ward LC, Burke V, Bhagat CI, Shiels L, Henley D, Gillett MJ, Gilbert R, Tanner M, Stuckey BG. Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double-blind, randomized clinical trial. J Clin Endocrinol Metab. 2006 Jul;91(7):2624-30. Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia. john.walsh@health.wa.gov.au *(Critic: could be due to the patients' need for additional T3 in the treatments)*

Studies that may support that there is a need to increase the dosage of thyroid treatment in thyroid treated patients who are biochemically euthyroid

Studies that show little benefit of thyroxine therapy if TSH reductions are only put into the range of 3–3.5 mU/IL. Mainly studies using dosage titration to TSH levels < 3.0 are associated with improvement in symptoms, lipid abnormalities, and cardiovascular function (except the study by Meier and colleagues that showed benefit with minimal TSH reductions in the 3-3.5 mIU/ml range)

98. 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

99. 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

100. Cooper DS 2001 Subclinical hypothyroidism. N Engl J Med 345:260–5

101. Ayala A, Wartofsky L. Minimally symptomatic (subclinical) hypothyroidism. Endocrinologist. 1997;7:44–50

102. 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)

Study that shows the persistence of impairment in psychological well-being and increased symptoms of hypothyroidism in hypothyroid patients treated with L-T4 alone, despite normal TSH levels

103. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of L-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf). 2002;57:577–85 (large, controlled, community-based study

Studies with beneficial effect of thyroid treatment on clinically hypothyroid, but biochemically euthyroid patients

In some of the double-blind placebo-controlled studies comparing treatment with levothyroxine alone with combinations of levothyroxine plus liothyronine in hypothyroid patients, **the patients preferred levothyroxine plus liothyronine combinations**, possibly indicating that the researchers were not investigating the rigtht psychological and physical parameters in the studies where they concluded to no significant effects of adding T4 to the patients with serum TSH within the reference range

104. 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 (double-blind placebo-controlled study)
105. Hertoghe T, Lo Cascio A., Hertoghe J. Considerable improvement of hypothyroid symptoms with two combined T3-T4 medication in patients still symptomatic with thyroxine treatment alone. Anti-Aging Medicine (Ed. German Society of Anti-Aging Medicine-Verlag 2003) 2004; 32-43 (open study)
106. Escobar-Morreale HF, Botella-Carretero JI, Escobar del Rey F, Morreale de Escobar G. REVIEW: Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. J Clin Endocrinol Metab. 2005 Aug;90(8):4946-54. Epub 2005 May 31. Department of Endocrinology, Hospital Ramon y Cajal, Madrid, Spain (double-blind placebo-controlled study)

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

107. 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
108. 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
109. Faber J, Petersen L, Wiinberg N, Schifter S, Mehisen J. Hemodynamic changes after levothyroxine treatment in subclinical hypothyroidism. Thyroid. 2002; 12:319–24
110. 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
111. 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
112. 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
113. 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
114. 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
115. 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
116. 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
117. 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
118. 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

Studies with beneficial effects thyroxine treatment of biochemically euthyroid patients with thyroid hyperplasia, nodules and/or goiter

Necessity to treat "harmless" biochemically "euthyroid" goiters in puberty with thyroxine because of: lipid abnormalities (higher average lipid values etc.), sign of disturbed efficacy of thyroid hormones

119. Ronnefarth G, Kauf E, Deschner F, Forberger M. [Euthyroid goiter in puberty--a harmless illness?] Klin Padiatr. 1996 Mar-Apr;208(2):77-82. Universitats-Kinderklinik Jena.

Studies where thyroxine was an effective and well–tolerated treatment of euthyroid nodules and goitre

120. Karges B, Muche R, Knerr I, Ertelt W, Wiesel T, Hub R, Neu A, Klinghammer A, Aufschild J, Rapp A, Schirbel A, Boehm BO, Debatin KM, Heinze E, Karges W. Levothyroxine in euthyroid autoimmune thyroiditis and type 1 diabetes: a randomized, controlled trial. J Clin Endocrinol Metab. 2007 May;92(5):1647-52. Division of Pediatric Endocrinology and Diabetes, University Children's Hospital,University of Ulm, Eythstrasse 24, D-89075 Ulm, Germany. beate.karges@uniklinik-ulm.de *(T4 treatment (1.3 microg/kg daily, 24 months) to biochemically euthyroid children and adolescents with type 1 diabetes and positive thyroid peroxidase antibodies, thyroglobulin antibodies, or both, reduced thyroid volume , but had no effect on thyroid function and serum autoantibody compared to diabetic controls, T4 leve*ls)
121. Peters H, Hackel D, Schleusener H. Treatment of euthyroid struma. Comparable volume reduction with 400 micrograms iodine, 100 micrograms levothyroxine combined with 100 micrograms iodine or individually dosed levothyroxine. Med Klin (Munich). 1997 Feb15;92(2):63-7 *(1/3rd volume reduction with T4 treatment)*
122. Svensson J, Ericsson UB, Nilsson P, Olsson C, Jonsson B, Lindberg B, Ivarsson SA. Levothyroxine treatment reduces thyroid size in children and adolescents with chronic autoimmune thyroiditis. J Clin Endocrinol Metab. 2006 May;91(5):1729-34.Department of Pediatrics, Malmö University Hospital, Lund University, SE-205 02 Malmö, Sweden. johan.svensson@med.lu.se
123. Güllü S, Gürses MA, Başkal N, Uysal AR, Kamel AN, Erdoğan G. Suppressive therapy with levothyroxine for euthyroid diffuse and nodular goiter. Endocr J. 1999 Feb;46(1):221-6. Department of Endocrinology and Metabolic Diseases, Ankara University Medical School, Turkey *(The mean decrease of thyroid volume at six months was about 20% in patients with diffuse goiter; a reduction of 50% or more in volume was detected in 31% of the patients. 54% of the patients showed a 10-49% decrease in nodule volume.)*
124. Hegedüs L, Hansen JM, Feldt-Rasmussen U, Hansen BM, Høier-Madsen M. Influence of thyroxine treatment on thyroid size and anti-thyroid peroxidase antibodies in Hashimoto's thyroiditis. Clin Endocrinol (Oxf). 1991 Sep;35(3):235-8. Department of Internal Medicine and Endocrinology F, Herlev Hospital, Denmark (32 %decrease of thyroid volume in 24 months of thyroxine therapy)
125. Lima N, Knobel M, Cavaliere H, Sztejnsznajd C, Tomimori E, Medeiros-Neto G. Levothyroxine suppressive therapy is partially effective in treating patients with benign, solid thyroid nodules and multinodular goiters. Thyroid. 1997 Oct;7(5):691-7 Department of Medicine, University of Sao Paulo Medical School, Brazil *(200 µg/day of levothyroxine for 12 months to euthyroid subjects with a benign, solitary, predominantly solid nodule: 37.1% patients with single, solid nodules had 50% or more regression of the nodular volume (responders), 20.3% patients had more than 20%, but less than 49.9% reduction of nodular volume (partial responders), nonresponders were 42.5%)*
126. Diacinti D, Salabè GB, Olivieri A, D'Erasmo E, Tomei E, Lotz-Salabè H, De Martinis C. Efficacy of L-thyroxine (L-T4) therapy on the volume of the thyroid gland and nodules in patients with euthyroid nodular goiter. Minerva Med. 1992 Nov;83(11):745-51. Istituto di Clinica Medica II, Università di Roma, La Sapienza *(the mean decrease of thyroid volume at nine months was 25% with thyroxine treatment)*

Publication where thyroxin therapy is proposed in young euthyroid (with normal serum TSH) patients with small, diffuse goiter

127. Hermus AR, Huysmans DA. Diagnosis and therapy of patients with euthyroid goiter. Ned Tijdschr Geneeskd. 2000 Aug 19;144(34):1623-7

Study where thyroxine treatment to euthyroid subjects in suppressive or replacement doses was not efficient to reduce nodule or goiter size

128. Celani MF.Levothyroxine suppressive therapy in the medical management of nontoxic benign multinodular goiter. Exp Clin Endocrinol. 1993;101(5):326-32 Department of Medicine, Castelfranco Emilia Hospital, Modena, Italy.

Studies with beneficial effects thyroxine treatment of biochemically euthyroid patients with auto-immune disease

Studies where thyroxine treatment to biochemically euthyroid patients with treated (drug-normalized) Graves' disease) reduced the production of thyroid antobodies

129. Mariotti S, Caturegli P, Piccolo P, Barbesino G, Pinchera A. Antithyroid peroxidase autoantibodies in thyroid diseases. J Clin Endocrinol Metab. 1990 Sep;71(3):661-9. Istituto di Endocrinologia, Università di Pisa, Italy *(reduced antibodies to TSH receptors and the frequency of recurrence of hyperthyroidism)*
130. Hashizume K, Ichikawa K, Sakurai A, Suzuki S, Takeda T, Kobayashi M, Miyamoto T, Arai M, Nagasawa T. Administration of thyroxine in treated Graves' disease. Effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. N Engl J Med. 1991 Apr 4;324(14):947-53 *(reduced anti-thyroid peroxidase antibodies)*

Studies where thyroxine treatment to biochemically "euthyroid" patients with Hashimoto's thyroiditis reduced the levels of thyroid antibodies

131. Aksoy DY, Kerimoglu U, Okur H, Canpinar H, Karaağaoğlu E, Yetgin S, Kansu E, Gedik O. Effects of prophylactic thyroid hormone replacement in euthyroid Hashimoto's thyroiditis. Endocr J. 2005 Jun;52(3):337-43. Section of Endocrinology and Metabolism, Department of Internal Medicine, Hacettepe University, Ankara, Turkey *(15 months of L-thyroxine treatment, there was a significant increase in free T4 and a significant decrease in TSH and anti-thyroglobulin and anti-thyroid peroxidase antibody levels; conclusion: prophylactic thyroid hormone therapy can be used in patients with Hashimoto's thyroiditis even if they are euthyroid)*
132. Rieu M, Richard A, Rosilio M, Laplanche S, Ropion V, Fombeur JP, Berrod JL. Effects of thyroid status on thyroid autoimmunity expression in euthyroid and hypothyroid patients with Hashimoto's thyroiditis. Clin Endocrinol (Oxf). 1994 Apr;40(4):529-35 Department of Endocrinology, Saint-Michel Hospital, Paris, France. *(12 months of L-thyroxine treatment reduces TSH-receptor antibodies and thyroid peroxidase antibodies in patients with euthyroid or hypothyroid goitrous Hashimoto's thyroiditis, and increased again after L-thyrxoine withdrawal)*
133. Chiovato L, Marcocci C, Mariotti S, Mori A, Pinchera A. L-thyroxine therapy induces a fall of thyroid microsomal and thyroglobulin antibodies in idiopathic myxedema and in hypothyroid, but not in euthyroid Hashimoto's thyroiditis. J Endocrinol Invest. 1986 Aug;9(4):299-305.
134. Padberg S, Heller K, Usadel KH, Schumm-Draeger PM. One-year prophylactic treatment of euthyroid Hashimoto's thyroiditis patients with levothyroxine: is there a benefit? Thyroid. 2001 Mar;11(3):249-55. Medica Clinic I, Endocrinology, Center of Internal Medicine, Johann Wolfgang Goethe-University, Frankfurt/Main, Germany.
135. Rink T, Schroth HJ, Holle LH, Garth H. Effect of iodine and thyroid hormones in the induction and therapy ofHashimoto's thyroiditis] Nuklearmedizin. 1999;38(5):144-9. Abteilung fÃ¼r Nuklearmedizin, Stadtkrankenhaus Hanau, Deutschland. Rink@em.uni-frankfurt.de *(thyroxine treatment is able to reduce the TgAb and the TPOAb levels even in euthyroid patients with Hashimoto's thyroiditis)*

Studies where thyroxine treatment to biochemically "euthyroid" patients with Hashimoto's thyroiditis did not significantly reduced the levels of anti-thyroid peroxidase antibodies

136. Hegedüs L, Hansen JM, Feldt-Rasmussen U, Hansen BM, Høier-Madsen M. Influence of thyroxine treatment on thyroid size and anti-thyroid peroxidase antibodies in Hashimoto's thyroiditis. Clin Endocrinol (Oxf). 1991 Sep;35(3):235-8. Department of Internal Medicine and Endocrinology F, Herlev Hospital, Denmark *(no significant change of anti-thyroid peroxidase antibodies after 24 months of thyroxine)*

IV. Transitory T3-hyperthyroidism or intolerance due to the presence of other hormone deficiencies

A. Intolerance to thyroid treatment because of adrenal deficiency

Intolerance to thyroid treatment because of adrenal deficiency

137. Shaikh MG, Lewis P, Kirk JM. Thyroxine unmasks Addison's disease. Acta Paediatr. 2004 Dec;93(12):1663-5. Department of Endocrinology, Birmingham Children's Hospital, Birmingham, United Kingdom. guftar.shaikh@bch.nhs.uk
138. Graves L, Klein RM, Walling AD. Addisonian crisis precipitated by thyroxine therapy: a complication of type 2 autoimmune polyglandular syndrome. South Med J. 2003 Aug;96(8):824-7. Division of Metabolism, Endocrinology and Genetics, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas 66160, USA. lgraves@kumc.edu
139. Rey L, Bulliard C, Pralong F, Waeber G. Adrenal insufficiency caused by treatment with levothyroxine. Schweiz Rundsch Med Prax. 2001 Nov 29;90(48):2103-8.Département de Médecine Interne, Centre Hospitalier Universitaire Vaudois, Lausanne.
140. Olukoga A, Horsman G, Stewart F. Lessons to be learned: a case study approach: severe hyponatraemia induced by primary hypothyroidism and associated with possible increased hepatic sensitivity to thyroxine replacement. J R Soc Health. 1999 Jun;119(2):117-20.
141. Rey L, Bulliard C, Pralong F, Waeber G. Adrenal insufficiency caused by treatment with levothyroxine] Schweiz Rundsch Med Prax. 2001 Nov 29;90(48):2103-8. Centre Hospitalier Universitaire Vaudois, Lausanne.
142. Miell J, Wassif W, McGregor A, Butler J, Ross R. Life-threatening hypercalcaemia in association with Addisonian crisis. Postgrad Med J. 1991 Aug;67(790):770-2. Department of Medicine, King's College Hospital School of Medicine, London, UK.
143. Davis J, Sheppard M. Acute adrenal crisis precipitated by thyroxine. BMJ. 1986;292:1595 Hosp. Pract. (Off. Ed.). 1986 May 15;21(5):132, 134.
144. Banitt PF, Munson AK. Addisonian crisis after thyroid replacement. Hosp. Pract. (Off. Ed.). 1986 May 15;21(5):132, 134.
145. Murray JS, Jayarajasingh R, Perros P. Deterioration of symptoms after start of thyroid hormone replacement. BMJ. 2001 August 11; 323(7308): 332–333. Freeman Hospital, High Heaton, Newcastle upon Tyne, UK
146. Osman A, Leslie P. Adrenal insufficiency should be excluded before thyroxine replacement is started. BMJ 1996;313:427

Increase in serum T3 in hypocorticism

147. Comtois R, Hebert J, Soucy JP. Increase in T3 levels during hypocorticism in patients with chronic secondary adrenocortical insufficiency. Acta Endocrinol. 1992 Apr;126(4):319-24. Department of Medicine, Notre-Dame Hospital, University of Montreal, Quebec, Canada.
148. Comtois R, Hebert J, Soucy JP. Reversible hypertriiodothyroninaemia due to adrenal insufficiency. J. Intern. Med. 1991 Jul;230(1):79-82. Department of Medicine, Notre-Dame Hospital, University of Montreal, QuÃ©bec, Canada.

Excessive thyroid hormone levels after lowering the cortisol levels through treatment of Cushing's syndrome

149. Arikan E, Guldiken S, Altun BU, Kara M, Tugrul A. Exacerbations of Graves' disease after unilateral adrenalectomy for Cushing's syndrome. J Endocrinol Invest. 2004 Jun;27(6):574-6. Medical Faculty of Trakya University, Edirne, Turkey. earikan@trakya.edu.tr
150. Takasu N, Komiya I, Nagasawa Y, Asawa T, Yamada T. Exacerbation of autoimmune thyroid dysfunction after unilateral adrenalectomy in patients with Cushing's syndrome due to an adrenocortical adenoma. N Engl J Med. 1990 Jun 14;322(24):1708-12. Department of Gerontology, Endocrinology, and Metabolism, Shinshu University School of Medicine, Nagano-ken, Japan.
151. Haraguchi K, Hiramatsu K, Onaya T. Transient thyrotoxicosis after unilateral adrenalectomy in two patients with Cushing's syndrome. Endocrinol Jpn. 1984 Oct;31(5):577-82.
152. Morita H, Isaji M, Mune T, Daido H, Isomura Y, Sarui H, Tanahashi T, Takeda N, Ishizuka T, Yasuda K. Transient Graves disease developing after surgery for Cushing disease. Am J Med Sci.

2002 Mar;323(3):162-5. Department of General Medicine, Gifu University School of Medicine, Japan. hmorita@cc.gifu-u.ac.jp

Glucocorticoids reduces the conversion of T4 into T3, reducing thereby thyroid activity

153. Re RN, Kourides IA, Ridgeway EC, Weintraub BD, Maloof F. The effect of glucocorticoid administation on human pituitary secretion of thyrotropin and prolactin. J Clin Endocrinol Metab. 1976; 43:338-46.
154. 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
155. Banos C, Tako J, Salamon F, Gyorgyi S, Czikkely R. Effect of ACTH-stimulated glucocorticoid hypersecretion on the serum concentrations of thyroxine-binding globulin, thyroxine, triiodothyronine, reverse triiodothyronine and on the TSH-response to TRH. Acta Med Acad Sci Hung. 1979;36(4):381-94.
156. Chopra IJ, Williams DE, Orgiazzi J, Solomon DH. Opposite effects of dexamethasone on serum concentrations of 3,3',5'-triiodothyronine (reverse T3) and 3,3'5-triiodothyronine (T3). J Clin Endocrinol Metab. 1975 Nov;41(5):911-20.
157. Jennings AS, Ferguson DC. Effect of dexamethasone on triiodothyronine production in the perfused rat liver and kidney. Endocrinology. 1984 Jan;114(1):31-6.
158. Cavalieri RR, Castle JN, McMahon FA. Effects of dexamethasone on kinetics and distribution of triiodothyronine in the rat. Endocrinology. 1984 Jan;114(1):215-21.
159. Yamamoto M, Saito S, Kaise K, Kaise N, Yoshida K, Yoshinaga K. Changes in thyroid hormones by treatment with aspirin and prednisolone in subacute thyroiditis with hyperthyroidism. Tohoku J Exp Med. 1979 Jan;127(1):85-95.
160. Westgren U, Ahren B, Burger A, Ingemansson S, Melander A . Effects of dexamethasone, desoxycorticosterone, and ACTH on serum concentrations of thyroxine, 3,5,3'-triiodothyronine and 3,3',5'-triiodothyronine. Acta Med Scand. 1977;202(1-2):89-92.

Glucocorticoids reduce more the T3 than the T4 in the treatment of hyperthyroidism

161. Williams DE, Chopra IJ, Orgiazzi J, Solomon DH. Acute effects of corticosteroids on thyroid activity in Graves' disease. J Clin Endocrinol Metab. 1975 Aug;41(2):354-61.

Glucocorticoids reduce the secretion of TSH, possibly reducing thereby thyroid active

162. Re RN, Kourides IA, Ridgeway EC, Weintraub BD, Maloof F. The effect of glucocorticoid administation on human pituitary secretion of thyrotropin and prolactin. J Clin Endocrinol Metab. 1976; 43:338-46.

B. Intolerance to thyroid treatment because of estrogen deficiency

Higher thyroid hormone levels (especially higher serum T3) in estrogen deficiency states such as in the postmenopause, improvement with estrogen therapy

163. Custro N, Scafidi V. Mild hyperthyroidism with inappropriate secretion of TSH in postmenopausal women. Acta Endocrinol (Copenh). 1986 Feb;111(2):204-8.
164. Wasyluk H, Chrabalowski Z, Doroszewski J, Hartwig W. Menopause and hyperthyroidism. Pol Arch Med Wewn. 1976 Nov;56(5):439-44.
165. Lederer J. Estrogen therapy of hyperthyroidism after castration or menopause; remote results. Ann Endocrinol (Paris). 1950;11(5):459-70.
166. Schoutens A, Laurent E, Markowicz E, Lisart J, De Maertelaer V. Serum triiodothyronine, bone turnover, and bone mass changes in euthyroid pre- and postmenopausal women. Calcif Tissue Int. 1991 Aug;49(2):95-100. Department of Nuclear Medicine, HÃ´pital Erasme-Free University of Brussels, Belgium.
167. Schoutens A, Laurent E, Markowicz E, Lisart J, De Maertelaer V. Serum triiodothyronine, bone turnover, and bone mass changes in euthyroid pre- and postmenopausal women. Calcif Tissue Int. 1991 Aug;49(2):95-100. Department of Nuclear Medicine, HÃ´pital Erasme-Free University of Brussels, Belgium (In postmenopausal women, serum iT3 corrected for thyroid binding globulin (TBG) (T3c) was higher in those receiving no estrogen replacement therapy.)

Estrogens reduce the conversion of T4 into T3, reducing thereby thyroid activity

168. El-Etreby MF, Graf KJ, Gunzel P, Neumann F. Evaluation of effects of sexual steroids on the hypothalamic-pituitary system of animals and man. Arch Toxicol Suppl. 1979;2:11-39
169. 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(1):52-7.
170. Vandorpe G, Kuhn ER. Estradiol-17 beta silastic implants in female Rana ridibunda depress thyroid hormone concentrations in plasma and the in vitro 5'-monodeiodination activity of kidney homogenates. Gen Comp Endocrinol. 1989 Dec;76(3):341-5. Laboratory of Comparative Endocrinology, Catholic University of Leuven, Belgium.
171. Cyr DG, MacLatchy DL, Eales JG. The influence of short-term 17 beta-estradiol treatment on plasma T3 levels and in vitro hepatic T4 5'-monodeiodinase activity in immature rainbow trout, Salmo gairdneri. Gen Comp Endocrinol. 1988 Mar;69(3):431-8. Department of Zoology, University of Manitoba, Winnipeg, Canada.
172. Chan V, Besser GM, Landon J. Effects of oestrogen on urinary thyrosine excretion. Br Med J. 1972 Dec 23;4(5842):699-701
173. 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

Estrogens increase serum TBG and reduce the conversion of T4 into T3, reducing thereby thyroid activity

174. Wiegratz I, Kutschera E, Lee JH, Moore C, Mellinger U, Winkler UH, Kuhl H. Effect of four oral contraceptives on thyroid hormones, adrenal and blood pressure parameters. Contraception. 2003 May;67(5):361-6. Center of Obstetrics and Gynecology, University Hospital of Frankfurt, Frankfurt, Germany.
175. Selenkow HA. Remission of hyperthyroidism and oral contraceptive therapy. [Answer to question]. JAMA. 1984 Nov 2;252(17):2463.

Other factors or conditions that may reduce the conversion of T4 into T3 (stress, acute exercise, perinatal period, posttraumatic stress disorder cold, nephritic syndrome, meals (n particular carbohydrate feeding), malathion (pesticide in food), and treatments with various supplements such as selenium, zinc (controversial), vitamin A, iodine, glutathione, growth hormone, IGF-1, TRH, etc.

176. Turakulov IaKh, Burikhanov RB, Patkhitdinov PP, Myslitskaia AI. Effect of immobilization stress on the level of thyroid hormone secretion Probl Endokrinol (Mosk). 1993 Sep-Oct;39(5):47-8.
177. Kellner K, Hecht K, Marek H, Aquino AM. Behavior of thyroid hormones, corticosterone, adrenocorticotropic hormone and insulin in the plasma of the rat under stress conditions. Z Gesamte Inn Med. 1980 May 15;35(10):418-21 *(an immobilization/hypokinase stress produced a decrease of the T4 and an increase of the T3)*
178. Opstad PK, Falch D, Oktedalen O, Fonnum F, Wergeland R. The thyroid function in young men during prolonged exercise and the effect of energy and sleep deprivation. Clin Endocrinol (Oxf). 1984 Jun;20(6):657-69 *(initial increase of T4 to T3 conversion with prolonged exercise, but if chronic followed by a reduced conversion of T4 to T3)*
179. Klein AH, Oddie TH, Fisher DA. Effect of parturition on serum iodothyronine concentrations in fetal sheep. Endocrinology. 1978 Oct;103(4):1453-7 *(increase in perinatal period of serum T3)*
180. Mason J, Southwick S, Yehuda R, Wang S, Riney S, Bremner D, Johnson D, Lubin H, Blake D, Zhou G. Elevation of serum free triiodothyronine, total triiodothyronine, thyroxine-binding globulin, and total thyroxine levels in combat-related posttraumatic stress disorder. Arch Gen Psychiatry. 1994 Aug;51(8):629-41. National Center for Posttraumatic Stress Disorder, Veterans Affairs Medical Center, West Haven, Conn.
181. Sawhney RC, Malhotra AS, Nair CS, Bajaj AC, Rajan KC, Pal K, Prasad R, Basu M. Thyroid function during a prolonged stay in Antarctica. Eur J Appl Physiol Occup Physiol. 1995;72(1-2):127-33. Defence Institute of Physiology and Allied Sciences, Delhi Cantt, India.
182. Konno N. Comparison between the thyrotropin response to thyrotropin-releasing hormone in summer and that in winter in normal subjects. Endocrinol Jpn. 1978 Dec;25(6):635-9 *(slight elevation of serum T3 concentration in winter but not in serum T4 level)*
183. Scammell JG, Barney CC, Fregly MJ. Proposed mechanism for increased thyroxine deiodination in cold-acclimated rats. J Appl Physiol. 1981 Nov;51(5):1157-61 *(The rates of hepatic and renal deiodination of T4 to T3 in rats exposed to 4 degree C for 20 days were 297 and 222% higher, respectively, than control).*

184. Glass AR, Vigersky RA, Rajatanavin R, Pardridge W, Smallridge RC, Wartofsky L, Burman KD. Low serum thyroxine and high serum triiodothyronine in nephrotic rats: etiology and implications for bioavailability of protein-bound hormone. Endocrinology. 1984 May;114(5):1745-53.
185. Glick Z, Wu SY, Lupien J, Reggio R, Bray GA, Fisher DA. Meal-induced brown fat thermogenesis and thyroid hormone metabolism in rats. Am J Physiol. 1985 Nov;249(5 Pt 1):E519-24.
186. Glade MJ, Reimers TJ. Effects of dietary energy supply on serum thyroxine, tri-iodothyronine and insulin concentrations in young horses. J Endocrinol. 1985 Jan;104(1):93-8.
187. Gavin LA, Moeller M, McMahon FA, Castle JN, Gulli R, Cavalieri RR. Carbohydrate feeding increases total body and specific tissue 3,5,3'-triiodothyronine neogenesis in the rat. Endocrinology. 1988 Aug;123(2):1075-81. Department of Medicine, Veterans' Administration Medical Center, San Francisco, California 94121.
188. Yadav AK, Singh TP. Effect of pesticide on circulating thyroid hormone levels in the freshwater catfish, Heteropneustes fossilis (Bloch). Environ Res. 1986 Feb;39(1):136-42 *(Malathion, an organophosphorus, seems to increase the plasma T3 level, probably by increasing the T4 to T3 conversion)*
189. Napolitano G, Bonomini M, Bomba G, Bucci I, Todisco V, Albertazzi A, Monaco F. Thyroid function and plasma selenium in chronic uremic patients on hemodialysis treatment. Biol Trace Elem Res. 1996 Dec;55(3):221-30. Chair of Endocrinology, University G. D'Annunzio, Chieti, Italy.
190. Kauf E, Dawczynski H, Jahreis G, Janitzky E, Winnefeld K. Sodium selenite therapy and thyroid-hormone status in cystic fibrosis and congenital hypothyroidism. Biol Trace Elem Res. 1994 Mar;40(3):247-53. Childrens Hospital, Friedrich-Schiller-University, Jena, Germany.
191. Chen MD, Lin WH, Lin PY, Wang JJ, Tsou CT. Investigation on the relationships among blood zinc, copper, insulin and thyroid hormones in non-insulin dependent diabetes mellitus and obesity. Zhonghua Yi Xue Za Zhi (Taipei). 1991 Dec;48(6):431-8. Department of Medicine, Taichung Veterans General Hospital, Taiwan, Republic of China (*Blood zinc concentration was inversely related to T3 level in diabetics and obese individuals)*
192. Morley JE, Melmed S, Reed A, Kasson BG, Levin SR, Pekary AE, Hershman JM. Effect of vitamin A on the hypothalamo-pituitary-thyroid axis. Am J Physiol. 1980 Feb;238(2):E174-9 *(In vitro, vitamin A enhanced T4 to T3 conversion in hepatic homogenates).*
193. Okamura K, Taurog A, Krulich L. Elevation of serum 3,5,3'-triiodothyronine and thyroxine levels in rats fed Remington diets; opposing effects of nutritional deficiency and iodine Endocrinology. 1981 Apr;108(4):1247-56. deficiency *(iodine increases T4 to T3 conversion)*
194. Ozawa Y, Shimizu T, Shishiba Y. Effect of sulfhydryl reagents on the conversion of thyroxine to 3,5,3'-triiodothyronine: direct action on thyroxine molecules. Endocrinology. 1982 Jan;110(1):241-5 *(reduced glutathione markedly enhanced subsequent T3 generation from T4 by the homogenate)*
195. Gomez Saez JM, Gomez Arnaiz N, Soler Ramon J. Changes in the lipid profile and thyroid function in adult patients with hypopituitarism after substitutive treatment with growth hormone. Med Clin (Barc). 1999 Dec 11;113(20):775-6.
196. Wolthers T, Groftne T, Moller N, Christiansen JS, Orskov H, Weeke J, Jorgensen JO. Calorigenic effects of growth hormone: the role of thyroid hormones. J Clin Endocrinol Metab. 1996 Apr;81(4):1416-9. Medical Department M, Aarhus University Hospital, Denmark
197. Sacco V, Maioli A, Citro G, Galasso R, Vinci ML, Zampino A. Effect of treatment with biosynthetic GH on thyroid function in patients with an isolated deficiency of GH] Minerva Endocrinol. 1992 Jan-Mar;17(1):13-20. Divisione di Endocrinologia, Ospedale San Carlo, Potenza.
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199. Hussain MA, Schmitz O, Jorgensen JO, Christiansen JS, Weeke J, Schmid C, Froesch ER. Insulin-like growth factor I alters peripheral thyroid hormone metabolism in humans: comparison with growth hormone. Eur J Endocrinol. 1996 May;134(5):563-7. Division of Endocrinology and Metabolism, University Hospital of Zurich, Switzerland.
200. Campos-Barros A, Kohler R, Muller F, Eravci M, Meinhold H, Wesemann W, Baumgartner A.The influence of sleep deprivation on thyroid hormone metabolism in rat frontal cortex. Neurosci Lett. 1993 Nov 12;162(1-2):145-8. Department of Nuclear Medicine (Radiochemistry), Universitätsklinikum Steglitz, Berlin, FRG.
201. Pirazzoli P, Cacciari E, Mandini M, Sganga T, Capelli M, Cicognani A, Gualandi S. Growth and thyroid function in children treated with growth hormone. J Pediatr. 1992 Aug;121(2):210-3. First Pediatric Clinic, University of Bologna, Italy.
202. Moller J, Jorgensen JO, Moller N, Christiansen JS, Weeke J. Effects of growth hormone administration on fuel oxidation and thyroid function in normal man. Metabolism. 1992

Jul;41(7):728-31. University Department of Internal Medicine and Endocrinology, Aarhus Kommunehospital, Denmark.
203. Peeters R, Buys N, Vanmontfort D, Van Isterdael J, Decuypere E, Kuhn ER. Preferential release of tri-iodothyronine following stimulation by thyrotrophin or thyrotrophin-releasing hormone in sheep of different ages. J Endocrinol. 1992 Jan;132(1):93-100. Laboratory for Physiology of Domestic Animals, Catholic University of Leuven, Belgium.
204. Valenta LJ, Eisenberg H, Ascher MS, Elias AN. Response of thyroid hormones in peripheral and thyroid venous blood to TRH administration in man. Horm Res. 1983;17(2):78-83.

Study to show that 40% of patients with chronic fatigue syndrome have lymphocytic infiltrate of the thyroid gland as demonstrated by fine needle aspiration but normal TSH who responded faourably to thyroid hormone prescription

205. Fine needle aspiration of the thyroid gland in chronic fatigue. Bo Wikland. Torsten Lowhagen. The Lancet, vol 357. March 24th 2004.