The International Hormone Society

www.intlhormonesociety.org

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

1. Brent GA, Larsen PR. Treatment of hypothyroidism. In: Braverman LE, Utiger RD, ed. Werner and Ingbar's. The Thyroid: A Fundamental and Clinical Text. 7th ed., 1996, Philadelphia, Ravens- Lippincott Publishers
2. Utiger RD. Hypothyroidism. In DeGroot LJ et al, eds. Endocrinology, Vol 1. 2nd ed. Philadelphia, Pa: WB Saunders Co, 1989;702-21
3. Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. Ann Intern Med 1993;119:492-502
4. Roti E, Braverman LE. Thyroid hormone therapy: when to use it, when to avoid it. Drug Therapy. 1994; 24(4):2-35.

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

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

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

Arguments pro treatment with T4 and T3 combinations

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

7. Saravanan P, Simmons DJ, Greenwood R, Peters TJ, Dayan CM. Partial substitution of thyroxine (T4) with tri-iodothyronine in patients on T4 replacement therapy: results of a large community-based randomized controlled trial. Clin Endocrinol Metab. 2005 Feb;90(2):805-12
8. 1032. Kloppenburg M, Dijkmans BA, Rasker JJ. Effect of therapy for thyroid dysfunction on musculoskeletal symptoms. Clin Rheumatol. 1993 Sep;12(3):341-5
9. 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
10. Pareira VG, Haron ES, Lima-Neto N, Medeiros-Neto GA. Management of myxedema coma: report on three successfully treated cases with nasogastric or intravenous administration of triiodothyronine. J Endocrinol Invest. 1982;5:331-4
11. Chernow B, Burman KD, Johnson DL, McGuire RA, O'Brian JT, Wartofsky L, Georges LP. T3 may be a better agent than T4 in the critically ill hypothyroid patient: evaluation of transport across the blood-brain barrier in a primate model. Crit Care Med. 1983 Feb;11(2):99-104
12. Arlot S, Debussche X, Lalau JD, Mesmacque A, Tolani M, Quichaud J, Fournier A. Myxoedema coma: response of thyroid hormones with oral and intravenous high-dose L-thyroxine treatment. Intensive Care Med. 1991;17(1):16-8

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

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

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

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

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

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

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

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

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

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

T3 is much more potent than T4

20. Gross J, Pitt-Rivers R. Physiological activity of 3:5:3'-L-triiodothyronine. Lancet. 1952 Mar 22;1(12):593-4
21. Gross J, Pitt-Rivers R. 3:5:3'-triiodothyronine. 2. Physiological activity. Biochem J. 1953 Mar;53(4):652-7

Conditions that reduce the conversion of T4 to T3 such as aging, obesity, disease, stress, exercise, malnutrition, etc., may reduce the efficacy of a T4 alone treatment. In these conditions addition of T3 to T4 in the treatment may increase the efficacy of thyroid treatment.

22. Burroughs V, Shenkman L. Thyroid function in the elderly. Am J Med Sci. 1982, 283 (1): 8-17
23. Carter JN, Eastman CJ, Corcoran JM, and Lazarus L. Inhibition of conversion of thyroxine to triiodothyronine in patients with severe chronic illness. Clin Endocrinol. 1976; 5: 587-94
24. Tulp OL and McKee TD Sr. Triiodothyronine neogenesis in lean and obese LA/N-cp rats. Biochem Biophys Res Communications. 1986; 140 (1): 134-42
25. Katzeff HI, Selgrad C. Impaired peripheral thyroid hormone metabolism in genetic obesity. Endocrinology. 1993; 132 (3): 989-95
26. Croxson MS and Ibbertson HK. Low serum triiodothyronine (T3) and hypothyroidism in anorexia nervosa. J Clin Endocrinol Metab. 1977; 44: 167-73
27. Harns ARC, Fang SH, Vagenakis AG, and Braverman LE. Effect of starvation, nutriment replacement, and hypothyroidism on in vitro hepatic T4 to T3 conversion in the rat. Metabolism. 1978;27(11):1680-90
28. Opstad PK, Falch D, Öktedalen O, Fonnum F, and Wergeland R. The thyroid function in young men during prolonged physical exercise and the effect of energy and sleep deprivation. Clin Endocrinol. 1984; 20: 657-69
29. Walfish PG. Triiodothyronine and thyroxine interrelationships in health and disease. Can Med Ass. J 1976, 115: 338-42

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

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

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

35. Burger AG, Lambert M, Cullen M. Interférence de substances médicamenteuses dans la conversion de T4 en T3 et rT3 chez l'homme. Ann Endocrinol (Paris). 1981,42:461-9
36. Grussendorf M, Hüfner M. Induction of the thyroxine to triiodothyronine converting enzyme in rat liver by thyroid hormones and analogs. Clin Chim Acta. 1977;80:61-6

37. Erickson VJ, Cavalieri RR, Rosenberg LL. Thyroxine-5'-diodinase of rat thyroid, but not that of liver, is dependent on thyrotropin. Endocrinology. 1982;111:434-40
38. Rezvani I, DiGeorge AM, Dowshen SA, Bourdony CJ. Action of human growth hormone on extrathyroidal conversion of thyroxine to triiodothyronine in children with hypopituitarism. Pediatr Res. 1981;15:6-9
39. Schröder-Van der elst JP, Van der heide D. Effects of streptozocin-induced diabetes and food restriction on quantities and source of T4 and T3 in rat tissues. Diabetes. 1992;41:147-52
40. Gavin LA, Mahon FA, Moeller M. The mechanism of impaired T3 production from T4 in diabetes. Diabetes. 1981;30:694-9
41. Hoover PA, Vaughan MK, Little JC, Reiter RJ. N-methyl-D-aspartate does not prevent effects of melatonin on the reproductive and thyroid axes of male Syrian hamsters. J Endocrinology. 1992;133:51-8
42. Chanoine J-P, Safran M, Farwell AP, Tranter P, Ekenbarger DM, Dubord S, Alex s, Arthur JR, Beckett GJ, Braverman LE, Leonard JL. Selenium deficiency and type II 5'-deiodinase regulation in the euthyroid and hypothyroid rat: evidence of a direct effect of thyroxine. Endocrinology. 1992;130:479-84
43. Arthur JR, Nicol F, Beckett GJ. Selenium deficiency, thyroid hormone metabolism, and thyroid hormone deiodinases. Am J Clin Nutr Suppl. 1993; 57:236S-9S
44. Beard J, Tobin B, and Green W. Evidence for thyroid hormone deficiency in iron-deficient anemic rats. J Nutr. 1989;772-8
45. Fujimoto S, Indo Y, Higashi A, Matsuda I, Kashiwabara N, and Nakashima I. Conversion of thyroxine into triiodothyronine in zinc deficient rat liver. J Pediatr Gastroenterol Nutr. 1986;5:799-805
46. Olin KI, Walter RM, and Keen CL. Copper deficiency affects selenoglutathione peroxidase and selenodeiodinase activities and antioxidant defense in weanling rats. Am J Clin Nutr 1994;59:654-8

On the other hand, excesses in hormones *(glucocorticoids, ACTH, estrogens,…) and trace elements (iodine, lithium, …)* **may slow down this conversion.**

47. Westgren U, Ahren B, Burger A, Ingemansson S, Melander A. Effects of dexamethasone, desoxycorticosterone, and ACTH on serum concentrations ot thyroxine, 3,5,3'-triiodothyronine and 3,3',5'-triiodothyronine. Acta Med Scand. 1977;202 (1-2): 89-92
48. Heyma P, Larkins RG. Glucocorticoids decrease the conversion of thyroxine into 3,5,3'-triiodothyronine by isolated rat renal tubules. Clin Science. 1982; 62: 215-20
49. Scammell JG, Shiverick KT, Fregly MJ. Effect of chronic treatment with estrogen and thyroxine, alone and combined, on the rate of deiodination of l-thyroxine to 3,5,3'-triiodothyronine in vitro. Pharmacology. 1986;33: 52-7
50. Aizawa T, Yamada T. Effects of thyroid hormones, antithyroid drugs and iodide on in vitro conversion of thyroxine to triiodothyronine. Clin Exp Pharmacol Physiol. 1981; 8: 215-25
51. Voss C, Schrober HC, Hartmann N. Einfluss von Lithium auf die in vitro-Deioderung von l-Thyroxin in der Ratten leber. Acta Biol Med Germ. 1977; 36:1061-5

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

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

Defects in the commercial T4 preparation[43,44]

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

Corrective Thyroid Therapy

Thyroid medications

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

Thyroxine

71. Oppenheimer JH, Braverman LE, Toft A, Jackson, IM, Ladenson, PW. Thyroid hormone treatment when and what? J Clin Endocrinol Metab. 1995;80:2873-83
72. Dong BJ, Brown CH. Hypothyroidism resulting from generic levothyroxine failure. J Am Board Fam. Pract. l991;4:167-70
73. Roti E, Minelli R, Gardini E, Braverman LE. The use of misuse of thyroid hormone. Endocrine Rev. 1993;14:401-23
74. Toft AD. Thyroxine therapy. N Engl J Med. 1994 Jul 21;331(3):174-80
75. USP Dispensing Information: Volume 1- Drug Information for Health Care Professionals. The United States Pharmacopeial Convention, Rockville, MD, 1997
76. Ridgway EC, McCammon JA, Benotti J, Maloof F. Acute metabolic responses in myxedema to large doses of intravenous L-thyroxine. Ann Intern Med. 1972;77:549-55

Thyroxine-triiodothyronine associations

77. Rees-Jones RW, Larsen PR. Triiodothyronine and thyroxine content of desiccated thyroid tablets. Metabolism. 1977 Nov;26(11):1213-8
78. Mangieri CN, Lund MH. Potency of United States Pharmacopeia desiccated thyroid tablets as determined by the antigoitrogenic assay in rats. J Clin Endocrinol Metab. 1970 Jan;30(1):102-4
79. Gaby AR. Sub-laboratory hypothyroidism and the empirical use of Armour thyroid. Altern Med Rev. 2004 Jun;9(2):157-79
80. 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
81. Hertoghe T. Many conditions related to age reduce the conversion of thyroxine to triiodothyronine - a rationale for prescribing preferentially a combined T3 + T4 preparation in hypothyroid adults. Anti-Aging Medical Therapeutics 2000; IV: 138-53

Frequency of use of thyroid hormone treatment

82. Kaufman SC, Gross GP, Kennedy DL. Thyroid hormone use: trends in the United States from 1960 through 1988. Thyroid 1997; 1:285-91
83. 100. . Sawin CT, Geller A, Hershman JM, Castelli W, Bacharach P. The aging thyroid: the use of thyroid hormone in older persons. JAMA 1989;261:2653-5

Thyroid treatment: thyroid hormone absorption and malabsorption

84. Hays MT, Nielsen KRK. Human thyroxine absorption: age effects and methodological analyses. Thyroid. 1994:4:55-64
85. Wenzel KW, Kirscheiper HE. Aspects of the absorption of oral 1-thyroxine in normal man. Metabolism. 1977;26:1-8
86. Benvenga S, Bartolone L, Squadrito S, Lo Giudice F, Trimarchi F. Delayed intestinal absorption of levothyroxine. Thyroid. 1995;5(4):249-53
87. Read DG, Hays MT, Hershman JM. Absorption of oral thyroxine in hypothyroid and normal man. J Clin Endocrinol Metab. 1970;30:798-9
88. Azizi F, Belur R, Albano J. Malabsorption of thyroid hormones after jejunoileal bypass for obesity. Ann Intern Med. 1979;90:941-2
89. Bevan JS, Munro JF. Thyroxine malabsorption following intestinal bypass surgery. Int J Obes. 1986; 10:245-6
90. Stone E, Leiter LA, Lambert JR, Silverberg JDH, Jeeyeebhoy KN, Burrow GN. L-Thyroxine absorption in patients with short bowel. J Clin Endocrinol Metab. 1984;59:139-41
91. Ain KB, Refetoff S, Fein HG, Weintraub BD. Pseudomalabsorption of levothyroxine. JAMA 1991;266:2118-20
92. Northcutt RC, Stiel JN, Hollifiels JW, Stant EG. The influence of cholestyramine on thyroxine absorption. JAMA. 1969;208:1857-61
93. Harmon SM, Siefert CF. Levothyroxine-cholestyramine interaction reemphasized. Ann Intern Med. 1991;115:658-9
94. Sperber AD, Liel Y. Evidence for interface with the intestinal absorption of levothyroxine sodium by aluminum hydroxide. Arch Intern Med 1992; 152:183-4
95. Campbell NR, Hasinoff BB, Stalts H, Rao B, Wong NC. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. Ann Intern Med. 1992;117:1010-3
96. Sherman SI, Tielens E, Ladenson PW. Sucralfate causes malabsorption of L-thyroxine. Am J Med. 1994;96:531-5
97. Liel Y, Harman-Boehm I, Shany S. Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult hypothyroid patients. J Clin Endocrinol Metab. 1996:80:857-9

Thyroid treatment: side effects, complications

98. Paul TL, Kerrigan J, Kelly AM, Braverman LE, Baran DT. Long-term L-thyroxine therapy is associated with decreased hip bone density in premenopausal women. JAMA. 1988;259:3137-41
99. Stall GM, Harris S, Sokoll LJ, Dawson-Hughes B. Accelerated bone loss in hypothyroid patients over treated with contemporary preparations. Ann Intern Med 1990; 105:11-5
100. Greenspan SL, Greenspan FS, Resnick NM, Block JE, Friedlander AL, Genant HK. Skeletal integrity in premenopausal and postmenopausal women receiving long-term L-thyroxine therapy Am J Med. 1991;91:5-14
101. Franklyn JA, Betteridge J, Daykin J, Holder R, Oates GD, Parle JV, et al. Long-term thyroxine treatment and bone mineral density. Lancet. 1992;340:9-13
102. Schneider DL, Barrett-Connor EL, Morton DJ. Thyroid hormone use and bone mineral density in elderly women. JAMA. 1994;271:1245-9
103. Sawin CT, Geller A, Wolk PA, et al. Low serum thyrotropin concentration as a risk factor for atrial fibrillation in older persons. N Engi J Med. 1994;331:1249-52
104. Shibata H, Hayakawa H, Hirukawa M, Tadokoro K, Ogata E. Hypersensitivity caused by synthetic thyroid hormones in a hypothyroid patient with Hashimoto's thyroiditis. Arch Intern Med. 1986; 146:1624-5
105. Magner J, Gerber P. Urticaria due to blue dye in synthroid tablets. Thyroid. 1994 Fall;4(3):341

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

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

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

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

57. Westgren U, Ahren B, Burger A, Ingemansson S, Melander A. Effects of dexamethasone, desoxycorticosterone, and ACTH on serum concentrations ot thyroxine, 3,5,3'-triiodothyronine and 3,3',5'-triiodothyronine. Acta Med Scand. 1977;202 (1-2): 89-92
58. Heyma P, Larkins RG. Glucocorticoids decrease the conversion of thyroxine into 3,5,3'-triiodothyronine by isolated rat renal tubules. Clin Science. 1982; 62: 215-20

Studies that show reduced T3 nuclear receptors in adrenal deficiency

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