



## *The International Hormone Society*

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# 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. 7<sup>th</sup> ed., 1996, Philadelphia, Ravens- Lippincott Publishers
2. Utiger RD. Hypothyroidism. In DeGroot LJ et al, eds. Endocrinology, Vol 1. 2<sup>nd</sup> ed. Philadelphia, Pa: WB Saunders Co, 1989;702-21
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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 triiodothyronine in patients on T4 replacement therapy: results of a large community-based randomized controlled trial. Clin Endocrinol Metab. 2005 Feb;90(2):805-12
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##### **T3-T4 treatment: adding T3 to T4 results in greater improvement of clinical symptoms and signs in hypothyroid patients**

13. Benevicius R, Kazanavicius G, 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.

##### **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 thyroid 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 comparison of the metabolic activities of 3,5,3'-triiodothyronine and L-thyroxine in myxedema. *Bull John Hopkins Hosp*. 1953; 93: 164
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**T3 is much more potent than T4**

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**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
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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

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

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

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**The absorption of oral T4 can be variable (50 to 73%<sup>40,41</sup>), contrasting with that of T3 that is more constant and efficient (95%)**

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#### **Defects in the commercial T4preparation<sup>43,44</sup>**

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### **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**

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#### **Thyroxine-triiodothyronine associations**

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### Frequency of use of thyroid hormone treatment

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### Thyroid treatment: thyroid hormone absorption and malabsorption

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### Thyroid treatment: side effects, complications

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

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

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

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

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#### **Studies that show reduced T3 nuclear receptors in adrenal deficiency**

De Nayer P et al. 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