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APPENDIX 1. Thierry Hertoghe, MD, short curriculum vitae

- President of the World Society of Anti-Aging Medicine (WOSAAM)
- President of the International Hormone Society (IHS)
- President of the European Academy of Quality of Life and Longevity medicine (Eaqual)
- Scientific director of the Anti-aging Medicine World Congress, the European Congress of Anti-aging Medicine, and the Eurasian Congress of Anti-aging Medicine
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APPENDIX 2: Narrower intraindividual variations in thyroid tests

Narrower intraindividual variations in thyroid tests => Population-based reference range may not be adequate as each individual has a narrow reference range for health half of 1/3 in width compared to that of the population reference range

1. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab. 2002 Mar;87(3):1068-72. Department of Endocrinology, Aalborg Hospital, Aalborg, Denmark DK-9000. stiga@dadlnet.dk

High individuality causes laboratory reference ranges to be insensitive to changes in test results that are significant for the individual. We undertook a longitudinal study of variation in thyroid function tests in 16 healthy men with monthly sampling for 12 months using standard procedures. We measured serum T(4), T(3), free T(4) index, and TSH. All individuals had different variations of thyroid function tests ($P < 0.001$ for all variables) around individual mean values (set points) ($P < 0.001$ for all variables). The width of the individual 95% confidence intervals were approximately half that of the group for all variables. Accordingly, the index of individuality was low: T(4) = 0.58; T(3) = 0.54; free T(4) index = 0.59; TSH = 0.49. One test result described the individual set point with a precision of +/- 25% for T(4), T(3), free T(4) index, and +/- 50% for TSH. The differences required to be 95% confident of significant changes in repeated testing were (average, range): T(4) = 28, 11-62 nmol/liter; T(3) = 0.55, 0.3--0.9 nmol/liter; free T4 index = 33, 15-61 nmol/liter; TSH = 0.75, 0.2-1.6 mU/liter. Our data indicate that each individual had a unique thyroid function. The individual reference ranges for test results were narrow, compared with group reference ranges used to develop laboratory reference ranges. Accordingly, a test result within laboratory reference limits is not necessarily normal for an individual. Because serum TSH responds with logarithmically amplified variation to minor changes in serum T(4) and T(3), abnormal serum TSH may indicate that serum T(4) and T(3) are not normal for an individual. A condition with abnormal serum TSH but with serum T(4) and T(3) within laboratory reference ranges is labeled subclinical thyroid disease. Our data indicate that the distinction between subclinical and overt thyroid disease (abnormal serum TSH and abnormal T(4) and/or T(3)) is somewhat arbitrary. For the same degree of thyroid function abnormality, the diagnosis depends to a considerable extent on the position of the patient's normal set point for T(4) and T(3) within the laboratory reference range.

2. Andersen S, Bruun NH, Pedersen KM, Laurberg P. Biologic variation is important for interpretation of thyroid function tests. Thyroid. 2003 Nov;13(11):1069-78. Department of Endocrinology and Medicine, University Hospital Aalborg, Aalborg, Denmark. stiga@dadlnet.dk

Large variations exist in thyrotropin (TSH) and thyroid hormones in serum. The components of variation include preanalytical, analytical, and biologic variation. This is divided into between- and within-individual variation. The latter consists of circadian and seasonal differences although there are indicators of a genetically determined starting point. The ratio of within- to between-individual variation describes the reliability of population-based reference ranges. This ratio is low for serum TSH, thyroxine (T(4)) and triiodothyronine (T(3)) indicating that laboratory reference ranges are relatively insensitive to aberrations from normality in the individual. Solutions are considered but reducing the analytical variation below the calculated analytical goals of 7%, 5% and 12% for serum T(3), T(4), and TSH does not improve diagnostic performance. Neither does determination of the individual set-point

and reference range. In practice this means that population-based reference ranges are necessary but that it is important to recognize their limitations for use in individuals. Serum TSH responds with amplification to minor alterations in T(4) and T(3). A consistently abnormal TSH probably indicates that T(4) and T(3) are not normal for the individual even when inside the laboratory reference range. This underlines the importance of TSH in diagnosis and monitoring of thyroid dysfunctions. Also, it implies that subclinical thyroid disease may be defined in purely biochemical terms. Under critical circumstances such as pregnancy where normal thyroid function is of importance for fetal brain development, subclinical thyroid disease should be treated. Even TSH within the reference range may be associated with slightly abnormal thyroid function of the individual. The clinical importance of such small abnormalities in thyroid function in small children and pregnant women for brain development remains to be elucidated.

3. Browning MC, Ford RP, Callaghan SJ, Fraser CG. Intra- and interindividual biological variation of five analytes used in assessing thyroid function: implications for necessary standards of performance and the interpretation of results. Clin Chem. 1986 Jun;32(6):962-6.

Intra- and interindividual components of biological variation have been determined for total thyroxin (TT4), free thyroxin (FT4), total triiodothyronine (TT3), free triiodothyronine (FT3), and thyrotropin (TSH). Calculated analytical goals (CV, %) for the precision required for optimal patient care are: TT4 less than or equal to 2.5, FT4 less than or equal to 4.7, TT3 less than or equal to 5.2, FT3 less than or equal to 3.9, and TSH less than or equal to 8.1. The marked degree of individuality demonstrated for all hormones indicates that, if conventional population-based reference ranges are used uncritically, major changes in hormone concentration may not be correctly identified for some patients because observed values continue to lie within the reference range. At analyte concentrations approximating the mean values found in this study, and for analytical performance meeting the appropriate analytical goal, the differences required for consecutive results to be significantly different (p less than or equal to 0.5) have been calculated as: TT4, 14.7 nmol/L; FT4, 5.7 pmol/L; TT3, 0.6 nmol/L; FT3, 1.3 pmol/L, and TSH, 0.7 milli-int. unit/L.

4. Nishi I, Ichihara K, Takeoka K, Miyai K, Amino N.[Intra-individual and seasonal variations of thyroid function tests in healthy subjects] [Article in Japanese] Rinsho Byori. 1996 Feb;44(2):159-62. Central Laboratory for Clinical Investigation, Osaka University Hospital, Suita.

We report intra-individual and seasonal variations of thyroid function tests in healthy subjects. Blood samples were obtained from thirteen healthy males and seven healthy females every two weeks over a period of one year, and totally 25 samplings of each were made. Serum thyrotropin (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) were measured after the completion of the sampling. The 25 samples from each subject were always assayed with the same assay run. Variations of FT4 and FT3 in each subject were narrow and approximately one-third of normal reference ranges. The magnitude of individual variation of TSH values was proportional to the average of TSH in each individual. Serum TSH and FT3 values during winter were significantly higher than those during summer, but such change was not observed on serum FT4.

5. Maes M, Mommen K, Hendrickx D, Peeters D, D'Hondt P, Ranjan R, De Meyer F, ScharpÃ© S Components of biological variation, including seasonality, in blood concentrations of TSH, TT3, FT4, PRL, cortisol and testosterone in healthy volunteers.

Clin Endocrinol (Oxf). 1997 May;46(5):587-98. University Department of Psychiatry, Antwerp, Belgium.

OBJECTIVE: There are few detailed studies of annual or seasonal variations in hormone concentrations in man. This study examines the components of biological variation, including seasonality, in plasma TSH, total T3 (TT3), free T4 (FT4), PRL, cortisol and testosterone in healthy volunteers. **DESIGN:** Monthly blood samplings for the assay of the above hormones were collected during one calendar year. **SUBJECTS:** Thirteen normal men and 13 normal women participated in the present study (mean age 38.7 +/- 13.4 years). **MEASUREMENTS:** Assays of TSH, TT3 and FT4 were carried out by means of immunoradiometric assays (IRMA), PRL by ELISA, cortisol by a fluorescence immunoassay, and testosterone with RIA. The time series were analysed by means of (bivariate or multivariate) spectral and cosinor analyses. **RESULTS:** Significant annual, four-monthly and biannual rhythms were detected in serum TSH; the lowest TSH values were observed in spring. A significant annual rhythm was detected in TT3, with lower values in spring and summer than in the other seasons. The peak-trough differences in the yearly variation expressed as a percentage of the mean were 29.1% and 8.2% for TSH and TT3, respectively. The yearly variation in plasma cortisol was significantly different between men and women: in men, 5.9% of the variation was explained by an annual rhythm, while in women 14.7% was explained by the fourth and seventh harmonical wave. The peak-trough differences in the yearly variation in plasma cortisol were 17.6% and 31.8% in men and women, respectively. There were no significant seasonal rhythms in PRL, FT4 or testosterone. The intraindividual/interindividual CV values were: TSH 29.3/48.4%, TT3 9.4/ 18.5%, FT4 7.1/9.1%, PRL 39.2/65.0%, cortisol 21.7/ 46.2%, and testosterone 12.6/40.8%. **CONCLUSIONS:** The degree of individuality measured in the plasma hormones is such that conventional population-based reference ranges may not correctly identify major alterations in these hormones in individual subjects.

6. Meier CA, Maisey MN, Lowry A, Müller J, Smith MA. Interindividual differences in the pituitary-thyroid axis influence the interpretation of thyroid function tests. Clin Endocrinol (Oxf). 1993 Jul;39(1):101-7. Department of Radiological Sciences, UMDS, Guy's Hospital, London, UK.

OBJECTIVE: We investigated interindividual differences in the shape, slope and setpoint of the pituitary-thyroid axis (PTA) in normal persons. Based on these physiological data we propose a novel bivariate concept for the interpretation of thyroid function tests which is less biased by interindividual differences in the PTA than the currently used univariate approach. **DESIGN:** In two separate trials (A and B), healthy volunteers were given small, increasing doses of T3 (7.5-45 micrograms/day orally) over 5 days. The regulation characteristics of the individual PTAs and the effects of age and gender were assessed by general linear regression models. In addition, serum samples were collected from normal persons to establish the proposed bivariate approach for the interpretation of thyroid function tests. **SUBJECTS:** The regulatory characteristics of the PTA were determined in a total of 21 normal volunteers (eight females, 13 males; age 24-49 years). Single blood samples were collected from 257 normal volunteers. The participants had no history of pituitary or thyroid disease. **MEASUREMENTS:** Free and total thyroid hormone and TSH concentrations were determined in the serum. All samples from one person were analysed in the same assay in duplicate. **RESULTS:** A log-linear relationship between T3 and TSH was found to describe best the individual PTA (multiple $r = 0.96$). However, significant differences in the setpoint ($P < 0.001$) and to a lesser degree in the slope ($P < \text{or} = 0.05$) of the PTA were detected; this variability was not dependent on age or gender. Since

these findings invalidate the assumptions on which the current univariate interpretation of thyroid function tests is based, we propose a novel model for the evaluation of thyroid function tests derived from the experimentally determined shape and average slope of the PTA. CONCLUSIONS: The presence of significant age and gender-independent interindividual variations in the setpoint of the pituitary-thyroid axis raises conceptual problems with the current approach for interpreting thyroid function tests. An easy to use graphical bivariate representation of the normal ranges for thyroid function tests is presented and exemplified by the thyroid hormone and TSH measurements in a large reference population. This concept should improve the diagnostic accuracy in the borderline-normal, and particularly subclinical hypothyroid region of these hormone measurements.

7. Harrop JS, Ashwell K, Hopton MR. Circannual and within-individual variation of thyroid function tests in normal subjects. *Ann Clin Biochem.* 1985 Jul;22 (Pt 4):371-5.

Blood was taken from normal subjects at monthly intervals over a period of one year for subsequent determination of serum thyroid hormone concentrations. Thyroid-stimulating hormone (TSH) responses to TSH-releasing hormone were performed at 3-monthly intervals. This study provided data on within-individual variation and on seasonally-related changes of these thyroid function tests. The results showed that, within an individual, thyroid hormone concentrations are maintained within narrow limits. For both thyroxine and triiodothyronine the component contribution of within-individual variation to the population-based variation (the latter also termed the 'reference interval', or colloquially the 'normal range') was small. This high degree of individuality implies that rigorous comparison of thyroid hormone results against a population-based 'normal range' can be potentially misleading. Despite the limited within-individual variation, seasonally-related changes in thyroid hormone concentrations were apparent, with higher thyroxine and triiodothyronine values seen in winter months. A tendency to a greater TSH response to TSH-releasing hormone was also noted at this time. Conceivably these changes could reflect a centrally-mediated response of the hypothalamic-pituitary-thyroid axis to environmental temperature.

8. Biersack HJ, Hartmann F, RÄ¶del R, Reinhardt M. Long term changes in serum T4, T3, and TSH in benign thyroid disease: proof of a narrow individual variation. *Nuklearmedizin.* 2004 Oct;43(5):158-60; quiz 162-3. Department of Nuclear Medicine, University Hospital Bonn, Sigmund-Freud-Strasse 25, 53127 Bonn, Germany.

Aim: The diagnosis of abnormalities of thyroid function is generally based on the measurement of thyroid hormones and TSH in blood. The recommended reference ranges for serum T4 and T3 as well as TSH are quite wide as the result of large differences in thyroid function tests in healthy persons. It has been proven that the individual variation within an individual is small, compared with the variation between individuals. We investigated long term variations of these parameters in patients with and without benign thyroid diseases. Methods: We performed long term follow-up serum determinations of T3, T4, and TSH in a total of 150 patients for a time period of 3 to 13 years. The majority of patients had been put on L-thyroxine. Values of total T3, total T4, free T4 were measured with an almost unmodified test (RIA) over the years. Results: The lowest relative coefficient of variation (<10%) was observed in the group of patients who had been treated with L-thyroxine only. Even for TSH, relatively low coefficients of variation were observed in this group. In the group of patients who had not received any medication, T3 and T4 showed also a variation of 10%. FT4 and TSH revealed a wider range of variation. Even after radioiodine therapy, T3 and T4 showed only a quite small variation, while TSH demonstrated a wide range with a

variation of >30%. Conclusion: Our data demonstrate that there are only narrow variations of serum T4 and T3 within individuals with and without thyroid disorders.

9. Nagayama I, Yamamoto K, Saito K, Kuzuya T, Saito T. Subject-based reference values in thyroid function tests. *Endocr J.* 1993 Oct;40(5):557-62. Division of Endocrinology and Metabolism, Jichi Medical School, Tochigi, Japan.

To evaluate the diagnostic value of subject-based reference values in thyroid function tests, we compared intra-individual and inter-individual variation. Five specimens were collected over a period of 2 weeks from each of 47 normal subjects, 29 women and 18 men, aged 20-47 yrs. T4, FT4, T3, and FT3 were assayed by RIA, and TSH by a sensitive immunoradiometric assay. One-way ANOVA for each test was statistically significant for a main subject effect, indicating that the subjects differed in their personal mean values for the thyroid function tests (T4, $P < 0.01$; FT4, $P < 0.05$; T3, $P < 0.01$; FT3, $P < 0.05$; TSH, $P < 0.01$). The ratio value (intra- over inter-individual variation) was T4, 0.41; FT4, 0.60; T3, 0.53; FT3, 0.63; TSH 0.36. The data indicate that conventional reference values are insensitive when compared to subject-based reference intervals in assessing the thyroid status of a given subject. Reactivity of the thyroid to the stimulation of endogenous TSH was assessed by the ratio $\Delta FT3/\Delta TSH$ in TRH stimulation tests. A positive correlation between basal FT3 and $\Delta FT3/\Delta TSH$ ($r = 0.566$, $P < 0.05$) indicates that the thyroid with higher reactivity to TSH secretes more daily thyroid hormone. Negative correlation between basal TSH and $\Delta FT3/\Delta TSH$ ($r = -0.536$, $P < 0.05$) means that a subject with lower reactivity of the thyroid needs a higher basal TSH level to compensate. The thyroid reactivity to TSH may be an important determinant for the individuality of the pituitary-thyroid axis.

10. Browning MC, Bennet WM, Kirkaldy AJ, Jung RT. Intra-individual variation of thyroxin, triiodothyronine, and thyrotropin in treated hypothyroid patients: implications for monitoring replacement therapy. *Clin Chem.* 1988 Apr;34(4):696-9. Department of Biomedical Medicine, Ninewells Hospital and Medical School, Dundee, Scotland.

We measured total thyroxin (TT4), free thyroxin (FT4), total triiodothyronine (TT3), free triiodothyronine (FT3), and thyrotropin (TSH) in serum sampled before and 1, 2, 4, 6, and 8 h after administration of prescribed doses of thyroxin to 12 patients with proven primary hypothyroidism. At 2, 4, and 6 h post-dose, the mean values for TT4 and FT4 and also that at 8 h for FT4 significantly (P less than 0.05) exceeded the corresponding pre-dose values. No significant changes were found for TT3, FT3, or TSH. The mean intra-individual CVs over the study period were TT4 4.9%, FT4 5.7%, TT3 8.7%, FT3 8.7%, and TSH 20.2%. Individual subjects showed small but predictable changes in TT4 and FT4. Changes in TT3 and FT3 were greater but random. Fluctuations in TSH were greatest, but in all subjects with detectable concentrations the variations were of similar magnitude. We conclude that strict adherence to timing of specimen collection in relation to dosage is probably unnecessary.

Different reference ranges for different populations may be needed

11. Hubl W, Schmieder J, Gladrow E, Demant T. Reference intervals for thyroid hormones on the architect analyser. *Clin Chem Lab Med.* 2002 Feb;40(2):165-6. Institut für Klinische Chemie und Laboratoriumsmedizin, Krankenhaus Dresden-Friedrichstadt, Dresden, Germany. hubl-wa@khdf.de

The objective of this study was to establish reference intervals for thyroid

stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), total thyroxine (TT4) and total triiodothyronine (TT3) on the Architect i2000 analyser (Abbott). Serum samples were obtained from apparently healthy adults (n=217, age 18-90 years) excluding individuals taking oral contraceptives or under hormone replacement therapy. The second group were ambulatory euthyroid patients (n=323) excluding those with a history of thyroid disorders. We also investigated thyroid hormones in sera from euthyroid hospitalised patients (n=490) excluding those with severe non-thyroidal illness. The reference intervals for the healthy adults were for TSH 0.17-4.23 mIU/l, for FT4 11.24-26.86 pmol/l, for FT3 2.56-6.36 pmol/l, for TT4 55.8-155.1 nmol/l and for TT3 0.90-2.54 nmol/l. TSH and TT3 concentrations were similar in males and females. However, FT4, FT3 and TT4 levels exhibited significant differences between females and males. No significant differences were observed between the concentrations of TSH, FT3, TT3, FT4 and TT4 in healthy subjects and in euthyroid ambulatory patients aged 18-90 years. TSH levels in healthy subjects were the same in younger and older individuals. In contrast, in outpatients and in hospitalised patients TSH concentrations were significantly lower (20%) in subjects older than 50 years compared to those younger than 50 years. For FT3 and TT3 we consistently observed in all three study groups 6-7% and 8-12% higher concentrations in the younger (< 50 years) compared to the older (> 50 years) subjects. For FT4 and TT4 no consistent pattern of correlation with age was detectable when the three study groups were analysed independently. The reference intervals for thyroid hormones determined in this study differ considerably from values found in other European and non-European countries. This underlines the need for population-specific reference ranges.

12. Dhatt GS, Griffin G, Agarwal MM. Thyroid hormone reference intervals in an ambulatory Arab population on the Abbott Architect i2000 immunoassay analyzer. *Clin Chim Acta*. 2006 Feb;364(1-2):226-9. Epub 2005 Aug 10. Department of Pathology, Tawam Hospital, PO Box 15258, Al Ain, Abu Dhabi, United Arab Emirates. gurdeep1@emirates.net.ae

BACKGROUND: Considerable differences in reference intervals for FT4 and TSH have been reported between countries. Method related differences in the distribution of free thyroxine (FT4) have also been reported. The aim of this study was to establish reference intervals for thyrotrophin (TSH) and FT4 in an ambulatory adult (16-75 y) Arab population attending a general practice clinic using the Abbott Architect i2000 immunoassay analyzer. **METHODS:** TSH and FT4 results from 959 consecutive ambulatory Arab subjects were available. After excluding data sets from pregnant women, patients with known and newly diagnosed thyroid disease, individuals taking medication that may affect TSH and FT4 and individuals with acute illness, 742 data sets were available for analysis. A 2-way between-groups ANOVA was conducted to explore the impact of age and gender on TSH and FT4. **RESULTS:** TSH showed a non-Gaussian distribution, FT4 showed a near normal distribution. There was no significant main effect on FT4 and TSH for age and gender. The interaction effect of age and gender also did not reach significance. The 95% reference intervals were: TSH 0.30-4.32 mU/l and FT4 9.8-18.6 pmol/l. The reference intervals for TSH and FT4 determined in this study differed from those reported from other countries using the same analytical platform and from the 99% reference intervals, provided by the manufacturer. **CONCLUSIONS:** These differences in reference intervals in different populations may affect patient management. The data reported reemphasize that each laboratory should determine population and method-specific reference intervals.

Broadening of the thyroid reference ranges due to inclusion of elderly persons

13. González-Sagrado M, Martín-Gil FJ. Population-specific reference values for thyroid hormones on the Abbott ARCHITECT i2000 analyzer. Clin Chem Lab Med. 2004 May;42(5):540-2. Unidad de Apoyo a la Investigación, Hospital Universitario "Del R o Hortega" Valladolid, Spain. gonzalez-sagrado@arrakis.es

Reliable reference ranges are important in the interpretation of laboratory data, and it is incumbent on each laboratory to verify that the ranges they use are appropriate for the patient population they serve. The objective of this study was to determine population-specific reference ranges for thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3) and total triiodothyronine (TT3) on the Abbott ARCHITECT 12000 analyzer. For this study, we used human serum samples collected from a population in Castilla y Le n, Spain. Serum samples were collected from 304 individuals (male, n = 151; female, n = 153; age 12-94 years) representing outpatients (n=100), hospitalized patients (n = 104) and apparently healthy subjects (n = 100). Individuals taking any medications, with a history of thyroid disorder, or severe non-thyroidal illness were excluded from the study. For healthy subjects, the following reference intervals were determined: TSH, 0.51-5.95 mIU/l; fT4, 0.84-1.42 ng/dl (10.77-18.21 pmol/l); fT3, 1.48-3.37 pg/ml (2.27-5.18 pmol/l); and TT3, 0.65-1.46 ng/ml (1.00-2.24 nmol/l). In this group, TSH and fT4 showed significant differences between men and women, but fT3 and TT3 did not. Conversely, fT3 and TT3 showed significant age-related differences, but TSH and fT4 did not. Within the outpatient group, no significant differences were seen between men and women for any of the hormones, but age-related differences were significant for fT3 and TT3. Within the hospitalized patient group, significant differences between men and women were found for TSH only, and age-related differences were significant for TSH, fT3 and TT3. Our findings are basically in accordance with previously published results for fT3, TT3 and TSH, but for fT4 our results differ from other data in the literature. This highlights the need for laboratories to confirm that the reference ranges they use are appropriate for the population they serve.

14. Davey R. Thyroxine, thyrotropin, and age in a euthyroid hospital patient population. Clin Chem. 1997 Nov;43(11):2143-8. Western Hospital, Footscray, Australia. Richard.Davey@whcn.org.au

The diagnosis of thyroid disease now often can be achieved reliably by measuring thyrotropin (TSH) alone. Thyroxine (T4), triiodothyronine, and other analytes are only needed if TSH and the accompanying clinical condition are discordant. We describe here work that confirms the age independence of TSH in both inpatient and outpatient euthyroid hospital populations between ages 20 and at least 80 years, and demonstrates that although free T4 does vary with age, the range of variation remains within the T4 reference interval. On this basis, TSH-based thyroid diagnostic algorithms can be used reliably in adults without reference to age-related reference intervals.

Broadening of the thyroid reference ranges due to inclusion of sick person

15. Midgley JE, Gruner KR. Effects of age and health on the euthyroid reference ranges for serum free thyroxine and free triiodothyronine. Nuklearmedizin. 1985 Apr;24(2):57-65.

Age-related trends in serum free thyroxine (fT4) and free triiodothyronine (fT3) concentrations were measured in 7248 euthyroid subjects (age-range 3 months to 106 years). 5700 were patients referred to hospitals for investigation of

suspected thyroid dysfunction, but who were diagnosed euthyroid. 1548 were healthy blood donors (age-range 18-63 years) with no indication of thyroid dysfunction. FT4 concentrations were little affected by the age, the sex or the state of health of the subjects in either group. Serum FT3 concentrations were significantly affected by both age and health factors. The upper limit of the euthyroid reference range for young subjects up to 15 years was about 20% higher (10.4 pmol/l) than for adult subjects older than 25 years (8.8 pmol/l). The change in the upper limits typical of young subjects to that typical of adults occurred steadily over the decade 15-25 years. After this age, little further change occurred, especially in healthy subjects. Additionally, the lower limit of the euthyroid range for FT3 was extended by the inclusion in the reference group of patients referred to hospitals. Compared with the lower limit of the FT3 range for healthy subjects (5 pmol/l), the corresponding limit for referred subjects (young or adult) was 3.5-3.8 pmol/l. Broadening of the FT3 reference range was probably brought about by a significant number of patients in the hospital-referred group with the "low-T3 syndrome" of mild non-thyroidal illness. Accordingly, FT3 was inferior to FT4 in the discrimination of hypothyroidism, as FT4 was unaffected by this phenomenon.(ABSTRACT TRUNCATED AT 250 WORDS)

Misinterpretation of an abnormal laboratory value as an aging change can lead to underdiagnosis and undertreatment in some instances (such as anemia).

16. Melillo KD. Interpretation of laboratory values in older adults. Nurse Pract. 1993 Jul;18(7):59-67. Graduate Nursing Program, College of Health Professions, University of Massachusetts, Lowell.

This article describes age-related physiologic changes in the older adult and the effect of these changes, if any, on commonly ordered laboratory tests. As reported in selected research studies and literature reviews, some laboratory parameters change minimally or not at all with age, still remaining within recommended reference ranges, while others are altered with age. Misinterpretation of an abnormal laboratory value as an aging change can lead to underdiagnosis and undertreatment in some instances (such as anemia). Failure to appreciate age-related changes can lead to overdiagnosis and overtreatment in others (such as hyperglycemia). The results from ongoing national studies are needed to establish uniform older adult reference intervals.

APPENDIX 3: IHS consensus 9 with references



The International Hormone Society

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Consensus # 9 on “The treatment of clinically hypothyroid, but biochemically euthyroid patients”

April 12, 2007

After an extensive literature review and discussions with physicians from all over the world who are well versed in treating patients with endocrine abnormalities, we, the Consensus Group of Experts of the International Hormone Society (IHS), think there is enough clinical and theoretical evidence to expand the application of thyroid treatment beyond the current conventional parameters.

Is the diagnosis of hypothyroidism based on biochemical evaluation or clinical evidence?

There is a controversy between groups of physicians. One group essentially diagnoses hypothyroidism solely with laboratory tests, while the other relies more on clinical factors. Solid scientific evidence does not support the idea that the diagnosis of hypothyroidism can or should only be based on laboratory tests. This would imply that hypothyroidism only exists in patients with a serum TSH beyond the actual upper reference range, and serum thyroxine (T4) and triiodothyronine (T3) levels below the lower reference range, and neglects the clinical signs and symptoms.

The IHS's position is intermediate. The decision to initiate (thyroid) therapy should be based on both clinical and laboratory findings, and not solely on the results of a single test, exactly as expressed in the medical journals *JAMA* and *Thyroid* presenting the American Thyroid Association's guidelines for use of laboratory tests in thyroid disorders¹. The diagnosis of hypothyroidism is further substantiated when treatment results in the relief of clinical signs and symptoms and the laboratory tests are improved.

Clinical information is essential in diagnosing a hormone deficiency. The clinical data needed to make a diagnosis of hypothyroidism include the physical and emotional complaints of patients, physical signs, personal and familial medical histories suggestive of a thyroid deficiency and the existence of a thyroid gland abnormality (nodule or goiter) and/or autoimmune thyroiditis.

The following evidence supports the existence of patients who are **clinically hypothyroid, but mistakenly considered biochemically euthyroid**, and who may benefit from thyroid treatment:

- 1) The normal reference ranges for thyroid tests are too broad and ignore specific individual reference ranges.**
 - **Excessively broad reference ranges:** Large reference intervals may include serum levels of T3, T4 and TSH that are compatible with thyroid dysfunction, in particular, with various degrees of mild thyroid failure. The experts on the consensus panel did not find any studies proving that the normal thyroid test reference ranges discriminate adequately

between hypo-, eu- and hyperthyroidism. On the contrary, we found studies whose data questioned the usefulness of these reference ranges, in particular, for serum TSH, T3 and T4. The data from these studies support the use of narrower ranges for these serum tests. The broader reference ranges include levels that may be consistent with thyroid dysfunction, especially in its milder forms. This is not surprising, as the reference ranges of a test are not values indicative of health, but merely values found in 95% of a population, generally the population of patients going to the laboratory. Levels compatible with both health and (thyroid) disease may be included.

- **The TSH reference range:** The difference between the upper and lower ends of the reference range is more than 20-fold (0.2-4.1 mIU per liter).
 - In several studies, a serum TSH above 1.5 or 2 mIU per liter has been linked with increased hypothyroid-associated lipid and inflammatory pathologies (such as higher serum levels of homocysteine, cholesterol and highly sensitive CRP). These higher TSH levels have also been linked with coronary and vascular abnormalities (such as higher coronary artery diseases scores, increased risk of multi-vessel disease, increased arterial stiffness), lower birth weight, premature birth of children from mothers with TSH above 2, and an increased risk of progression from mild to overt hypothyroidism. Depending on the study, at TSH levels above 0.4 or 0.9 mIU per liter there is an increased risk of thyroid malignancy in patients with morphological abnormalities of the thyroid. The increased risk may be reversed by treatment with thyroid medication. Other disorders have been observed in patients with a serum TSH within the reference range but above the 25th percentile such as a higher risk of severe depression, a poorer response to antidepressants, an increased incidence of somatic disease, a higher body mass index, an increased waist circumference, higher systolic and diastolic blood pressures, and higher serum glucose and triglycerides. Medicating these patients who are apparently in mild thyroid failure and have a high risk of becoming overtly hypothyroid may prevent the important sequelae associated with the progression of hypothyroidism.
 - Other data support the need for improved serum TSH reference ranges. If the serum TSH reference range is based upon a cohort of truly normal individuals, for example, with no personal or family history of thyroid dysfunction, no visible or palpable goiter, no medication use, no thyroid peroxidase antibodies – and with fasting blood samples taken in the morning (6–10 AM) – then the TSH reference range would be 0.4–2.5 mIU per liter. The data support the acceptance of a value below 3 as an upper limit for the TSH reference range. When data for subjects with positive thyroid peroxidase antibodies or a family history of autoimmune thyroid disease are excluded, the normal reference interval becomes much tighter, i.e. 0.4–2.0 mIU per liter.
 - Moreover, the results of several investigations indicate a mean serum TSH of 1.5 mIU per liter for an iodine-sufficient population, demonstrating that the reference range of 0.1 – 5.1 mIU per liter is far too broad.
 - Ethnic differences should also be taken into account: A study has shown the mean TSH level in African-Americans to be 1.18 mU/liter, in contrast to a mean of 1.40 mU/liter in Caucasians, due to the greater frequency of autoimmune thyroid disease in whites. This may have skewed the upper end of the TSH curve (NHANES data). For African-Americans, the TSH reference range is possibly lower than in whites.
 - The American Association of Clinical Endocrinologists in 2002 therefore narrowed the serum TSH reference range to 0.3-3.0 mIU/L, lowering the upper reference end to 3. The National Academy of Clinical Biochemistry reduced the upper end of the reference range from 5.5 to 4.1 mIU per liter in 2003. The latter group also stated

that “more than 95% of healthy, euthyroid subjects have a serum TSH between 0.4 - 2.5 mIU per liter” and that “patients with a serum TSH above 2.5 mIU per liter, when confirmed by repeat TSH measurement made after three to four weeks, may be in the early stages of thyroid failure, especially if thyroid peroxidase antibodies are detected.” In 2003, the consensus panel (Endocrine Society, American Association of Clinical Endocrinologists, and American Thyroid Association) recommended a target TSH range of 1.0 to 1.5 mIU per liter in patients already receiving thyroxine therapy.

- **Erroneously low TSH:** Some patients may suffer from centralized hypothyroidism and will have a low TSH even with a low T4 and a low T3. TSH is currently the primary thyroid screening test recommended. In this population of patients, a hypothyroid disorder will be missed if the low TSH is not followed up by testing free T3 and free T4.
- **Serum free T3 and T4 reference ranges:** The difference between the upper and lower reference ends is more than two-fold (1.8-3.7 ng per liter for free T3 and 0.8-1.8 ng per deciliter for free T4). Although the size of the reference range of free, unbound thyroid hormones is less impressive than that of serum TSH, a patient whose thyroid hormones are borderline high (while still within the normal reference range) may have twice the amount of thyroid hormones in his/her blood than a patient who is borderline low (but also in the reference range of euthyroid patients). If one of these patients is clinically well, then the other probably has a thyroid dysfunction. Patients with a serum T3 in the lower third of the reference range have been documented to undergo more inflammatory processes, to have an increased risk of breast cancer and increased severity of coronary heart disease. Cardiac function has been observed to be decreased in patients with serum T3 in the lower quintile (20%) of the reference range. Studies can be found where lower serum free or total T3 levels within the reference range are correlated with increased severity of illness and/or worse prognosis of a disease, including an increased mortality rate. This is particularly true in cases of myocardial infarction, chronic heart failure and stroke. For serum T4 values within the lower half of the normal reference range in children, there are reports that maximal intellectual development has been impaired, while in the same lower half of the serum T4 range, the rate of depression in patients with Alzheimer’s disease appears to be significantly higher. Moreover, a serum T4 in the lower third of the reference range has been associated with increased insulin resistance, premature atherosclerosis (with significantly higher levels of CRP), increased memory loss, and increased mortality. There is enough data to support the need for a profound revision of thyroid hormone reference ranges, where narrower reference ranges with higher lower ends would provide more useful, truly healthy, reference ranges.
- **Need for narrower reference ranges for thyroid tests:** In light of the above data and considerations, the IHS consensus panel of experts stresses the importance of undertaking studies to establish more accurate and narrower reference ranges that reflect true euthyroidism. Narrower reference ranges allow more patients with mild thyroid failure or excess to be detected and treated. Mild thyroid failure is reflected by borderline low serum T3 and T4 and/or borderline high serum TSH. The panel is aware of at least one study in which the treatment of clinically hypothyroid, but biochemically euthyroid, patients was done using thyroxine with no beneficial result. Possibly, the dose or the type of thyroid treatment, namely thyroxine alone, was insufficient to obtain beneficial clinical results. A higher dose or a combined thyroxine-triiodothyronine medication might have been more appropriate. In one study of patients with coronary heart disease, for example, the progression of coronary atherosclerosis over one year was apparent in all patients taking 100 micrograms or less of thyroxine per day, while only one sixth of patients taking 150 micrograms or more had disease progression. Earlier studies have shown significantly better efficacy of combined thyroxin-triiodothyronine medications, compared to thyroxine alone. Improvement was found in

such divergent parameters as serum cholesterol, mental and physical symptoms, and, in animals, goiter formation and intracellular triiodothyronine (T3) euthyroidism, to name a few of the possible increased benefits.

- **Specific individual reference ranges:** The optimal reference ranges for an individual can be different from the population reference ranges used by laboratories. Individual reference ranges are usually narrower (for example, 0.5 to 1.5 mIU per liter of serum TSH, rather than 0.2-4.1). Moreover, specific cut-off points between eu- and hypothyroidism may differ from one individual to another. One person may be euthyroid at a serum TSH of 0.5 and hypothyroid at 0.6, while another may be euthyroid at a TSH of 2 and hypothyroid at 2.1. Because of such inter-subject variations, when the results of thyroid tests don't match the clinical picture of thyroid dysfunction, the clinical impression of the experienced physician who has examined the patient should prevail and, if the patient is clinically hypothyroid, a therapeutic trial of thyroid hormones administered, starting at low doses.
 - **Tertiles, quartiles or quintiles of insufficiency may have to be considered to diagnosis hypothyroidism, rather than values below or above the reference range.** Serum levels of thyroid hormones in the lower tertile, quartile or quintile, and serum levels of TSH in the upper half of the reference range, have been associated with increased disease and mortality rates, as mentioned above.
- 2) **Excessive fluctuations of serum levels of T3, T4 and TSH:** Differences up to three-fold in serum TSH and serum T4 have been found within the same individual during a single day. Such dramatic variations put the reliability of thyroid tests in question. At the time of the blood draw a person may be at his/her lowest TSH level, which is well under the upper reference range and looks reassuringly normal, while at other times s/he may be clearly above the upper reference range with a value consistent with subclinical or even overt hypothyroidism.
- 3) **Thyroid dysfunction at the cellular level, undetectable by classical laboratory tests.** A lack of thyroid activity may also be caused by a decline in the number, availability or affinity of thyroid nuclear cell receptors, in particular of T3. It is known from animal experiments that thyroid (T3) nuclear cell receptors decrease with age. This has also been observed in some human hormone deficiencies such as Addison's disease. A decline in cell receptors cannot be confirmed by classical thyroid tests, as tests for T3 nuclear cell receptors are not currently available in conventional laboratories. The only way to detect insufficient thyroid cell receptors is to evaluate the psychological and somatic effects of thyroid hormones on the body. This must be done through physical examination and interview, checking for hypothyroid signs and symptoms. Useful information might be deduced by testing the peripheral effects of thyroid hormones on serum parameters that increase in proportion to thyroid activity, such as serum SHBG (sex hormone binding globulin), alkaline phosphatase or osteocalcin, and/or that decrease with increasing thyroid function, such as serum total cholesterol. Alternatively, we could test for direct metabolites of T3, namely the T2's (diiodothyronines), but these tests are not yet available. Furthermore, even if thyroid hormone serum levels and receptors are optimal, vitamins, trace elements, minerals or amino acids necessary for enzyme production or function could be deficient, thereby reducing the efficacy of metabolic reactions under control of thyroid hormones.

Thyroid treatment of clinically hypothyroid, though biochemical euthyroid, patients:

If a patient is clinically hypothyroid, presenting with several signs and symptoms of hypothyroidism, but is considered biochemically euthyroid, with low normal laboratory levels of serum T3 and/or T4, and/or high normal serum TSH according to the actual reference range, **a trial of thyroid therapy** may be started to see if the patient's signs and symptoms regress under therapy. Thyroid hormone levels may be considered low normal when in the lower third or half of

the reference range, while the serum TSH may be considered high normal when in the upper third or half of the actual TSH reference range (0.2-4.1 mU per liter). In these zones, the patient may be hypothyroid, as demonstrated by several studies in which hypothyroidism is reflected by upcoming disorders such as lipid, vascular, cardiac, insulin and mental disturbances, and cancer and mortality risks, and sharp increases in risk of progression to overt hypothyroidism, as discussed above. These pathologies suggest mild thyroid failure that may regress under therapy.

We recommend that physicians be careful to exclude, before thyroid intervention, other pathologies that may explain the symptoms. A trial of thyroid hormones should be started at low doses that are progressively increased, and progress should be carefully evaluated, taking care that the patient is not overdosed.

Is there any danger in treating thyroid dysfunction? The most common adverse effect is iatrogenic hyperthyroidism. This is caused either by overdose or intolerance. Intolerance with peaks of T3-hyperthyroidism can be caused by excess conversion of thyroxine (T4) into triiodothyronine (T3), thus accelerating thyroid activity, and is more likely to occur with other hormone deficiencies, such as an adrenal insufficiency (cortisol), a lack of estrogens, and other hormone inadequacies that stimulate the conversion of T4 to T3. Safety can be increased by starting at low doses.

Follow-up on thyroid treatment of clinically hypothyroid, though biochemical euthyroid, patients:

Under treatment, most initially **clinically hypothyroid** (though mistakenly considered biochemically euthyroid) **patients, should have normal lab values (with levels of T3, T4 and TSH inside the reference range when the tests are done more than 9 hours after taking thyroid medication)**. They should become *clinically* euthyroid. However, peak serum levels of T4 and T3 may be found that are not representative of the patient's real thyroid activity during the first 9 hours after intake of thyroid medication, and some studies suggest that between 36 and 47 % of patients clinically euthyroid under thyroid therapy have an undetectable serum TSH.

Conclusion: Clinically hypothyroid, though biochemically euthyroid, patients may have a mild degree of thyroid failure. Such patients may benefit from a trial with thyroid hormones starting at low doses that are progressively increased. Before commencing the trial, other pathologies that may be causing the clinical signs and symptoms should be excluded. Careful monitoring is recommended.

¹. JAMA 1993, 269:2736, Thyroid, 1993; 3 (4): 353-54

References of Consensus 9 on the Treatment of Clinically Hypothyroid, but Biochemically Euthyroid Patients

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

Studies with data that indicate that

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

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 Pathophysiology 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 Paulo, 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 mU/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) 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

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) 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

12. Evrengul H, Tanriverdi H, Enli Y, Kuru O, Selecic 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) Associations between a low serum free T3 within the reference range and pathological parameters

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. Studies that show association of disease (markers) with serum T4 levels within the reference range

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) The healthiest serum T4 levels may be found in the upper quartile of the reference range

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 risk 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) The healthiest serum T4 levels may be found in the upper tertile of the reference range

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 “biochemically euthyroid” patients, otherwise, at lower serum free T4 levels within the reference range, the risk 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 “biochemically 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) The healthiest serum T4 levels may be found in the upper three quartiles of the reference range

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

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) The healthiest serum T levels may be found in the upper 90 % of the reference range (above the 10th percentile)

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, Kuijpers 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) 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)

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. References of studies that show association of disease (markers) with serum TSH levels within the reference range

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
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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 healthiest serum TSH levels may be found below the 3 mU/L

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, Pigiariu F, Putzu C, Pisano L, Vargiu S, Deidda M, Mariotti S, Mercurio 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) The healthiest serum TSH levels may be found in the lower half of the reference range

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. sieiorj@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. Dagle 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, Pipingos 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 School Rotterdam, The Netherlands.

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

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 hypothyroidism 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) The healthiest serum TSH levels may be found in the lower quartile (lower 25%) of the reference range

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) Adverse associations between serum TSH within the reference range & pathological parameters

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. 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

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. Publications on the need for more narrow reference ranges for the thyroid tests:

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. Excessive fluctuations of serum levels of T3, T4 and TSH:

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 Bugoslavskaja 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 serum T3 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. Thyroid dysfunction at cellular level, undetectable by classical laboratory tests

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 mononuclear 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, Vandepuy Y, Bottazzo FC, Crabbe J. Altered interaction between triiodothyronine and its nuclear receptors in absence of cortisol: a proposed mechanism for increased TSH secretion in corticosteroid deficiency states. *J Clin Invest* 1987; 17(2): 106-10

Study that shows that in obesity the affinity of T4 nuclear receptors is 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. Szabolcs I, Weber M, Kovacs Z, Irsy G, Goth M, Halasz T, Szilagyi G. 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. Smeulders J, Visser TJ, Burger AK, Docter R, Hennemann G. Decreased triiodothyronine (T3) production in constant reverse T3 production in advanced age. *Ned Tijdschr Geneesk.* 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/L. 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, Gugliemetti 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, Gugliemetti 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 right 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, Zalinkovicus 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, Pipingos 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, Pipingos 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 JPP, 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. Universitäts-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 levels)
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, Szejnsznajd 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'Erasmus 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 autoimmune disease

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

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, Fombour 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-thyroxine 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 of Hashimoto's thyroiditis] *Nuklearmedizin.* 1999;38(5):144-9. Abteilung für 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. igraves@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 hypertriiodothyronaemia 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 administration 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 administration 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. Raymond 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. Wiegatz 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, Patkhidinov PP, Myslitskaia AI. Effect of immobilization stress on the level of thyroid hormone secretion *Probl Endokrinol (Mosk)*. 1993 Sep-Oct;39(5):47-8.
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APPENDIX 4: Double-blind studies on thyroid treatment

Double blind placebo-controlled studies comparing thyroid treatments with T4-T3 versus those with T4 alone

Studies with significant superior effects of T4-T3 versus T4 alone

1. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N Engl J Med.* 1999 Feb 11;340(6):424-9. Institute of Endocrinology, Kaunas Medical University, Lithuania.

Comment in:

Ann Intern Med. 2005 Oct 4;143(7):543; author reply 543-4.

N Engl J Med. 1999 Feb 11;340(6):469-70.

BACKGROUND: Patients with hypothyroidism are usually treated with thyroxine (levothyroxine) only, although both thyroxine and triiodothyronine are secreted by the normal thyroid gland. Whether thyroid secretion of triiodothyronine is physiologically important is unknown. **METHODS:** We compared the effects of thyroxine alone with those of thyroxine plus triiodothyronine (liothyronine) in 33 patients with hypothyroidism. Each patient was studied for two five-week periods. During one period, the patient received his or her usual dose of thyroxine. During the other, the patient received a regimen in which 50 microg of the usual dose of thyroxine was replaced by 12.5 microg of triiodothyronine. The order in which each patient received the two treatments was randomized. Biochemical, physiologic, and psychological tests were performed at the end of each treatment period. **RESULTS:** The patients had lower serum free and total thyroxine concentrations and higher serum total triiodothyronine concentrations after treatment with thyroxine plus triiodothyronine than after thyroxine alone, whereas the serum thyrotropin concentrations were similar after both treatments. Among 17 scores on tests of cognitive performance and assessments of mood, 6 were better or closer to normal after treatment with thyroxine plus triiodothyronine. Similarly, among 15 visual-analogue scales used to indicate mood and physical status, the results for 10 were significantly better after treatment with thyroxine plus triiodothyronine. The pulse rate and serum sex hormone-binding globulin concentrations were slightly higher after treatment with thyroxine plus triiodothyronine, but blood pressure, serum lipid concentrations, and the results of neurophysiologic tests were similar after the two treatments. **CONCLUSIONS:** In patients with hypothyroidism, partial substitution of triiodothyronine for thyroxine may improve mood and neuropsychological function; this finding suggests a specific effect of the triiodothyronine normally secreted by the thyroid gland.

Studies with near significantly superior effects of T4-T3 versus T4 alone

2. Bunevicius R, Jakubonien N, Jurkevicius R, Cernicat J, Lasas L, Prange AJ. Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease. *Endocrine.* 2002 Jul;18(2):129-33 Institute of Endocrinology, Clinic of the Kaunas Medical University, Lithuania. (no significant differences were found on measures of mood, cognition, or physiologic variables between treatments, but symptoms of hypothyroidism and of hyperthyroidism tended to decrease on a standard symptom scale after combined treatment, mental state tended to improve on some mood scales)

It was recently demonstrated that treatment with levorotatory thyroxine (T4) plus triiodothyronine (T3) compared with treatment with T4 alone improves psychologic

functioning in hypothyroid patients with thyroid cancer or autoimmune thyroiditis. In the present double-blind crossover study, we again compared the effects of combined thyroid replacement vs monotherapy on psychologic function, endocrine function, cardiovascular function, and body composition. The patients were women who were hypothyroid after thyroidectomy for Graves' disease. The substitution of 10 microg of T3 for 50 microg of T4 caused a statistically significant decrease in free T4 concentration but no significant change in T3 or thyroid-stimulating hormone concentration. Symptoms of hypothyroidism and of hyperthyroidism tended to decrease on a standard symptom scale after combined treatment. With combined hormone replacement, mental state tended to improve on some mood scales but not on cognitive tests. We found alterations in left ventricular diastolic function but no change in body composition after the combined treatment regimen. These preliminary findings in a small group of patients with Graves' disease are consistent with earlier findings that thyroid replacement with T4-T3 combination improves mental functioning.

Study with globally no superior significant effects of T4-T3 versus T4 alone, except on one parameter where the patients on T4-T3 combinations did better:

3. Clyde PW, Harari AE, Getka EJ, Shakir KM. Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. JAMA. 2003 Dec 10;290(22):2952-8. Department of Endocrinology and Metabolism, Nation Naval Medical Center, Bethesda, Md 20889-5600, USA. pwclyde@mar.med.navy.mil

CONTEXT: Standard therapy for patients with primary hypothyroidism is replacement with synthetic thyroxine, which undergoes peripheral conversion to triiodothyronine, the active form of thyroid hormone. Within the lay population and in some medical communities, there is a perception that adding synthetic triiodothyronine, or liothyronine, to levothyroxine improves the symptoms of hypothyroidism despite insufficient evidence to support this practice.

OBJECTIVE: To evaluate the benefits of treating primary hypothyroidism with levothyroxine plus liothyronine combination therapy vs levothyroxine monotherapy. DESIGN, SETTING, AND PATIENTS: Randomized, double-blind, placebo-controlled trial conducted from May 2000 to February 2002 at a military treatment facility that serves active duty and retired military personnel and their family members. The trial included a total of 46 patients aged 24 to 65 years with at least a 6-month history of treatment with levothyroxine for primary hypothyroidism. INTERVENTION: Patients received either their usual dose of levothyroxine (n = 23) or combination therapy (n = 23), in which their usual levothyroxine dose was reduced by 50 microg/d and substituted with liothyronine, 7.5 microg, taken twice daily for 4 months. MAIN OUTCOME MEASURES: Scores on a hypothyroid-specific health-related quality-of-life (HRQL) questionnaire, body weight, serum lipid levels, and 13 neuropsychological tests measured before and after treatment. RESULTS: Serum thyrotropin levels remained similar and within the normal range in both treatment groups from baseline to 4 months. Body weight and serum lipid levels did not change. The HRQL questionnaire scores improved significantly in both the control group (23%; P<.001) and the combination therapy group (12%; P =.02), but these changes were statistically similar (P =.54). In 12 of 13 neuropsychological tests, outcomes between groups were not significantly different; the 1 remaining test (Grooved Peg Board) showed better performance in the control group. CONCLUSION: Compared with levothyroxine alone, treatment of primary hypothyroidism with combination levothyroxine plus liothyronine demonstrated no beneficial changes in body weight, serum lipid levels, hypothyroid symptoms as measured by a HRQL questionnaire, and standard measures of cognitive performance.

Studies with no superior significant effects of T4-T3 versus T4 alone, but most patients preferred the T4-T3 combinations:

As these studies was done in a double-blind fashion, this would prove that the T3-T4

combination thyroid treatment was better on parameters that the researcher didn't search for (in other words the primary and secondary outcomes the researchers searchh for were not the good ones)

4. Escobar-Morreale HF, Botella-Carretero JI, Gomez-Bueno M, Galan JM, Barrios V, Sancho J. Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. *Ann Intern Med.* 2005 Mar 15;142(6):412-24. Department of Endocrinology, Hospital Ramon y Cajal, Madrid, Spain. hescobarm.hrc@salud.madrid.org
Summary for patients in: *Ann Intern Med.* 2005 Mar 15;142(6):l55 (18/24 patients preferred the T3-T4 combinations)

BACKGROUND: Substituting part of the dose of l-thyroxine with small but suprathyroid doses of liothyronine in hypothyroid patients has yielded conflicting results. OBJECTIVE: To evaluate combinations of L-thyroxine plus liothyronine in hypothyroid patients that match the proportions present in normal secretions of the human thyroid gland. DESIGN: Randomized, double-blind, crossover trial. SETTING: Academic research hospital. PARTICIPANTS: 28 women with overt primary hypothyroidism. INTERVENTION: **Crossover trial** comparing treatment with l-thyroxine, 100 microg/d (standard treatment), versus treatment with L-thyroxine, 75 microg/d, plus liothyronine, 5 microg/d (combination treatment), for 8-week periods. All patients also received L-thyroxine, 87.5 microg/d, plus liothyronine, 7.5 microg/d (add-on combination treatment), for a final 8-week add-on period. MEASUREMENTS: Primary outcomes included serum thyroid hormone levels, results of quality-of-life and psychometric tests, and patients' preference. Multiple biological thyroid hormone end points were studied as secondary outcomes. RESULTS: Compared with standard treatment, combination treatment led to lower free thyroxine levels (decrease, 3.9 pmol/L [95% CI, 2.5 to 5.3 pmol/L]), slightly higher serum levels of thyroid-stimulating hormone (increase, 0.62 mU/L [CI, 0.01 to 1.23 mU/L]), and unchanged free triiodothyronine levels. No improvement was observed in the other primary and secondary end points after combination treatment, with the exception of the Digit Span Test, in which the mean backward score and the mean total score increased slightly (0.6 digit [CI, 0.1 to 1.0 digit] and 0.8 digit [CI, 0.2 to 1.4 digits], respectively). The add-on combination treatment resulted in overreplacement. Levels of thyroid-stimulating hormone decreased by 0.85 mU/L (CI, 0.27 to 1.43 mU/L) and serum free triiodothyronine levels increased by 0.8 pmol/L (CI, 0.1 to 1.5 pmol/L) compared with standard treatment; 10 patients had levels of thyroid-stimulating hormone that were below the normal range. Twelve patients preferred combination treatment, 6 patients preferred the add-on combination treatment, 2 patients preferred standard treatment, and 6 patients had no preference (P = 0.015). LIMITATIONS: Treatment with L-thyroxine, 87.5 microg/d, plus liothyronine, 7.5 microg/d, was an add-on regimen and was not randomized. CONCLUSIONS: Physiologic combinations of L-thyroxine plus liothyronine do not offer any objective advantage over l-thyroxine alone, **yet patients prefer combination treatment.**

Comment in: *Ann Intern Med.* 2005 Oct 4;143(7):543; author reply 543-4.

5. Appelhof BC, Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JG, Endert E, van Weert HC, Wiersinga WM. Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. *J Clin Endocrinol Metab.* 2005 May;90(5):2666-74. Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, F5-161, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands. b.c.appelhof@amc.uva.nl

Controversy remains about the value of combined treatment with levothyroxine (LT4) and liothyronine (LT3), compared with LT4 alone in primary hypothyroidism.

We compared combined treatment with LT4 and LT3 in a ratio of 5:1 or 10:1 with LT4 monotherapy. We conducted a double-blind, randomized, controlled trial in 141 patients (18-70 yr old) with primary autoimmune hypothyroidism, recruited via general practitioners. Inclusion criteria included: LT4 treatment for 6 months or more, a stable dose for 6 wk or more, and serum TSH levels between 0.11 and 4.0 microU/ml (mU/liter). Randomization groups were: 1) continuation of LT4 (n = 48); 2) LT4/LT3, ratio 10:1 (n = 46); and 3) LT4/LT3, ratio 5:1 (n = 47). Subjective preference of study medication after 15 wk, compared with usual LT4, was the primary outcome measure. Secondary outcomes included scores on questionnaires on mood, fatigue, psychological symptoms, and a substantial set of neurocognitive tests. Study medication was preferred to usual treatment by 29.2, 41.3, and 52.2% in the LT4, 10:1 ratio, and 5:1 ratio groups, respectively (chi2 test for trend, P = 0.024). This linear trend was not substantiated by results on any of the secondary outcome measures: scores on questionnaires and neurocognitive tests consistently ameliorated, but the amelioration was not different among the treatment groups. Median end point serum TSH was 0.64 microU/ml (mU/liter), 0.35 microU/ml (mU/liter), and 0.07 microU/ml (mU/liter), respectively [ANOVA on ln(TSH) for linear trend, P < 0.01]. Mean body weight change was +0.1, -0.5, and -1.7 kg, respectively (ANOVA for trend, P = 0.01). Decrease in weight, but not decrease in serum TSH was correlated with increased satisfaction with study medication. Of the patients who preferred combined LT4/LT3 therapy, 44% had serum TSH less than 0.11 microU/ml (mU/liter). Patients preferred combined LT4/LT3 therapy to usual LT4 therapy, but changes in mood, fatigue, well-being, and neurocognitive functions could not satisfactorily explain why the primary outcome was in favor of LT4/LT3 combination therapy. Decrease in body weight was associated with satisfaction with study medication.

6. Saravanan P, Simmons DJ, Greenwood R, Peters TJ, Dayan CM. Partial substitution of thyroxine (T4) with tri-iodothyronine in patients on T4 replacement therapy: results of a large community-based randomized controlled trial. *J Clin Endocrinol Metab.* 2005 Feb;90(2):805-12. Epub 2004 Dec 7. Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Whitson Street, Bristol BS1 3NY, UK.

Conflicting results have recently been published about the benefits of combined T(4) and T(3) in treating hypothyroid patients. However, these studies may have been underpowered to detect differences in psychological well-being specifically related to T(4) replacement. We conducted a large, double-blind, randomized controlled trial of partial substitution of 50 microg T(4) by 10 microg T(3) vs. the original dose of T(4) in 697 hypothyroid patients. Thyroid function showed a rise in TSH (132%), a fall in free T(4) (35%, P < 0.001), and unchanged basal free T(3) levels (P = 0.92). At 3 months, there was a large (39%) placebo effect improvement in psychiatric caseness defined by the General Health Questionnaire (GHQ) 12 score in the control group compared with baseline, and this was sustained at 12 months. Differences vs. the intervention (T(3)) group were more modest with improvements in GHQ caseness (odds ratio, 0.61; 95% confidence interval, 0.42, 0.90; P = 0.01) and Hospital Anxiety and Depression questionnaire-anxiety scores at 3 months (P < 0.03) but not GHQ Likert scores, Hospital Anxiety and Depression questionnaire-depression, thyroid symptoms, or visual analog scales of mood and the initial differences were lost at 12 months. These results may be consistent with a subgroup of patients showing transient improvement after partial substitution with T(3) but do not provide conclusive evidence of specific benefit from partial substitution of T(4) by T(3) in patients on T(4) replacement. They also emphasize the large and sustained placebo effect that can follow changes in thyroid hormone administration.

Placebo-controlled trial : no difference in effects between T3-T4 vs T4 alone, but patients with T3-T4 kept a higher TSH (indicative of a too low dose)

7. Walsh JP, Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BG, Dhaliwal SS, Chew GT,

Bhagat MC, Cussons AJ. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. *J Clin Endocrinol Metab.* 2003 Oct;88(10):4543-50. Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia. john.walsh@health.wa.gov.au

T(4) is standard treatment for hypothyroidism. A recent study reported that combined T(4)/liothyronine (T(3)) treatment improved well-being and cognitive function compared with T(4) alone. We conducted a double-blind, randomized, controlled trial with a crossover design in 110 patients (101 completers) with primary hypothyroidism in which liothyronine 10 micro g was substituted for 50 micro g of the patients' usual T(4) dose. No significant ($P < 0.05$) difference between T(4) and combined T(4)/T(3) treatment was demonstrated on cognitive function, quality of life scores, Thyroid Symptom Questionnaire scores, subjective satisfaction with treatment, or eight of 10 visual analog scales assessing symptoms. For the General Health Questionnaire-28 and visual analog scales assessing anxiety and nausea, scores were significantly ($P < 0.05$) worse for combined treatment than for T(4) alone. Serum TSH was lower during T(4) treatment than during combined T(4)/T(3) treatment (mean \pm SEM, 1.5 \pm 0.2 vs. 3.1 \pm 0.2 mU/liter; $P < 0.001$), a potentially confounding factor; however, subgroup analysis of subjects with comparable serum TSH concentrations during each treatment showed no benefit from combined treatment compared with T(4) alone. We conclude that in the doses used in this study, combined T(4)/T(3) treatment does not improve well-being, cognitive function, or quality of life compared with T(4) alone.

Studies with no superior effects of T4-T3 versus T4 alone

8. Siegmund W, Spieker K, Weike AI, Giessmann T, Modess C, Dabers T, Kirsch G, Sanger E, Engel G, Hamm AO, Nauck M, Meng W. Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14 : 1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. *Clin Endocrinol (Oxf).* 2004 Jun;60(6):750-7. Department of Clinical Pharmacology of the Peter Holtz Research Centre of Pharmacology and Experimental Therapeutics, Ernst Moritz Arndt University, Greifswald, Germany.

OBJECTIVES: There is evidence from recent controlled clinical studies that replacement therapy of hypothyroidism with T4 in combination with a small amount of T3 may improve the well-being of the patients. As the issue is still the subject of controversial discussion, our study was assigned to confirm the superiority of a physiological combination of thyroid hormones (absorbed molar ratio 14 : 1) over T4 alone with regard to mood states and cognitive functioning. **DESIGN AND PATIENTS:** After a run-in period with the T4 study medication for 4 weeks, a controlled, randomized, double-blind, two-period (each 12 weeks), cross-over study without washout between the treatment periods was performed in 23 hypothyroid patients (three males, 20 females, age 23-69 years, 21 subjects after surgery/radioiodine, two with autoimmune thyroiditis) to compare the effects of the previous individual T4 dose (100-175 micro g) with a treatment in which 5% of the respective T4 dose was substituted by T3.

MEASUREMENTS: Standard hormonal characteristics and standardized psychological tests to quantify mood and cognitive performance were measured after the run-in period and at the end of each treatment period. In 12 subjects, the concentration-time profiles of fT3 and fT4 were compared after the last administration of the respective study medication. TSH, fT3 and fT4 were measured with immunological assays. **CLINICAL RESULTS:** Replacement therapy with T4 and T4/T3 was not different in all steady-state hormonal, metabolic and cardiovascular characteristics except for TSH, which was more suppressed after T4/T3. The efficacy of replacement therapy with the T4/T3 combination was not

different from the T4 monotherapy with regard to all psychological test scores describing mood and cognitive functioning of the patients. Mood was even significantly impaired by the T4/T3 combination in eight subjects, with TSH < 0.02 mU/l, compared to patients with normal TSH (Beck Depression Inventory: 8.25 +/- 5.01 vs. 4.07 +/- 5.60, P = 0.026). PHARMACOKINETIC RESULTS: The area under the concentration-time curve (AUC(0-8h)) of fT3 was significantly higher after T4/T3 compared to the T4 monotherapy (42.8 +/- 9.03 pmol x h/l vs. 36.3 +/- 8.50 pmol x h/l, P < 0.05) and was significantly correlated to serum TSH (r(s) = -0.609, P < 0.05). After T4/T3, patients with a history of Graves' disease or autoimmune thyroiditis had significantly higher serum trough levels of fT3 whereas the fT4 concentrations were significantly lower in patients with a nonautoimmune background. CONCLUSION: Replacement therapy of hypothyroidism with T4 plus T3 does not improve mood and cognitive performance compared to the standard T4 monotherapy. There is even a higher risk of signs of subclinical hyperthyroidism associated with impaired well-being of the patients, which is clearly caused by significant fluctuations in the steady-state fT3 serum concentrations.

9. Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT. Does a combination regimen of thyroxine (T4) and 3,5,3'-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. J Clin Endocrinol Metab. 2003 Oct;88(10):4551-5. Department of Medicine and Division of Endocrinology and Metabolism, McMaster University, Hamilton, Ontario, Canada. Comment in: J Clin Endocrinol Metab. 2004 Mar;89(3):1486-7; author reply 1487-8.

Some hypothyroid patients receiving levothyroxine replacement therapy complain of depressive symptoms despite normal TSH measurements. It is not known whether adding T(3) can reverse such symptoms. We randomized 40 individuals with depressive symptoms who were taking a stable dose of levothyroxine for treatment of hypothyroidism (excluding those who underwent thyroidectomy or radioactive iodine ablation of the thyroid) to receive T(4) plus placebo or the combination of T(4) plus T(3) in a double-blind manner for 15 wk. Participants receiving combination therapy had their prestudy dose of T(4) dropped by 50%, and T(3) was started at a dose of 12.5 micro g, twice daily. T(4) and T(3) doses were adjusted to keep goal TSH concentrations within the normal range. Compared with the group taking T(4) alone, the group taking both T(4) plus T(3) did not report any improvement in self-rated mood and well-being scores that included all subscales of the Symptom Check-List-90, the Comprehensive Epidemiological Screen for Depression, and the Multiple Outcome Study (P > 0.05 for all indexes). In conclusion, the current data do not support the routine use of combined T(3) and T(4) therapy in hypothyroid patients with depressive symptoms.

10. Rodriguez T, Lavis VR, Meininger JC, Kapadia AS, Stafford LF. Substitution of liothyronine at a 1:5 ratio for a portion of levothyroxine: effect on fatigue, symptoms of depression, and working memory versus treatment with levothyroxine alone. Endocr Pract. 2005 Jul-Aug;11(4):223-33. College of Nursing, Texas Woman's University, Institute of Health Sciences, Houston, Texas 77030, USA.

OBJECTIVE: To attempt to confirm a previous report of superior effectiveness of using two thyroid hormones rather than one hormone to treat hypothyroidism. METHODS: This trial attempted to replicate prior findings, which suggested that substituting 12.5 microg of liothyronine (LT(3)) for 50 microg of levothyroxine (LT(4)) might improve mood, cognition, and physical symptoms in patients with primary hypothyroidism. Additionally, this trial aimed to extend the previous findings to fatigue and to assess for differential effects in subjects with low fatigue and high fatigue at baseline. A randomized, double-blind, two-period, crossover design was used. At an endocrinology and diabetes clinic, 30 adult subjects with primary hypothyroidism stabilized on LT(4) were recruited.

Patients randomly assigned to treatment sequence 1 received their standard LT(4) dose in one capsule and placebo in another. Patients assigned to sequence 2 received their usual LT(4) dose minus 50 microg in one capsule and 10 microg of LT(3) in the other. At the end of the first 6 weeks, subjects were crossed over to receive the other treatment. Carryover and treatment effects were assessed by t tests. RESULTS: Of the 30 enrolled study subjects, 27 completed the trial. The mean LT(4) dose was 121 +/- 26 microg/day at baseline. No significant differences in fatigue and symptoms of depression were found between treatments. Measures of working memory were unchanged. During substitution treatment, the free thyroxine index was reduced by 0.7 (P<0.001), total serum thyroxine was reduced by 3.0 microg/dL (P<0.001), and total serum triiodothyronine was increased by 20.5 ng/dL (P = 0.004). CONCLUSION: With regard to the outcomes measured, substitution of LT(3) at a 1:5 ratio for a portion of baseline LT(4) yielded no better results than did treatment with the original dose of LT(4) alone.

Non-placebo-controlled trial : no difference in effects between T3-T4 vs T4 alone, but patients with T3-T4 kept a higher TSH and relatively lower T4 (sign of a too low dose)

11. Cassio A, Cacciari E, Cicognani A, Damiani G, Missiroli G, Corbelli E, Balsamo A, Bal M, Gualandi S. Treatment for congenital hypothyroidism: thyroxine alone or thyroxine plus triiodothyronine? Pediatrics. 2003 May;111(5 Pt 1):1055-60. Department of Pediatrics, University of Bologna, Bologna, Italy.

OBJECTIVE: To compare the effects of therapy with thyroxine (T4) plus triiodothyronine (T3) versus T4 alone **from the first days of life in screened congenital hypothyroid (CH) infants.** METHODS: We examined 14 CH infants diagnosed by neonatal screening and a group of control infants. CH patients were divided randomly into 2 groups, 1 treated with T4 alone (group 1) and the other treated with T4 plus T3 (liothyronine; group 2). In all patients electrocardiography and thyroid hormone evaluations were performed **before and 15 and 30 days and 3, 6, and 12 months after the beginning of therapy.** Psychological tests were also performed at 6 and 12 months of age in CH patients and in other matched controls. RESULTS: **After 15 days of treatment,** serum thyrotropin (TSH) levels become normal in 5 of 7 cases of group 1 (median TSH level 10.7 micro U/ml) and in 1 of 7 cases of group 2 (median TSH level 72.5 micro U/ml). At the same period, serum-free thyroid hormone levels were within the normal range in both groups, but free T4 values were significantly higher in group 1 than in group 2 and in controls. At the subsequent examinations, free T4 values were within the upper normal limit in group 1, whereas they remained within the normal range in group 2. No clinical or electrocardiographic signs of heart disease were found in any of the patients. **The psychometric quotient in CH infants was significantly lower than in controls, but similar in patients of group 1 and group 2.** CONCLUSIONS: The combined treatment with T4 plus T3 seems not to show significant advantages, at least in our experimental conditions, compared with the traditional treatment with T4 alone in early treated CH infants. A further longer and more extensive follow-up is mandatory.

About the hormone concentrations TSH, T3, and T4 during T3-T4 versus T4 alone therapy: **L-T4 replacement therapy is associated with non-physiologically high FT4 and low FT3 levels**

12. Fadeyev VV, Morgunova TB, Sytch JP, Melnichenko GA. TSH and thyroid hormones concentrations in patients with hypothyroidism receiving replacement therapy with L-thyroxine alone or in combination with L-triiodothyronine. Hormones (Athens). 2005 Apr-Jun;4(2):101-7. Department of Endocrinology of Moscow Medical Academy, Moscow, 119992, Russia. walfad@nccom.ru

Comment in: Hormones (Athens). 2005 Apr-Jun;4(2):108-10.

The aim of this study was to evaluate parameters of thyroid function in patients with primary hypothyroidism receiving either monotherapy with L-T4 or combination L-T4+L-T3. Fifty-eight women with primary hypothyroidism receiving L-T4 were enrolled in the study. The patients were randomised into two groups: Group 1 (n=42) patients continued monotherapy with L-T4, and Group 2 (n=16) patients were switched to combined therapy with L-T4+L-T3 (25 microg L-T4 was replaced with 12.5 microg L-T3). The final examination was carried out 6 months thereafter. There was also a third group of 20 healthy women (control group). Under monotherapy with L-T4, serum FT4 levels were higher ($p < 0.05$) and FT3 lower ($p < 0.05$) than in the control group, while the monotherapy subgroup of patients with low-normal TSH had serum FT4 levels higher than in the control group ($p < 0.05$). Serum FT4 under combined therapy was significantly lower than in both control and monotherapy groups. FT3 levels did not differ between the two groups of combined and monotherapy subjects; the highest FT3 levels were in the control group. L-T4 replacement therapy is associated with non-physiologically high FT4 and low FT3 levels. Therapy with L-T3 once a day does not simulate the normal production of T3 by the thyroid.

No effect of small dosages of T4 on hypothyroid symptoms: necessity of small doses of T3 for effects?

13. 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. Epub 2006 May 2. Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia. john.walsh@health.wa.gov.au

CONTEXT: In patients with primary hypothyroidism, anecdotal evidence suggests that well-being is optimized by fine adjustment of T(4) dosage, aiming for a serum TSH concentration in the lower reference range. This has not been tested in a clinical trial. OBJECTIVE: Our objective was to test whether adjustment of T(4) dosage aiming for a serum TSH concentration less than 2 mU/liter improves well-being compared with a serum TSH concentration in the upper reference range.

DESIGN: We conducted a double-blind, randomized clinical trial with a crossover design. PARTICIPANTS: Fifty-six subjects (52 females) with primary hypothyroidism taking T(4) (≥ 100 microg/d) with baseline serum TSH 0.1-4.8 mU/liter participated. INTERVENTIONS: Each subject received three T(4) doses (low, middle, and high in 25-microg increments) in random order. OUTCOME MEASURES: Outcome measures included visual analog scales assessing well-being (the primary endpoint) and hypothyroid symptoms, quality of life instruments (General Health Questionnaire 28, Short Form 36, and Thyroid Symptom Questionnaire), cognitive function tests, and treatment preference. RESULTS: Mean (\pm sem) serum TSH concentrations were 2.8 \pm 0.4, 1.0 \pm 0.2, and 0.3 \pm 0.1 mU/liter for the three treatments. There were no significant treatment effects on any of the instruments assessing well-being, symptoms, quality of life, or cognitive function and no significant treatment preference.

CONCLUSIONS: Small changes in T(4) dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life, despite the expected changes in serum TSH and markers of thyroid hormone action. 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.

APPENDIX 5: IHS consensus 1 on Thyroid Hormone Therapy of Hypothyroidism



The International Hormone Society

www.intlhormonesociety.org

Consensus # 1 on “Thyroid Hormone Therapy of Hypothyroidism
September 29, 2005”

After having reviewed the scientific literature and exchanged experiences between physicians from all over the world who are competent in hormone therapies, we, members of the Consensus Group of Experts of the International Hormone Society, think the time is ripe to reconsider current concepts on thyroid treatment of hypothyroidism.

The view that hypothyroidism is best treated by thyroxin alone is not based on solid scientific evidence. The studies comparing the efficacy of thyroxin alone versus that of combination thyroxin and triiodothyronine medications have in general **not shown superiority of thyroxin alone** above the combination of thyroxin with a smaller dose of triiodothyronine. On the contrary, **a few studies** have shown a **significantly greater efficacy of combined thyroxin-triiodothyronine medications** compared to the use of thyroxin alone in humans on such divergent parameters as serum cholesterol, mental and physical symptoms, and in animals on goitre formation and intracellular triiodothyronine(T3)-euthyroidism, just to name some of the greater benefits. The facts that T3 is the major intracellular thyroid hormone, and that a low serum level of T3 is more often than a low serum T4 (thyroxin) or a high TSH, the critical parameter in mortality studies, especially cardiovascular, and that the absorption of T3 is much more efficient and stable than that of T4, give credibility to the view that a combination of thyroxin with triiodothyronine may be better for the hypothyroid patient.

The evidence is sufficient to guarantee the physician a **freedom of choice in thyroid medication: either thyroxin alone or thyroxin and triiodothyronine.**

As hypothyroidism has serious adverse consequences on the quality of life and health of patients, we recommend that physicians, in light of the solid evidence here collected, should **first** try to treat hypothyroid patients with a **combined thyroxin and triiodothyronine preparation.**

As the combination treatment contains the immediately active triiodothyronine, we recommend that physicians **follow some safety guidelines**, in addition to the obvious one of avoiding overdoses when they administer thyroxin and triiodothyronine medications. Following the measures listed below increases the safety and tolerance of the treatment:

1. The **first** guideline is to start the treatment at very low doses and then to slowly and gradually increase the dose until clinical eu-thyroidism is reached.
2. The **second** guideline is to tell the patient to avoid all caffeinated and similar stimulating drinks that may increase the orthosympathic activity.
3. The **third** guideline is to regularly follow-up the patient with a good clinical interview and examination and laboratory tests every two to twelve months depending on the patient's needs.

4. The **fourth** guideline is to carefully screen for adrenal deficiency in hypothyroid patients, as some patients with low or borderline low cortisol levels may poorly tolerate any type of thyroid medication, and in particular thyroxin-triiodothyronine combinations. The intolerance may come from over-activity of the orthosympathic nervous system that often accompanies states of low Cortisol, and an excessive and rapid conversion of thyroxin to triiodothyronine that puts these patients easily into a state of excess T3 and thus hyperthyroidism, and further increases the orthosympathic activity. In patients with Cortisol deficiency, we recommend the physician to treat the low cortisol state prior to or simultaneously with the thyroid treatment. If not, thyroxin alone may be the better treatment of hypothyroidism in the presence of an untreated cortisol deficiency. In most other instances, thyroxin and triiodothyronine remains the first, but not exclusive, choice for treatment of hypothyroidism for the International Hormone Society's Consensus Group.

Concerning the debate about which combination treatment works best: **synthetic T3-T4 or desiccated thyroid**, the Consensus Group states the following:

Reports of patients feeling better on desiccated thyroid may have scientific evidence as these preparations contain along with T3 and T4 a number of other substances that may have some thyroid activity as diiodo- and monoiodo-thyronines. In addition, the binding of much of the thyroid hormones to the bigger thyroglobulin molecule allows a slower intestinal absorption and, later, once arrived in the bloodstream, a slower release of thyroid hormones in the blood, thereby insuring a more persistent action and a better tolerance by spreading the action over a longer period of time. Thus, desiccated thyroid may work better.

The view that the potency of thyroid preparations of animal origin may have more fluctuations has arguments. For this reason, preference is given to preparations that are officially registered and well-controlled. It must be said that the frequent FDA-recalls of poorly reliable, less potent than announced thyroxin preparations of various pharmaceutical firms in the USA, makes thyroxin not a better alternative. In the light of the Mad Cow's Disease, the International Hormone Society does not recommend the use of desiccated thyroid of beef origin. For these reasons, the position adopted by the Consensus Group members of The International Hormone Society is that both type of T3 -T4 preparations have their pros and cons, and the freedom of choice between these two should be left over to the physician."

References of consensus 1 on Thyroid Hormone Therapy of Hypothyroidism

I) The view that hypothyroidism would be better treated by thyroxine alone is not based on solid scientific evidence

Arguments for treatment with T4 alone:

Guidelines on T4 recommendation

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

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

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Arguments pro treatment with T4 and T3 combinations

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

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T3-T4 treatment: adding T3 to T4 results in greater improvement of clinical symptoms and signs in hypothyroid patients

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When T3 and T4 are both supplemented to the food simultaneously with goitrogens, a much better prevention of goiter is obtained than when solely T4 is added, even if T4 is given at doses 7 times higher those of T3-T4 treatments

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

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

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

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Corrective Thyroid Therapy

Thyroid medications

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