



In observing patients taking either Levothyroxine (L-thyroxine) USP (eg, Synthroid, Levoxyl) or Dessicated Thyroid USP (eg, Armour Thyroid, Westhroid, Naturethroid), it has become apparent that a significant percentage continue to suffer from thyroid-related symptoms in spite of optimal blood levels of thyroid hormones. This became even more apparent when the American Association of Clinical Endocrinologists (AACE) changed its guidelines for optimal thyroid-stimulating hormone (TSH) values in patients receiving thyroid replacement. The old reference values, while varying somewhat depending on the laboratory test kit used, ranged from 0.5 to 5.0 $\mu\text{IU/mL}$. The new guidelines for TSH optimization, adopted in 2003, are in the range 0.3 to 3.0 $\mu\text{IU/mL}$. This change required that many patients' dose of thyroid replacement be raised so that their serum levels would fall into the new range. Although this change was intended to optimize treatment outcomes, many hypothyroid patients continued to suffer from a range of hypothyroid symptoms, presumably because their dose of thyroid replacement is suboptimal. The most common lingering complaints include fatigue, impaired concentration, and persistent difficulty losing weight in spite of adequate exercise and reasonable caloric restrictions.

In 1996, I began tracking patients who were taking levothyroxine as their thyroid replacement medication and closely monitoring their symptoms. Although their dosages seemed adequate on the basis of serum testing, it became apparent that more than 75% of the patients continued to suffer from common hypothyroid symptoms. I asked these patients to track their basal body temperature by keeping daily records of either first morning axillary (armpit) tempera-

Hypothyroidism: Optimizing Medication with Slow-Release Compounded Thyroid Replacement

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tures or serial oral temperatures 3, 6, and 9 hours after rising. Both methods revealed temperatures almost always below 98.0°F. Low temperature is commonly reported as a sign of hypometabolism, as described eloquently by Broda Barnes, MD, in the classic text *Hypothyroidism: The Unsuspected Illness* (see the list of Suggested Reading that accompanies this article).

Incidence of Hypothyroidism

It is estimated that approximately 2% of the US population—5.8 million people—are afflicted with hypothyroidism. Women are more likely to develop hypothyroidism than men, and the incidence increases with age. A list of the most common signs and symptoms of hypothyroidism is presented in the accompanying box.

Signs and Symptoms of Hypothyroidism

The AACE names the following as the most common signs and symptoms of hypothyroidism:

- Ataxia
- Bradycardia
- Coarsening or loss of hair
- Cold intolerance
- Constipation
- Decreased concentration
- Delay in the relaxation phase of deep tendon reflexes
- Depression
- Dry, yellow skin
- Fatigue
- Goiter (thyroid gland enlargement)
- Hoarseness
- Hyperlipidemia
- Hypothermia
- Infertility
- Irregular or heavy menses
- Memory and mental impairment
- Myalgias (muscle aches)
- Myxedema (fluid infiltration of tissues)
- Weight gain from fluid retention
- Worsening hypercholesterolemia

Adequacy of Synthetic and Glandular Thyroid Replacement

If a patient is taking thyroid replacement and symptoms persist, the condition is not being optimally managed. The medication most commonly prescribed for hypothyroidism is synthetic thyroid hormone, or levothyroxine (T_4). But it is the active form of the hormone, triiodothyronine (T_3), that we use in our cells and tissues. The conversion of T_4 to T_3 happens in the liver and in the cells themselves. T_4 is converted into both T_3 and reverse T_3 . Reverse T_3 is a stereoisomer of T_3 and has no biological activity. T_4 can be compared to a key that has not yet been cut by a locksmith to fit in the lock (the thyroid receptor site). When it is cut properly (as T_3), it fits in the lock and opens the door. The reverse T_3 stereoisomer of T_3 is a mirror image of the active T_3 molecule—a key that is cut differently enough by the locksmith that it fits in the lock (receptor site) yet doesn't open the door. When there is an excess of reverse T_3 , no thyroid metabolism is stimulated.

Reverse T_3 is biologically essential to slow down metabolism as a natural compensation mechanism during times of starvation or famine. In fact, reverse T_3 creates more powerful negative feedback on the production of T_3 than vice versa. Under varying stressors such as extreme caloric restrictions, pregnancy, and emotional stress, the conversion of T_4 to T_3 can become unbalanced as the body produces excessive amounts of reverse T_3 . Reverse T_3 exerts its negative feedback on T_3 and ties up thyroid receptors. Reverse T_3 must be displaced by the proper biologically active T_3 if metabolism is to normalize. This is impossible, however, if a patient is being given synthetic T_4 only. In these cases, there is no replacement source of the T_3 that is needed to displace the excess accumulations of reverse T_3 in the circulation and receptors. In the absence of adequate biologically active T_3 , symptoms of hypothyroidism remain, despite an adequate level of T_4 in the serum and a normal TSH level. Since most of the conversion of T_4 into T_3 happens in the cells, serum levels of free T_3 and reverse T_3 may be normal even when T_3 and reverse T_3 levels are not in balance. It is as though the cells are starving for biologically active T_3 in the midst of plenty. Unfortunately the "plenty" is plenty of T_4 and reverse T_3 rather than the essential biologically active T_3 . I see many examples of this in my clinical practice. Many patients continue to suffer with hypothyroid symptoms even though they are taking T_4 100 μg (0.1 mg) per day. Their blood levels of TSH and T_4 are normal, yet symptoms persist.

T_3 is available as a manufactured drug in the form of liothyronine sodium (Cytomel). This synthetic T_3 is released immediately, without delay, and is manufactured only in 5 μg and 25 μg doses. T_3 is three to four times more biologically active than T_4 and exerts its effects more rapidly and vigorously than T_4 . The half-life of T_3 is 0.75 days, while that of T_4 is 6.7 days (Table 1). Patients are much more likely to experience side effects from Cytomel than from compounded, slowly released T_3 . These side effects include, yet are not limited to, tachycardia, arrhythmia, anxiety, nervousness, agitation, irritability, sweating, headaches, increased bowel motility, and menstrual irregularities. Angina, congestive heart failure, and atrial fibrillation can be aggravated or induced by excessive doses of T_3 .

Other physiological distinctions between T_4 and T_3 are worth noting. They are best summarized by Williams and Williams in their Textbook of Endocrinology (see Suggested Reading).

USP desiccated thyroid or Armour Thyroid is made with a ratio of four parts of T_4 for every one part of T_3 . This ratio is comparable to those in the human and porcine thyroid glands, which produce 75% T_4 and 25% T_3 . One grain of Armour Thyroid contains 36 μg of T_4 and 9 μg of T_3 . The T_3 is released all at once, not slowly.

Another manufactured drug, liotrix (Thyrolar), contains T_3 in a similar ratio of 75% T_4 to 25% T_3 . Again, the T_3 in Thyrolar is not released slowly. Because T_3 is generally considered to be four times more potent than T_4 , a 25- μg dose of T_3 is equivalent to a 100- μg dose of T_4 .

The amount of slow-release T_3 prescribed, whether formulated in combination with T_4 or taken separately from T_4 , should be about 25% more than the mathematical equivalencies would suggest. This is because T_4 blunts the utilization of T_3 to some extent. The compounded slow-release form seems to allow for less total drug absorption. This can vary considerably from patient to patient. The best approach is to monitor serum levels of free T_4 , free T_3 , and TSH in patients taking T_4 and slow-release T_3 replacement 6 to 8 weeks after every dose adjustment. Further dose adjustments can then be made if necessary. Since T_3 has a short half-life and serum levels tend to peak 3 to 4 hours after dosing of compounded slow-release T_3 , we instruct patients to not take their morning slow-release medication until after their blood draw. This allows measurement of their 24-hour lowest levels of circulating serum T_4 and T_3 . These equivalencies are summarized in the accompanying box.

T_4 and T_3 Equivalencies

$$T_4 \ 100 \mu\text{g} = T_3 \ 25 \mu\text{g}$$

$$\text{Armour Thyroid 1 grain} = T_4 \ 36 \mu\text{g}, T_3 \ 9 \mu\text{g}$$

$$T_3 \ 9 \mu\text{g} \times 4 = T_4 \ \text{equivalency of } 36 \mu\text{g}$$

$$\text{Armour Thyroid 1 grain} = T_4 \ \text{total equivalency of } 72 \mu\text{g}$$

$$(36 \mu\text{g directly from } T_4 \ \text{and } 36 \mu\text{g from } T_3 \ 9 \mu\text{g} \times 4)$$

Nutrients as Cofactors in Thyroid Metabolism

Selenium is an essential cofactor in the conversion of T_4 into T_3 . T_4 is converted into T_3 by the selenium-dependent enzyme 5'-deiodinase. Selenium depletion of soil is common in many areas of the US, and many individuals do not supplement adequately to counteract this deficiency. Iodine is also essential in the conversion of T_4 into T_3 . While iodine depletion is common in US soils, many Americans use iodized salt to counteract this. Commercial farming methods used in the last century, which fertilized soil only with nitrogen, phosphorus, and potassium, have allowed soils formerly rich in selenium and iodine to become fully depleted. Other nutrients essential to optimizing thyroid metabolism are tyrosine, zinc, copper, and

Table 1. Comparison of Triiodothyroxine (T₃) and Thyroxine (T₄) in Humans.

	T ₃	T ₄
Production rate (nmol/day)	50.00	110.00
Fraction from thyroid	0.20	1.00
Relative metabolic potency	1.00	0.30
Serum concentrations ^a		
■ Total (nmol/L)	1.80	100.00
■ Free (pmol/L)	5.00	20.00
Fraction of total hormone in free form (x 10 ⁻²)	0.30	0.02
Distribution volume (L)	40.00	10.00
Fraction intracellular	0.64	0.15
Half-life (days)	0.75	6.70

^aTo convert T₄ from nmol/L to µg/dL (total) or pmol/L to ng/dL (free), divide by 12.87. To convert T₃ from nmol/L to ng/dL (total) or pmol/L to pg/dL (free), multiply by 65.1.

essential fatty acids. In a sense, all of the essential nutrients play a role in optimizing the health of the thyroid gland (essential amino acids, essential fatty acids, vitamins, minerals, and trace minerals).

The Solution

Over the years, I have developed several different replacement strategies as alternatives to the use of the standard therapies, levothyroxine and desiccated thyroid. These replacement strategies have in common some blend of T₄ with slow-release T₃. The example used in the first case is best suited to the patient who has higher demands for energy during the day and/or suffers from some type of sleep disorder at night. The approach used in Case 1 is also best for patients who have a hard time taking more than one pill daily or have financial constraints, since this is the least expensive option.

Case Reports

In each of these cases, we start with a patient who is currently taking T₄ 100 µg as the starting dose. We will be changing each patient's therapy to a blend of T₄ and T₃, slowly released.

Case 1

This patient's starting TSH is 2.5 µIU/mL, and we have a target of 1.0 µIU/mL to optimize quality of life and minimize hypothyroid symptoms. The patient's dose of T₄ should be increased to 125 µg or 150 µg to drive the TSH level down from 2.5 to 1.0 µIU/mL. For discussion purposes, this final T₄ dose is 150 µg. This dose of T₄ must be converted to an appropriate combination of slow-release T₄ and T₃ at the correct ratio. As already discussed, the thyroid gland maintains a T₄:T₃ ratio of 4:1, but most patients who are symptomatic are converting an excessive amount of T₄ into reverse T₃. They need a ratio of T₄:T₃ of perhaps 3:1 or 2:1 or, rarely, even more T₃ relative to T₄. This is especially the case at the beginning of therapy. If we decide on a T₄:T₃ ratio of 2:1, converting 150 µg of T₄ to a blend of slowly released T₄ and T₃

mathematically calculates to 50 µg of T₄ and 25 µg of T₃. The 25 µg of T₃ multiplied by 4 represents a T₄ equivalency of 100 µg. Adding the 50 µg of T₄ brings the total T₄ dose to 150 µg.

Keep in mind, however, that doses of slow-release combinations need to be increased by approximately 25% because of differences in absorption. Mathematical equivalencies are just that, and often a delivery form can increase or reduce absorption from what is mathematically assumed. If we increase this initial dose of 150 µg of T₄ by 25% to accommodate this, the correct dose of T₄ is 187.5 µg. The equivalency of this dose in a T₄:T₃ ratio of 2:1 would be about 60 µg of T₄ and 30 µg of T₃. The 30 µg of T₃ multiplied by 4 equals 120 µg of T₄ on an equivalency basis; with the 60 µg of T₄, this adds up to a finished equivalency of 180 µg, slightly shy of the 187.5 µg target. A formula can be used to make the calculations easier, as follows:

T₄ dose divided by 3 = new T₄ dose

T₄ dose divided by 6 = new T₃ dose

A 300 µg T₄ dose would convert to (300/3 = 100 µg T₄) plus (300/6 = 50 µg T₃)

The same mathematics apply to increasing or decreasing the T₄:T₃ ratio in subsequent prescriptions. From a practical perspective, however, the levels of T₄ and T₃ in the patient's serum should guide the prescriber to the proper proportional or disproportional dose adjustments needed to reach targeted serum levels of free T₄, free T₃, and TSH.

If the degree of thyroid resistance and need for active T₃ is not as extreme, we might consider a T₄:T₃ ratio of 3:1. An equivalency of 187.5 µg would convert to 81 µg of T₄ and 27 µg of T₃. Multiplication of 27 µg T₃ by 4 equals 108 µg; this added to the 81 µg T₄ equals approximately 190 µg of T₄. The easiest way to calculate this is to realize that the amount of T₃ will be slightly less than that needed for the 2:1 ratio (ie, T₄ 60 µg/T₃ 30 µg). Multiply the 27 µg T₃ by 3 to preserve the 3:1 ratio and calculate the finished equivalency. These ratios are modified as indicated by remaining symptoms, temperature log results, and balance of free T₄, free T₃, and TSH in the blood.

Case 2

In this case, the patient (who is initially taking 100 µg of T₄) also requires a dose increase to 150 µg to get her TSH level down to a target of 1.0 µIU/mL. The patient could continue to take T₄, yet at a lower dose of 50 µg. These medications come in doses of 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 µg. Because it has no food dyes or coloring added, I like to use the 50-µg tablet and divide the dose. If the target desired dose is 60 µg as in Case 1, the closest we can get is 50 µg. The 30 µg of T₃ needed to make up the correct T₄:T₃ ratio is compounded as a slow-release tablet, either as 30 µg once daily or 15 µg every 12 hours. I prefer the slow-release capsule to be taken first, upon rising; ideally the patient would then wait 1 hour before eating breakfast and take the T₄ pill 3 hours after the T₃. The patient then takes the second T₃ capsule, if appropriate, 12 hours after the first. Some patients need their T₃ slowly released over 24 hours, especially as the doses are increased to avoid side effects or to optimize distribution of energy throughout the day to be more even and to avoid fatigue in the late afternoon or evening.

This dosage regime is more complicated for patients. Remember, these are hypothyroid patients who will take medication daily for the rest of their life. Asking someone to take a morning dose, another dose 3 hours later, and a third 12 hours after the first can be a compliance nightmare. Some patients feel best on this protocol, however, and are not significantly bothered by the routine. It can be simplified by taking the entire day's dose of T_3 in the morning and the T_4 3 hours later, or even further by taking the T_4 and T_3 together upon rising. (The T_4 does not have to be released slowly, since its half-life is 7 days.) Most convenient for the patient is compounding the T_4 together with the slow-release T_3 in one capsule, so that the patient has to take only one capsule in the morning.

Armour and USP Thyroid

Recall that there is a good chance that a hypothyroid patient with lingering chronic hypothyroid symptoms is converting too much T_4 into reverse T_3 , which is biologically inert. By replacing some of the prescribed T_4 with slow-release T_3 , the reverse T_3 gets displaced by the active T_3 and metabolism returns to normal.

Glandular Thyroid USP (Armour Thyroid) delivers approximately four parts T_4 to one part T_3 . T_3 is about four times more potent than T_4 but is metabolized three times faster. The T_3 in Armour Thyroid is not released slowly and therefore gets delivered

unevenly throughout the day. This is not the way the thyroid gland and tissues work. T_3 , owing to its high biological activity, should be delivered in even amounts. Compounded slow-release T_3 does just that. Furthermore, accurately adjusting the dose of Glandular Thyroid USP is difficult. Amounts of T_4 and T_3 can vary from batch to batch and from manufacturer to manufacturer. USP thyroid comes in limited strengths, including one-quarter grain, one-half grain, 1 grain, 2 grains, and 3 grains. Optimizing the dose in sensitive and difficult cases may be very challenging.

Please note that I do not advocate treating hypothyroidism with slow-release T_3 alone, as the only form of thyroid replacement. T_3 works best when combined with T_4 . Too much T_3 without T_4 can cause other problems, including osteoporosis and heart arrhythmias. T_4 also helps blunt the risk of side effects from T_3 , which can occur even with slow-release T_3 . Finally, T_4 offers a reservoir of thyroid hormone material with which to make more T_3 as needed.

Many patients suffering from years of lingering hypothyroid symptoms while being treated with synthetic T_4 or Armour Thyroid will feel much better if their treatment is changed. Appropriate changes include either a lowered dose of the current medication combined with slow-release T_3 or a customized compounded blend of slow-release T_4 and T_3 .

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I urge patients to consult with their endocrinologist before making any change in thyroid medication. They should be aware, though, that very few physicians are knowledgeable about slow-release T_3 and its proper use. Although some available drugs deliver T_3 (Cytomel, for example) or combine T_4 with T_3 (Thyrolar), the T_3 in these preparations is not released slowly. As a result, patients continue to suffer from the symptoms that result from uneven T_3 distribution.

Compounded Slow-Release T_4 and T_3

In making the medication, a compounding pharmacist uses properly aliquoted concentrations of T_4 and T_3 . The T_4 and/or T_3 are combined together with cellulose derivatives that regulate their slow release. This mixture is then either tumbled for at least 6 hours or blended fully in a V mixer to assure even distribution of the active ingredients. The finished material is then placed into capsules. Once swallowed, the capsule forms a bolus in the stomach and slowly releases T_4 and T_3 . The T_4 and T_3 used in compounding are synthetic, yet they are biologically identical to the T_4 and T_3 made by the human thyroid gland (T_4 = levothyroxine sodium or 3,3',5,5'-tetraiodothyronine sodium, and T_3 = L-triiodothyronine).

Monitoring Medication Adjustments

The $T_4:T_3$ ratio initially prescribed is arbitrary and will most likely be adjusted up or down. Adjustments are based on ongoing symptoms, body temperatures, and the balance of serum levels of free T_4 , free T_3 , and TSH reported after 6 to 8 weeks on a stable dose. In the most severe cases of thyroid resistance, which require the highest doses of T_3 , the dose will need to be adjusted until the serum TSH level is 0.2-1 μ U/mL, with the free T_4 level at the low end of normal or even below normal, while the free T_3 level is at the high end of normal or even above normal.

Since T_3 is so biologically active, we like to instruct our patients to take no thyroid medication the morning of the blood draw. We have them come in for this blood draw as the first patient scheduled in the morning (8 to 9 AM). This allows us to capture their lowest level of circulating T_3 in the 24-hour period. They are instructed to take their medication immediately after the blood draw.

When changing from T_4 to a slow-release blend of T_4 and T_3 , the initial dose is an estimate. The guidelines already described are only guidelines; actual dose varies from patient to patient depending upon that patient's intestinal health and absorption of thyroid hormone. In our initial change of prescription, we authorize patients to return in 3 weeks for repeat blood work if they are feeling poorly and in 2 months if they are doing well. Within 3 weeks after a dose adjustment, the serum levels of T_4 and T_3 have reached their new steady state. If an individual is feeling poorly from either underdosing or overdosing, we can check at this early juncture their circulating blood levels of free T_4 and free T_3 . TSH level will not stabilize for 6 to 8 weeks after a dose change.

Drug-Drug and Drug-Nutrient Interactions

Thyroid hormone can potentiate the effects of warfarin, requiring a lowering of blood warfarin level to avoid excessive anticoagulation. Digoxin level can be potentiated by thyroid medication, requiring lowering of the dose of digoxin. Antidepressant drugs can be mildly potentiated by thyroid hormone. Lithium carbonate,

given for the treatment of bipolar disorder, can induce hypothyroidism. Patients taking thyroid in excessive doses for weight loss can develop life-threatening symptoms of toxicity and/or arrhythmia, especially when the thyroid is given in association with sympathomimetic amines for their anorexic and weight loss effects. No interactions of thyroid with alcohol or tobacco have been documented. Estrogen replacement and estrogen dominance can increase the need for thyroid replacement. As hypothyroid women approach menopause and accumulate more estrogen dominance, their thyroid replacement dose may need to increase. Similarly, estrogen replacement therapy can increase a woman's need for thyroid replacement. Insulin requirements can increase as thyroid replacement dose increases. Thyroid medication can increase the adrenergic effects of epinephrine.

Calcium supplements can reduce utilization of thyroid hormone, especially when taken in high doses. Thyroid hormone replacement is best taken in the morning and calcium is best absorbed in the evening. Taking calcium with dinner minimizes any impairment of utilization of thyroid taken in the morning. High levels of soy in the diet can impair thyroid hormone utilization. Soy is best eaten in small amounts in the evening meal. Iodine and selenium potentiate the conversion of T_4 into T_3 , acting as cofactors in the conversion. Brassica vegetables (broccoli, cauliflower, brussel sprouts) can reduce thyroid hormone utilization.

Conclusion

Hypothyroidism is a common condition. A large percentage of patients remain significantly symptomatic in spite of apparently adequate replacement therapy. Symptoms may include intractable chronic fatigue, impaired concentration, and weight gain. These symptoms may have devastating consequences on quality of life. Changing medication to a blend of T_4 with slow-release T_3 resolves many of these limitations of patients' quality of life. The compounding of exact customized levels of T_4 and T_3 enables the clinician to achieve optimal targeted serum levels of TSH, free T_4 , and free T_3 with precision. These levels can be carefully customized to optimize symptom resolution while improving metabolic temperature status. Customized compounding allows dose adjustments to achieve whatever balance of T_4 and T_3 is necessary to achieve optimal health and resolution of symptoms.

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