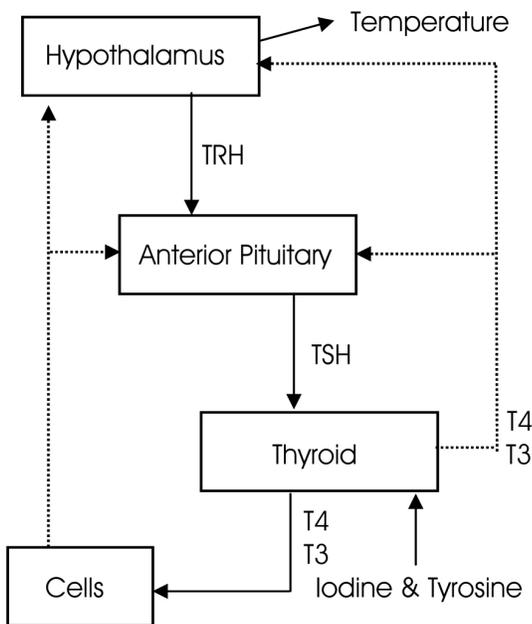


Calculating Thyroid Replacement Hormones

John A. Allocca, D.Sc., Ph.D.
Allocca Biotechnology, LLC
www.allocca.com
December 17, 2014

Thyroid Pituitary Hypothalamus Function



The pituitary gland is a small endocrine gland located at the base of the brain. It secretes polypeptide hormones that circulate unbound in the bloodstream. These hormones stimulate other endocrine glands including the thyroid gland. The thyroid gland is a 2-lobe gland located on each side of the trachea. Thyroid stimulating hormone (TSH) also called (thyrotropin) is produced by the pituitary gland to stimulate the thyroid gland. Thyroid stimulating hormone secretion is stimulated by TRH (thyrotropin-releasing hormone), which is produced by the hypothalamus. The two primary hormones produced by the thyroid gland are thyroxine (T4) and triiodothyronine (T3). Thyroxine and triiodothyronine secretion will suppress TSH secretion by direct negative feedback to the pituitary gland. There is little direct feedback to the hypothalamus. However, high thyroid hormone levels may desensitize the pituitary to the stimulation of TRH. Thus, there is a continuous relationship between the pituitary and thyroid glands to regulate metabolism.

TSH stimulates the thyroid gland to take up iodine. Iodine is combined with tyrosine to form monoiodotyrosine, then to diiodotyrosine. Monoiodotyrosine combines with diiodotyrosine to form triiodothyronine. Two molecules of Diiodotyrosine combine to form thyroxine. About 93% of the hormone produced is thyroxine and 7% triiodothyronine. Thyroxine and triiodothyronine are cleaved from the thyroglobulin molecule to form free thyroxine and free triiodothyronine molecules. In the circulating blood, 99.975% of thyroxine and 99.7% of triiodothyronine is bound to thyroglobulin. Thyroglobulin is a large glycoprotein molecule. Only 25% of tyrosine becomes thyroid hormones. The remaining 75% remains as monoiodotyrosine and diiodotyrosine. Iodine is cleaved from the monoiodotyrosine and diiodotyrosine molecules by the deiodinase enzyme and recycled. Congenital absence of deiodinase results in an iodine deficiency. One iodine molecule is removed from the circulating thyroxine to form triiodothyronine. Approximately 90% of hormone that binds with receptors is triiodothyronine and 10% thyroxine.

The hypothalamus helps to stimulate or inhibit many bodily functions such as, heart rate, blood pressure, body temperature, fluid and electrolyte balance including thirst, appetite, body weight, glandular secretions of the stomach and intestines, production of substances that influence the pituitary gland to release hormones, and sleep cycles. The hypothalamus receives information from almost all sections of the nervous system. It is the link between the nervous system and the endocrine system. The hypothalamus controls body weight and temperature through the thermogenesis process. Lopez et al demonstrate that central administration of triiodothyronine (T3) in rats lead to sympathetic nervous system activation and up-regulation of brown adipose tissue thermogenesis via reduction in hypothalamic AMP-Activated Protein Kinase (AMPK) activity. Inhibition of hypothalamic AMPK pathway results in activation of lipogenic enzyme acetyl-CoA carboxylase and subsequent activation acetyl-CoA carboxylase and fatty acid synthase as well as inhibition of carnitine palmitoyltransferase I (CPT1), resulting in de novo lipogenesis specifically in the hypothalamus.

Approximately 60% of the T4 is converted into T3, 20% into reverse T3, and 20% into T3 sulfate (T3S) and triiodothyroacetic acid (T3AC). Reverse T3 is a substance that is produced when there is excess T4 or when the body needs to conserve energy. Reverse T3 binds to T3 receptors and block T3 transport. When there is too much cortisol or too little cortisol, the liver will suppress detoxification and clearance of reverse T3. Cortisol will also suppress TSH production resulting in low thyroid function. The conversion of T3 to reverse T3 can be stimulated by an activated Immune system, excess adrenaline, excess free radicals, aging, fasting, stress, prolonged illness, and elevated insulin levels. Adrenal exhaustion can cause low thyroid symptoms due to the lack of cortisol production. Too much cortisol can inhibit the activation of thyroid hormone and too little cortisol can also inhibit the activation of thyroid hormone. Selenium, antioxidants, iron, magnesium, zinc, vitamin A, vitamin B6 and B12 deficiencies can lead to poor conversion of T4 to T3, T4 and T3 production, and T3 receptor binding. Too much T4 can cause too much cortisol, which can lead to weight gain. Consideration must be taken when dosing T4 in a 4 to 1 balance with T3. High cortisol levels can occur from too much T4 and from too much emotional stress. The half life for T4 is 7 days. The half life for T3 is 1 day.

Fat cells in the stomach are especially sensitive to cortisol and store energy. Consequently, high cortisol levels and weight gain tends to collect around the stomach. Cortisol also reduces testosterone in men and women, which leads to muscle loss. Muscle burns more calories than body fat. When the body loses muscle, the body burns calories less efficiently. Also, cortisol increases fatigue, which makes it more likely that you won't exercise to burn off excess calories. Lack of sleep can increase cortisol levels too. DHEA can lower plasma cortisol levels in men and women, according to a University of Pittsburgh study published in the "Journal of Clinical Psychopharmacology" in February 2003.

Clinical observation and patient feedback suggests there is a delicate balance of thyroid hormone supplementation. Too much or too little T4, or too much or too little T3, or not in a 4:1 balance, can cause an increase in cortisol levels and consequent weight gain and other adverse side effects. Patients should monitor their body temperature upon awakening and their resting pulse rate several times throughout the day.

"First of all, 75 or 100 mcg. of thyroxine are a modest dosage for most adults. A well-known professor of endocrinology is convinced that a good "rule of thumb" eventual dose for most of his patients is one microgram per pound of body weight. For instance, a woman who weighs 137 pounds might do well with 137 mcg. of thyroxine (a few brands other than Synthroid are available in pills at this exact dose). A man who weighs 175 pounds might do well with the 175 mcg. pill. Before acquiescing to your doctor's test-result edict of final dose, you might want to ask for a short clinical trial of the medical center professor's protocol of "one mcg per pound of body weight". Keep in mind that the rule of thumb dosage is only a general initial guide, and that it might not apply well in cases of obesity." - Richard Shames MD.

Using the aforementioned rule of thumb for Synthroid (LT4), it would be logical to modify it for combination therapy as follows: **Body weight (pounds) = T4 + (4 x T3) in mcg**. Due to adverse side effects of Cytomel (LT3) (headache, skin rashes, etc), there may be a limit of how much Cytomel a patient can tolerate. It may be advisable to start with low dose of Synthroid and 5 mcg of Cytomel, increasing Cytomel weekly by 5 mcg until a reasonable dose is determined. Then, adjust the dose of Synthroid according to the rule of thumb. Be sure both are taken on an empty stomach 30 minutes before eating and 4 hours away from calcium supplements.

Example: A 165 pound patient can only tolerate 10 mcg Cytomel.

Body weight (pounds) = T4 + (4 x T3) in mcg
T4 = Body weight (pounds) - (4 x T3) in mcg

T4 = 165 - (4 x 10)

T4 = 165 - 40

T4 = 125 mcg (estimated rule of thumb, may not be final dose)

Because 99.7% of T3 is bound to thyroglobulin, a Free T3 blood test would be of tremendous value over T3, T4, and TSH alone.

Combination T4 and T3 Therapy for Hypothyroidism Literature

Many people prefer the natural Armour (Desiccated porcine) thyroid from pigs over the synthetic forms of thyroid hormones and for many people it works well. However, some people have difficulty in absorbing desiccated thyroid, or have an allergy to it, or develop an allergy to it. Whichever form of thyroid hormones that are used, they should be used in the combination of T4 and T3. The following are some published articles relating to combination T3 and T4 therapy for hypothyroidism.

“Effects of Thyroxine as Compared with Thyroxine plus Triiodothyronine in Patients with Hypothyroidism”

Robertas Buneveius, M.D., Ph.D., Gintautas Kazanavicius, M.D., Ph.D., Rimas Zalinkevicius, M.D., and Arthur J. Prange, M.D. - The New England Journal of Medicine, February 11, 1999.

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 µg of the usual dose of thyroxine was replaced by 12.5 µg 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.”

“Animal studies have shown that T4 is only partially absorbed from the gastrointestinal tract. The degree of absorption is dependent on the vehicle used for its administration and by the character of the intestinal contents, the intestinal flora, including plasma protein, soluble dietary factors, all of which bind thyroid and thereby make it unavailable for diffusion. Only 41% is absorbed when given in a gelatin capsule as opposed to a 74 percent absorption when given with an albumin carrier.

Depending on other factors, absorption has varied from 48 to 79% of the administered dose.

Fasting increases absorption. Malabsorption syndromes, as well as dietary factors (children's soybean formula, concomitant use of anionic exchange resins such as cholestyramine), cause excessive fecal loss. T3 is almost totally absorbed, (95% in 4

hours). The hormones contained in the natural preparations are absorbed in a manner similar to the synthetic hormones." - Park-Davis Pharmaceutical Company."

"Combination L-T3 and L-T4 therapy for hypothyroidism.

Curr Opin Endocrinol Diabetes Obes. 2013 Oct;20(5):460-6. doi: 10.1097/01.med.0000432611.03732.49.

Wartofsky L.

ABSTRACT

PURPOSE OF REVIEW:

Because of the longstanding controversy regarding whether hypothyroid patients can be optimally replaced by treatment with levothyroxine (L-T4) alone, numerous studies have addressed potential benefits of combined therapy of triiodothyronine (T3) with L-T4. Results of these studies have failed to support a potential benefit of combined therapy. A strong argument for the addition of L-T3 to L-T4 monotherapy has been lacking until recent genetic studies indicated a rationale for such therapy among a small fraction of the hypothyroid patient population.

RECENT FINDINGS:

Interest in this issue has focused on the importance of the deiodinases in maintaining the euthyroid state and the role of genetic polymorphisms in the deiodinase genes that would affect thyroid hormone concentrations in both blood and tissues. One such polymorphism in the D2 gene, Thr92Ala, is associated with reduced T4 to T3 activation in skeletal muscle and thyroid, linked to obesity and alterations in thyroid-pituitary feedback, and in responses to thyroid hormone treatment.

SUMMARY:

Although our professional organizations continue to recommend L-T4 alone for the treatment of hypothyroidism, the possibility of a D2 gene polymorphism should be considered in patients on L-T4 monotherapy who continue to complain of fatigue in spite of dosage achieving low normal serum thyroid stimulating hormone levels. A suggestive clue to the presence of this polymorphism could be a higher than normal free T4/free T3 ratio. Clinicians could consider adding T3 as a therapeutic trial in selected patients. Future well controlled clinical trials will be required to more fully resolve the controversy.

PMID: 23974776 [PubMed - indexed for MEDLINE]"

Armour Thyroid, Synthroid, and Cytomel Information

Desiccated Thyroid (Armour) is derived from the thyroid gland of pigs. This can sometimes result in an allergy to desiccated thyroid. It is supplied in ¼, ½, 1, 1 ½, 2, 3, 4, and 5 grain tablets. They provide 38 mcg levothyroxine (T4) and 9 mcg liothyronine (T3) per grain of thyroid. Take this medicine on an empty stomach, 30 minutes before eating. Amour Thyroid and calcium should not be taken within 4 hours of each other since the calcium can decrease the absorption of thyroid hormones. Also, caution is advised when using Biaxin (clarithromycin) and Detrol LA (tolterodine) because the effects of Detrol LA may be increased.

Synthroid is a synthetic form of thyroxine (LT4) called levothyroxine sodium, which is supplied in 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets. The average full replacement dose of levothyroxine sodium is approximately 1.7 mcg/kg/day (e.g., 100-125 mcg/day for a 70 kg adult) with gradual increase every 2-4 weeks if needed. Older patients may require less than 1 mcg/kg/day. Levothyroxine sodium doses greater than 200 mcg/day are seldom required. Take this medicine on an empty stomach, 30 minutes before eating. Synthroid (levothyroxine) and calcium should not be taken within 4 hours of each other since the calcium can decrease the absorption of thyroid hormones. Also,

caution is advised when using Biaxin (clarithromycin) and Detrol LA (tolterodine) because the effects of Detrol LA may be increased.

Cytomel is a synthetic form of triiodothyronine (LT3) called Liothyronine sodium, which is supplied in 5, 25, 50 mcg tablets. The recommended starting dosage is 5 mcg 1-2 times daily. Daily dosage then may be increased by 5 mcg 1-2 times daily every 1 or 2 weeks. Usual maintenance dose is 25 to 75 mcg daily. There may or may not be a need to decrease Levothyroxine (LT4) as Liothyronine (LT3) is increased. Liothyronine is 4 times as effective as Levothyroxine. The manufacturer does not provide any information that Cytomel should be taken on an empty stomach or with food. To be on the safe side, take this medicine on an empty stomach, 30 minutes before eating.

Thyrolar (liotrix) is a combination LT3 and LT4, which is supplied as follows:

Thyrolar-1/4	Liothyronine sodium (LT3)	3.1 mcg/	Levothyroxine sodium (LT4)	12.5 mcg
Thyrolar-1/2	Liothyronine sodium (LT3)	6.25 mcg/	Levothyroxine sodium (LT4)	25 mcg
Thyrolar-1	Liothyronine sodium (LT3)	12.5 mcg/	Levothyroxine sodium (LT4)	50 mcg
Thyrolar-2	Liothyronine sodium (LT3)	25 mcg/	Levothyroxine sodium (LT4)	100 mcg
Thyrolar-3	Liothyronine sodium (LT3)	37.5 mcg/	Levothyroxine sodium (LT4)	150 mcg

The usual starting dose is one tablet of Thyrolar (liotrix) ½ with increments of one tablet of Thyrolar (liotrix) every 2 to 3 weeks. Take this medicine on an empty stomach, 30 minutes before eating.

Approximate Strengths Chart

Desiccated Thyroid	Thyrolar (Liotrix) (T3/T4)	Cytomel (Liothyronine)	Synthroid (Levothyroxine)
1/4 grain (15 mg)	1/4 (3.1 mcg / 12.5 mcg)		25 mcg (0.025 mg)
1/2 grain (30 mg)	1/2 (6.25 mcg / 25 mcg)	12.5 mcg	50 mcg (0.050 mg)
1 grain (60 mg)	1/2 (12.5 mcg / 50 mcg)	25 mcg	100 mcg (0.1 mg)
1-1/2 grain (90 mg)		37.5 mcg	150 mcg (0.15 mg)
2 grains (120 mg)	2 (25 mcg / 100 mcg)	50 mcg	200 mcg (0.2 mg)
3 grains (180 mg)	3 (37.5 mcg / 150 mcg)	75 mcg	300 mcg (0.3 mg)

Source: United States Pharmacopoeia - Drug Information 2000, 20th edition