Integrative Treatment of Hypothyroidism

As a major regulator of cellular metabolism, the thyroid gland influences an astonishing number of physiologic processes with include development and growth, thermogenesis, lipid and carbohydrate metabolism, cardiac myocyte activity, reproduction and cognitive functioning. This important gland is characteristic of vertebrates, and its secretions presumably affect every cell in the body, generally increasing metabolic rate. Accordingly, dysfunctional states of the thyroid gland are associated with numerous and fairly non-specific symptoms. Given the non-specific expressions and common occurrence of thyroid disease, concerns about thyroid function are frequently raised by clinicians and patients alike.

SIGNS AND SYMPTOMS OF HYPOTHYROIDISM[1]	
Fatigue	Constipation
Weight gain from fluid retention	Memory and mental impairment
Dry skin and cold intolerance	Decreased concentration
Yellow skin	Depression
Coarse hair or loss of hair	Irregular or heavy menses and infertility
Hoarseness	Myalgias
Goiter	Hyperlipidemia
Reflex delay, relaxation phase	Bradycardia and hypothermia
Ataxia	Myxedema fluid infiltration of tissues

The array of thyroid disorders focuses on the outliers along the continuum of thyroid function (namely hypothyroidism and hyperthyroidism) based upon the production of T3 (triiodothyronine) and T4 (thyroxine). Hypothyroidism is the most common thyroid disease and is estimated to affect between 0.1 and 2% of the population,[2] with rates in women as much as 10 times higher than in men.[3] The elderly and pregnant also experience higher rates of hypothyroidism. Worldwide, iodine deficiency remains the most common cause of hypothyroidism,[4] whereas in industrially developed parts of the world autoimmune hypothyroidism (Hashimoto's disease) is the most common thyroid disease. In the United States many cases of hyperthyroidism eventually lead to hypothyroidism either due to autoimmune "burnout" of the thyroid gland or medical interventions.

Worldwide, iodine deficiency remains the most common cause of hypothyroidism, whereas in industrially developed parts of the world autoimmune hypothyroidism (Hashimoto's disease) is the leading cause of thyroid disease.

It is important for clinicians to be aware of recent controversies over the diagnosis of hypothyroidism. Some physicians, patients and CAM practitioners argue that thyroid function is too critical and complex to define dysfunction based on established normal values of TSH, which neglects the continuum of thyroid function and demand. The controversy over diagnosis of hypothyroidism is also reflected in the changes in normal ranges of TSH, which have been the attention of large consensus statements by professional organizations.[1,5] The diagnostic challenges of thyroid diseases have also warranted the creation of new hybrid diagnoses, namely *subclinical hypothyroidism* and *subclinical hyperthyroidism* to account for more of the observed spectrum of thyroid function and dysfunction.[1,6] For the integrative clinician, it is helpful to develop a clear approach to the diagnosis and management of thyroid disease that addresses both the established facts and uncertainties, population characteristics and individual differences. (For more on diagnosis, watch our accompanying video on an integrative approach to diagnosing hypothyroidism).

TREATMENT

General principles

Ideally, the first step in treatment is to eliminate or mitigate the effects of known or suspected causes of the thyroid dysfunction, such as medications, nutrient deficiencies, or systemic illnesses. In most cases one need not delay treatment of primary hypothyroidism to determine the exact cause. Once treatment is begun, using a slightly narrower target serum TSH range (0.5-3.0 micro units/ml) may produce better results than simply targeting the normal range (0.4-4.0 micro units/ml).[3] While the goal of therapy conventionally focuses on the restoration of objective measures of a euthyroid state (such as normalization of TSH, body temperature, etc), successful resolution or improvement of symptoms also must be targeted in the larger care plan. Articulating such goals between physician and patient may be helpful.

CAUSES OF HYPOTHYROIDISM	
CAUSE	***DIAGNOSTIC CLUES***
Primary hypothyroidism	
Chronic autoimmune thyroiditis (aka Hashimoto's thyroiditis)	TPO antibodies, thyroglobulin antibodies
Iodine deficiency or excess	Goiter, hx of at-risk location (e.g., land-locked), diet (e.g., seafood) or excessive iodine supplementation
Iatrogenic	Hx of surgery or radiation
Drugs	Amiodarone, iodinated contrast or lithium
Postpartum thyroiditis.	TPO antibodies, thyroglobulin antibodies
Infiltrative diseases	Hx of sarcoidosis, tuberculosis
Agenesis/dysgenesis	Congenital hypothyroidism
Non-thyroid illness	Hx acute severe illness or trauma, transient changes in TSH
Central hypothyroidism	
Secondary hypothyroidism (pituitary lesion)	Low, normal or mildly elevated TSH; low free T4 and total T3
Tertiary hypothyroidism (hypothalamic lesion)	Low, normal or mildly elevated TSH; low free T4 and total T3

1. Nutrition and Supplements

- **Iodine.** Dietary iodine is an essential nutrient upon which thyroid function depends. Iodine is concentrated in the thyroid gland and is incorporated into the thyroid hormones. (See diagram on page 6). Noting the ubiquitous need of iodine by cells throughout the range of life, some have posited that the thyroid gland developed as a means of concentrating and storing this plentiful ocean resource as vertebrate life moved onto land.[7]

As mentioned previously, iodine deficiency remains a significant cause of hypothyroidism worldwide, typically in land-locked, impoverished parts of the world. Such chronic, overt deficiency is associated with diets containing less than 50 mcg/day, but this is rare in industrially developed nations.[8] Iodized salt, saltwater fish and sea vegetables are the main dietary sources of iodine. While urinary iodine and thyroglobulin levels have been successfully utilized as biomarkers of iodine status in human populations, it is unclear how reliable they are in diagnosing iodine deficiency states or response to treatment in individuals.[8,9] Although uncertainty may remain, the best test at this time for iodine deficiency is a 24 hour urine iodine of less than 100 mcg/L.[9,10]

Standard supplementation of dietary salt and vegetable oil has eliminated iodine deficiency in many parts of the world.[11] The Recommended Dietary Allowance (RDA) of iodine is 150 mcg per day for adults.[12] One half teaspoon of iodized salt supplies about enough to satisfy this recommendation. The average American gets more than twice this amount of sodium daily. However, some individuals, such as those on a strict sodium restriction diet, may not meet this RDA for iodine; such individuals may consider including sea vegetables in their diets.

The Tolerable Upper Intake (TUI) level of iodine is 1,100 mcg per day for adults.[12] Excess iodine can actually cause a transient hypothyroidism that resolves with discontinuation of high doses. This can be seen in individuals or populations consuming large amounts of seafood, iodine supplements or sea vegetables (see *Botanicals* below.)

- **Selenium.** Adequate selenium is also required for proper thyroid function.[13] (See diagram on page 6). Specifically, selenium facilitates conversion of T4 to the active T3 through selenium-dependent deiodinases.[10] Correcting selenium deficiency may improve concurrent thyroid dysfunction.

It is unclear to what extent selenium benefits patients with hypothyroidism in the absence of a selenium deficiency. There is some evidence that selenium supplementation does reduce thyroid peroxidase antibody (TPO) levels in patients with autoimmune thyroiditis.[14] It has also been found to improve well-being and mood in this population.[14]

Caution should be taken, as selenium can worsen thyroid function with concurrent iodine deficiency. In such cases, selenium and iodine can be supplemented simultaneously. Selenium can also be associated with toxicity. The RDA for selenium is 55 mcg per day.[12] The TUI is 400 mcg per day for adults (e.g., 3-4 Brazil nuts).

- **Other nutrients: Vitamin A, Iron and Zinc.** A myriad of other vitamins and nutrients influence thyroid function, most notably Vitamin A, iron and zinc. (See diagram on page 6). By various mechanisms, these three have been experimentally demonstrated to be permissive and supportive of thyroid function.[10,15,16] Consider supplementing with them in hypothyroidism, especially if deficiency states are suspected.

  Recommended daily doses based on the RDAs and TUI for adults are as follows:
  - ***Zinc*** 10-40 mg/day. (Avoid taking with other minerals due to absorption inhibition)
  - ***Iron*** 12-45 mg/day (in elemental iron… 5 mg ferrous sulfate provides 1 mg elemental iron.)
  - ***Vitamin A*** 800-3,000 mcg/day.

- **L-Tyrosine.** Thyroxin (T4) is naturally produced from the iodination of tyrosine, a non-essential amino obtained both from dietary sources and endogenous conversion of phenylalanine. (See diagram on page 6). Supplementation with L-tyrosine (one of its naturally occurring isomers) is commonly used to support thyroid function. Given its role in thyroxin production, tyrosine availability could theoretically affect thyroid function.[17] While L-tyrosine has been shown to improve sleep deprivation associated deficits,[18] the time of onset (~3 hours) makes it unlikely that these effects are mediated by a change in thyroid function. While such observed effects as improved alertness and psychomotor function[17] could potentially improve symptoms of hypothyroidism, these effects of tyrosine could be mediated via its role in the production in melatonin, dopamine and/or norepinephrine. Regardless, this dietary nutrient is generally safe. The usual dose is 500 mg L-tyrosine 2-3 times daily before meals.

2. Botanicals and Sea Vegetables

- **Sea Vegetables.** Sea vegetables or seaweeds contain variable amounts of iodine depending on the species, local environment and preparation. Consider including them in the diet for those with suspected iodine deficiency and reducing or eliminating them for those suspected as having excess iodine.

COMPARISON OF SEA VEGETABLES TO OTHER SOURCES OF IODINE[19,20]		
Food	**Minimum Amount Needed to Meet Daily Intake Requirement***	**Maximum Amount for Daily Intake Requirement***
Sea vegetables		
Kelp	9 mg = 0.0003 oz/day	70 mg = 0.0025 oz/day
Nori	9 g = 0.3 oz/day	69 g = 2.4 oz/day
Dulse	2 g = 0.07 oz/day	15 g = 0.5 oz/day
Other foods		
Iodized Salt	2 g or ~1/3 tsp/day	14g or ~2.5 tsp/day
Cod	4.5 oz/day (~1.5 servings)	33 oz/day
Cow's Milk	3 cups/day	20 cups/day
Potato (with peel)	2.5 medium size	18 medium size

*These amounts are estimates. Actual content of foods vary considerably based upon growing conditions, storage and preparation.

- **Guggulu (*Commiphora wightii*).** Guggulu (variously known as or guggal, guggul lipid, etc) is a gum resin of a small tree used in Ayurvedic medicine. Its high fiber content is used as a possible cholesterol-lowering agent. A fraction called guggulsterone has been found to have thyroid stimulating effects,[21] but further research is needed.

- **Goitrogens.** There are numerous foods that may contribute to thyroid dysfunction. The brassica genus of vegetables (broccoli, cabbage, cauliflower, turnips, etc) and soy both impair thyroid function by directly inhibiting thyroid perioxidase. (See diagram on page 6). Other potentially important goitrogens include cassava and millet. Notably, these negative effects (specifically with soy and brassica vegetables) are not seen in the absence of iodine deficiency.[10,22] Making sure iodine consumption is adequate is probably the best way to avoid goitrogenic effects of these otherwise generally healthy foods. Others have suggested that cooking helps to prevent or mitigate the effects of these goitrogenic foods.

What Can I Try to Encourage Thyroid Health in a Patient before Starting Hormones?

As most clinicians know, many patients prefer trying safe but possibly ineffective treatments before trying possibly unsafe but effective remedies. Similarly, patients frequently avoid recommended pharmaceutical drugs to avoid potential side effects such as psychological or physiological dependence. Subclinical hypothyroidism is one scenario where these concerns may seem particularly relevant.

Let's say we have a patient with subclinical hypothyroidism (a slightly elevated TSH and a normal serum T4 and T3) that is mildly symptomatic. One could argue that prematurely starting levothyroxine could potentially further suppress an already low level of endogenous thyroid synthesis. Furthermore, in the absence of good assays for the many nutrients and enzymes involved in thyroid production, how do we know that exogenous hormones would not mask a reversible cause?

Given the potential for harm with early hormone treatment, it is reasonable to offer patients a closely monitored trial of maximized non-drug thyroid support:

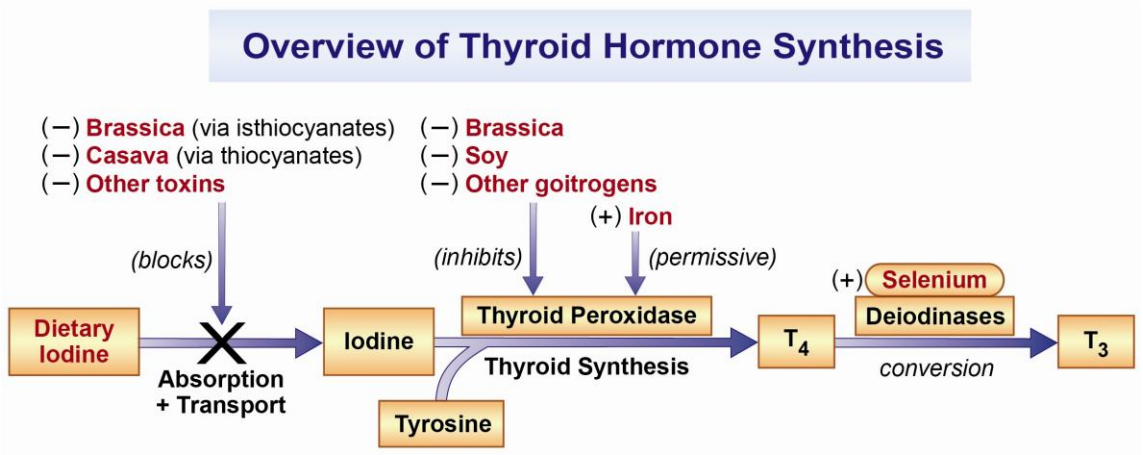
- Iodine 150-600 mcg PO daily (for those at risk of deficiency.)
- Reduction of dietary iodine if excess suspected.
- Selenium 50-300 mcg PO daily (~2 brazil nuts daily.)
- Zinc 10-40 mg PO daily.
- Ferrous sulfate 325 mg PO daily *(65 mg elemental iron)*.
- Vitamin A 800-3,000 mcg PO daily.
- L-Tyrosine 500 mg PO 3 times daily.

3. Pharmaceuticals

- **Synthetic T4 (levothyroxine).** Synthetic T4 is the conventional treatment of choice in most cases of hypothyroidism. Initiate at a dose of 12.5-50 mcg per day and adjust based on TSH every 6-8 weeks. Alternately a dose of about 1.6 mcg/kg/day can be initiated for young healthy individuals. Maximum dose is ~300 mcg per day. Levothyroxine in IV form in the range of 75-500 mcg per day is indicated for myxedema coma.

- **Synthetic T3 (liothyronine).** Synthetic T3 is rarely used conventionally in combination with T4 to treat hypothyroidism. T3 is much more bio-active than T4; it has a quicker onset of action and thus has greater potential for more instability of serum levels when administered exogenously.

In euthyroid individuals, the majority of thyroid activity in the body results from peripheral conversion of T4 to the more active T3 by deiodinase enzymes. About 80% of the active T3 form is produced by this peripheral conversion, with the remaining 20% of T3 being produced by the thyroid gland. The presence of individual and organ tissue variance of deiodinase enzyme activity raises concerns that for some patients with hypothyroidism, supplemental T4 alone may not be adequate.



Numerous trials and one meta-analysis have evaluated the potential advantages of combined T3 and T4 replacement over T4 alone, with mixed results. [23-28] One meta-analysis involving 1,216 patients concluded that there was no advantage to combined T4 and T3 over T4 alone in terms of several patient and clinician-oriented measures.[28] However, there was considerable heterogeneity in the populations included in this meta-analysis. A subsequent double-blind randomized cross over study did show a benefit to combined therapy vs. T4 alone therapy in terms of numerous patient-oriented quality of life and well-being measures.[25]

Given the possibility of benefits to sub-groups of hypothyroidism patients, an empirical trial of combined T3 and T4 could be considered in cases refractory to T4 alone, especially those with persistent low or low normal T3 levels. In such cases liothyronine (T3) can be co-administered with levothyroxine (T4) at a dosing ratio of 1:4; porcine thyroid also approximates this ratio to T3:T4.

- **Porcine thyroid:**
  Ground pig thyroid (Armour Thyroid, NP Thyroid and Nature-Thyroid) is an older form of supplemental thyroid hormone that is still used by many patients. Like endogenous human thyroid secretions, porcine thyroid preparations contain a combination of about 80% T4 and 20% T3, in addition to other possibly active iodinated compounds. Many patients consider this to be more natural and experience better results with this form.[29] Monitoring response to treatment may be done just as with standard synthetic levothyroxine, based on symptoms and TSH after 6-8 wks of therapy. 1 grain (60 mg) of porcine thyroid = 100 mcg of levothyroxine. The starting dose is 0.5 grains in young healthy adults.

> ***Dosing equivalents of thyroid preparations (approximations):***
> *100 mcg of levothyroxine (synthetic T4) = 1 grain (60 mg) of ground porcine thyroid (e.g., Armour Thyroid) or 1 grain (60 mg) of liotrix (synthetic T4 and T3).*

Optimizing treatments

- **Time of Day.** Historically there has been a consensus recommendation to take thyroid medications in the morning on an empty stomach. This was reasoned, at least in part, to prevent interference with absorption from other nutrients or medications. However a recent randomized double-blind crossover trial demonstrated that levothyroxine taken at bedtime was associated with higher plasma thyroid levels, but did not affect quality of life or plasma lipid measures.[30] Based on this evidence, it is reasonable to instruct patients to take levothyroxine before bed, although taking it in the morning is acceptable if this would improve adherence.

- **Optimizing Absorption.** Many medications, supplements and food nutrients can interfere with absorption of thyroid medication. For this reason, it is best to take thyroid medication on an empty stomach. Common medications and supplements that interfere with absorption include proton pump inhibiters, antacids, anticonvulsants, calcium and iron.

4. Other CAM to Consider: (Relatively Safe, but Speculative)

- **Yoga.** There is a particular yoga *asana* or posture that is often purported to stimulate the thyroid gland and its function: *Sharvangasana*, or the shoulder stand. This claim has apparently not been investigated scientifically, but it is generally safe under the guidance of a qualified teacher.

- **Hydrotherapy.** Hydrotherapy is a general term for therapeutic modalities that use submersion in water for various healing purposes. This approach has extensive historical roots, spanning from ancient civilizations to contemporary spas. Most often, variable temperatures of water are used. Given the central role the thyroid gland plays in regulating thermogenesis, it is possible that hydrotherapy might affect thyroid function. Future research is needed.

Summary of Recommendations

- Identify, eliminate and mitigate known or suspected causes of hypothyroidism.
- Articulate goals of therapy that include both objective criteria (e.g., TSH 0.5-3.0 micro units/ml) and individual symptom patterns (e.g., resolution of fatigue.)
- Consider optimizing nutrition and/or supplementing with the following:
  - Iodine 150-600 mcg PO daily (for those at risk of deficiency.)
  - Reduction of dietary iodine if excess suspected.
  - Selenium 50-300 mcg PO daily (~2 brazil nuts daily.)
  - Zinc 10-40 mg PO daily.
  - Ferrous sulfate 325 mg PO daily.
  - Vitamin A 800-3,000 mcg PO daily.
  - L-Tyrosine 500 mg PO 3 times daily.
- For the majority of hypothyroid patients, treatment with synthetic T4 (levothyroxine) is sufficient.
- Consider a trial with the following for refractory cases or to match the patient's preference for a more natural alternative:
  - Synthetic T3 (liothyronine) plus T4 at a ratio of 1:4.
  - Ground porcine thyroid (1 grain = ~100 mcg of levothyroxine)
- Optimize absorption of thyroid supplements by recommending patient take them at night on an empty stomach.

A corresponding handout for patients is also available.

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