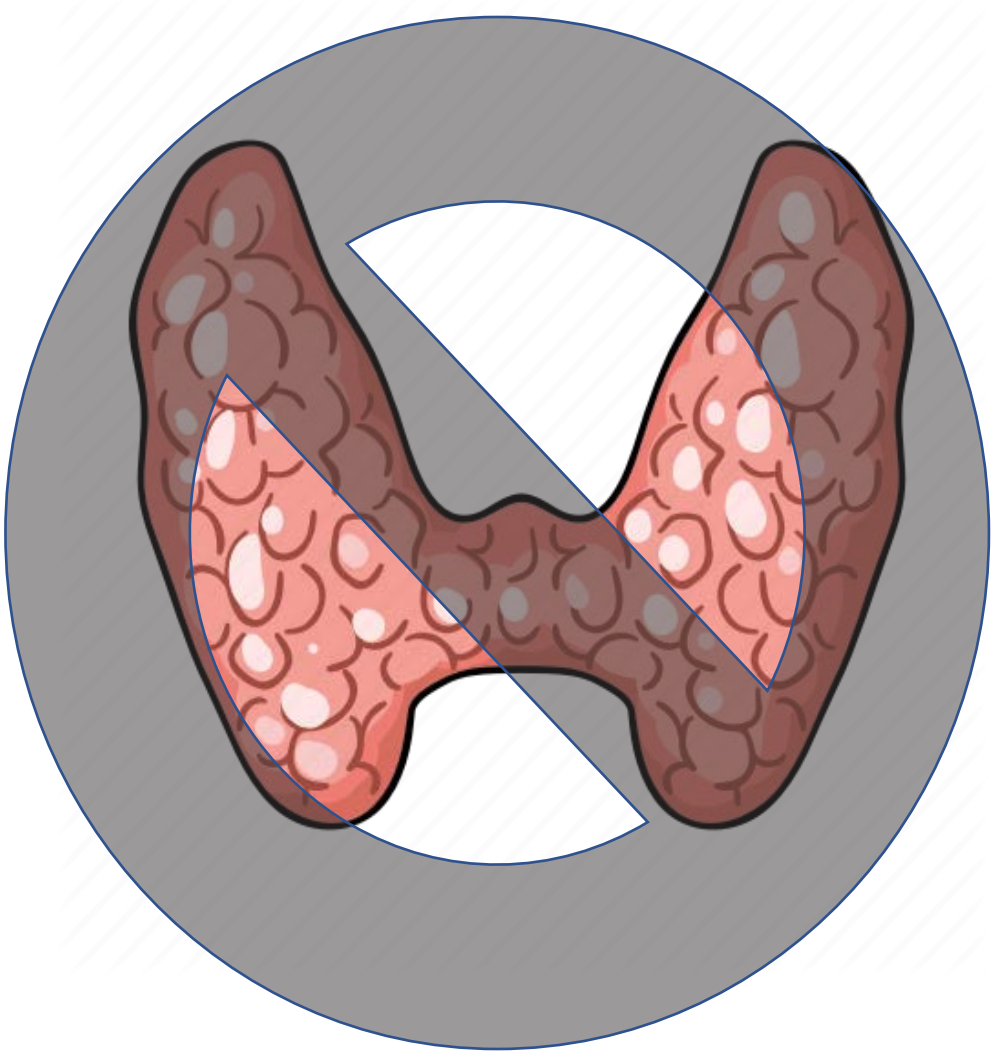

It’s not your thyroid… (probably)

The Friday the 13th Version of September 2019 Medicine Grand Rounds

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This is to acknowledge that Alex Tessnow, MD has disclosed that he does have financial interests or other relationships with commercial concerns related directly to this program. Dr. Tessnow will not be discussing off-label uses in his presentation.

Alex Tessnow, MD is a graduate of UT Southwestern Medical School and an Associate Professor of Internal Medicine in the Division of Endocrinology. He specializes in the care of individuals with thyroid disorders, predominantly thyroid nodules and cancer.

It is his hope that at the end of this lecture, the participant should be able to:

1. Understand the pharmacologic differences in the composition between desiccated pork thyroid products and synthetic thyroid hormone products
2. Understand that the symptoms of thyroid hormone excess/deficiency are low in specificity. Many patients who are "adequately treated with levothyroxine" still endorse these symptoms. Whether these symptoms reflect inadequate thyroid hormone replacement is controversial.
3. Describe the pathway of thyroid hormone signaling and the controversy that exists in T3-containing thyroid hormone replacement regimens.

Introduction:

Hypothyroidism is one of the most commonly encountered disease states. In the Colorado Heart Study as many as 15% of women over the age of 55 had an abnormal thyroid stimulating hormone (TSH) level. The percentage of people with abnormal thyroid hormone levels continues to increase with age, with the overwhelming majority having low circulating thyroid hormone levels, or hypothyroidism. Currently in the US, approximately 123 million prescriptions for thyroid hormone replacement are dispensed, indicating how prevalent this disease state is.

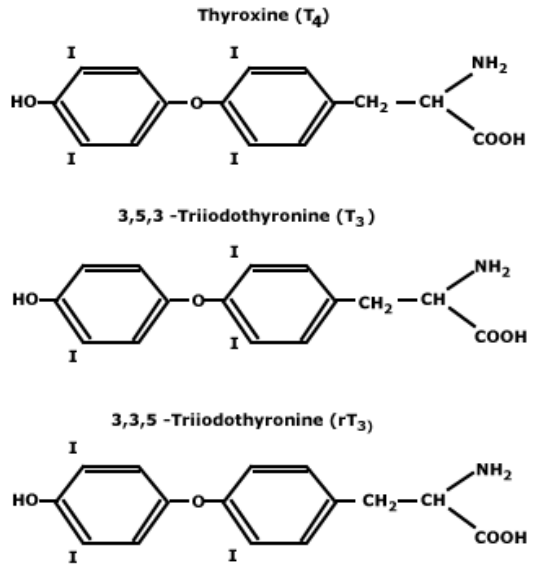
The only way to adequately treat thyroid hormone deficiency is with thyroid hormone replacement. Controversies exist, however, as to the ideal regimen for such replacement. Historically, the first such supplements were made from pork or bovine thyroid. Desiccated products, particularly of pork derivation are still widely available. Subsequently, synthetic human products of tetrathyiodothyronine (T4) and triiodothyronine (T3) became available. Are synthetic human products superior to pork? Is monotherapy with synthetic T4 just as effective as combination of T3 and T4 or desiccated products as the American Thyroid Association recommends? The purpose of this paper is to explore the available data to answer these questions.

Case History:

Our patient is a 48-year-old woman who underwent complete thyroidectomy for papillary thyroid carcinoma 3 years ago. Prior to her surgery, she had no history of thyroid dysfunction. She had an excellent response to initial treatment and her serum tumor markers and routine imaging show no evidence of persistent malignancy. She is taking 112 mcg daily of levothyroxine for her hormone replacement and TSH at the time of her visit is 2.2 mIU/L (ref range: 0.4-4.2 mIU/L) and free T4 of 1.3 ng/dL (ref range: 0.9-1.8 ng/dL). Despite being euthyroid based on her TSH, she complains of fatigue, "brain fog", constantly feeling cold and difficulty losing weight. She states the symptoms began following her thyroid surgery and she has never felt the same since.

Physiology:

The human thyroid gland produces two thyroid hormones (T3 and T4) that differ only by the number of iodine atoms contained. T3 is the more potent, biologically active form of the hormone and is responsible for carrying out the hormone system's activity. It only constitutes 10-20% of daily thyroid gland output with the remainder being in the form of T4. T4 is the prohormone and is converted to T3 by deiodinase enzymes expressed throughout the body.



Deiodinase enzymes are produced in virtually every tissue with two predominant isoforms, DiO1 and DiO2.

DiO1 is expressed mainly in liver, kidney and thyroid and is inhibited by propylthiouracil (PTU). DiO2 is more widely expressed (in pituitary, muscle and other tissues). It is not suppressed by PTU. The fact that the body contains more than one isoform of this activating enzyme (with differing enzymatic activities) implies that various tissues are differentially affected by circulating thyroid hormone levels.

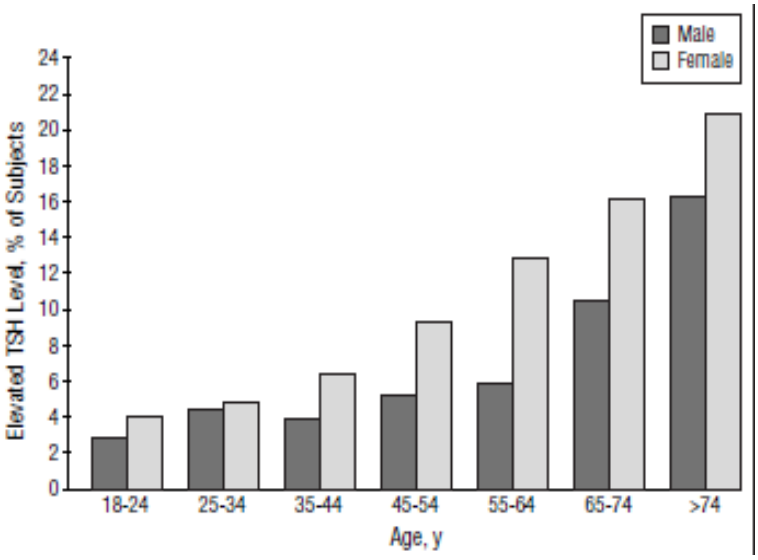
Thyroid hormone regulation however begins at the level of the hypothalamus. Thyrotropin releasing hormone (TRH) is secreted by the neurons present there and travels via the hypothalamic-hypophyseal portal system of veins to the anterior pituitary. There, TRH stimulates thyrotrophs to secrete thyroid stimulating hormone (TSH). Once TSH is bound to its receptor on thyroid follicular cells, a cascade of events occurs. First, sodium-iodine symporters become more abundant on the basal cellular surface augmenting the intracellular iodine content. Iodine is then transported to the apical surface where it is transported to the lumen of the thyroid follicle and subject to the action of the thyroid peroxidase enzyme (TPO). TPO organifies the iodine by catalyzing its binding to tyrosine residues on the protein, thyroglobulin. TPO further couples these iodotyrosines to make T3 and T4. When required, these thyroid hormones can be endocytosed back into the follicular cells, released from thyroglobulin and secreted into the rich capillary blood supply within the thyroid gland.

Daily, the human thyroid gland produces roughly 85 mcg of T4 and 33 mcg of T3 (7 mcg from direct secretion from the gland and 26 mcg from peripheral conversion of T4 to T3 by the deiodinase enzymes).

Once thyroid hormone reaches its target tissue, T3 (or T4 from deiodination) enters the cell nucleus and bind to the thyroid hormone receptor. This complex then bind to another set of proteins, RXR, and then attaches to specific sequences of DNA. From here, downstream genes may either be transcribed/activated or suppressed depending on the cell type/gene involved.[1]

Etiology of Hypothyroidism:

Most hypothyroidism in our country is the result of autoimmune disease. In 1912. Dr. Hakaru Hashimoto described the infiltration of the thyroid gland with an abundant number of lymphocytes that he suspected were leading to a reduction of thyroid hormone production.



Today, > 90% of hypothyroidism is attributed to "Hashimoto's disease," and refers to a chronic lymphocytic infiltration of the thyroid parenchyma. The etiology of Hashimoto's disease remains unclear.

What is clear is there exists a strong predilection for this disease with family history and female gender. As one can easily see from the Colorado Health Fair Survey, the incidence of hypothyroid based on elevated TSH values increases with age and at all age intervals is significantly greater among females. The prevalence

of an elevated TSH reached 20% among women over the age of 74.[2] Hence, thyroid autoimmunity shows a female predominance like many other autoimmune disorders such as Systemic Lupus Erythematosus or Rheumatoid Arthritis.

A variety of other causes make up the remaining 10% of hypothyroid etiologies. These include postsurgical hypothyroidism following thyroidectomy, postablative hypothyroidism following radioactive iodine treatment for hyperthyroidism, postpartum thyroiditis, use of drugs that affect thyroid function (e.g. amiodarone, lithium) and pituitary or hypothalamic disease (so-called secondary or tertiary hypothyroidism).

Clinical presentation:

The fact that thyroid hormone is used by virtually every tissue to regulate gene transcription explains the multitude of clinical presentations that hypothyroidism may elicit. The most common presenting symptoms include fatigue, poor memory/concentration, constipation, myalgia and arthralgia, cold intolerance, heavy menses and weight gain. Due to the nonspecific nature of the symptoms, many patients are initially misdiagnosed as having depression, arthritis, irritable bowel syndrome and a variety of other maladies.

Laboratory evaluation usually demonstrates an elevated TSH, low T3 and T4 levels, and if due to autoimmune thyroid disease ("Hashimoto's"), may also show elevated levels of thyroid peroxidase antibodies (TPO) and/or thyroglobulin antibodies.

Pharmacology:

The only proven treatment for hypothyroidism is thyroid hormone replacement. Various herbal remedies and "thyroid support vitamins" are available on the internet and in health food stores.

These preparations may contain Iodine, Gugulipid (commiphoramukul), Bacopin (bacopamonniera), Ashwagandha (withaniasomnifera) among other preparations. Commiphora mukul has been linked to increased iodine uptake and thyroid peroxidase activity in rodents though no published human studies are available demonstrating a change in thyroid function.[3] Similarly, bacopa monnieri was shown to increase T4 levels in mice though no human studies are available.[4] One small study using ashwagandha root extract in 25 subclinical hypothyroid patients showed improvement in TSH and free T4 when given for 8 weeks versus placebo though this data has not been reproduced.[5]

In 2013, a study published in the journal *Thyroid* analyzed 10 over the counter "thyroid support" vitamins and found that 9 out of 10 products had detectable T3 and 5 out of 10 contained T4.[6]

TABLE 1. MEASURED THYROXINE AND THYRONINE IN OVER-THE-COUNTER THYROID SUPPLEMENTS

Sample ID no.	L-tyrosine[a] (mg)	Iodine[a] (μg)	T4 (μg/tab)[b]	T3 (μg/tab)[b]	Recommended daily dose	Total daily dose T4 (μg/day)[c]	Total daily dose T3 (μg/day)[c]
1	150	150	Undetectable	2.73 ± 0.38	1 capsule daily	—	2.73
2	300	150	5.77 ± 1.07	1.83 ± 0.68	3 capsules daily	17.30	5.50
3	700	240	22.90 ± 1.83	4.13 ± 0.40	4 capsules daily	91.60	16.53
4	500	100	Undetectable	8.03 ± 0.23	2 capsules 1–2 × daily	—	32.13
5	1000	225	< 0.5	5.00 ± 1.01	2 capsules 2 × daily	< 1.0	20.00
6	—	—	Undetectable	3.67 ± 0.31	1 capsule daily	—	3.67
7	—	—	Undetectable	Undetectable	1 tablet daily	—	—
8	—	—	Undetectable	2.30 ± 0.52	1 capsule daily	—	2.30
9	200	—	8.57 ± 0.12	25.40 ± 0.53	1 capsule daily	8.57	25.40
10	—	—	9.40 ± 1.27	1.27 ± 0.12	> 1 tablet daily	9.40	1.27

[a]As provided on the label.
[b]Mean ± SD.
[c]Calculated maximum/total daily dose (mean) per recommended daily intake dose.
ID, identification; T3, triiodothyronine; T4, thyroxine.

Kang et al Thyroid 2013

It is important to educate patients that their supplements may contain significant amounts of thyroid hormone and can lead to over-replacement. Moreover, excess iodine given to an individual with autoimmune thyroid disease may suppress thyroid function rather than enhance it. This is due to failure to escape the Wolff-Chaikoff effect, a phenomenon in which the normal thyroid will suppress organification

of iodine in the setting of excess iodine levels. Normally, the thyroid will "escape" this suppression within a few days though diseased glands may fail to do so. This results in lowering serum thyroid concentrations. [7]

Thyroid hormone (not "thyroid support vitamins" or iodine products) is the only treatment for hypothyroidism. Initially, the only available thyroid hormone supplements were produced from desiccated pork or bovine thyroids. In the 1960s, synthetic human T4 became available (levothyroxine). Currently in the US, FDA approved products include synthetic human T4, both branded and generic, synthetic human T3 (liothyronine) and desiccated pork thyroid. The American Thyroid Association recommends levothyroxine (LT4) monotherapy as the treatment of choice "due to its efficacy in resolving the symptoms of hypothyroidism, long-term experience of its benefits, favorable side effect profile, ease of administration, good intestinal absorption, long serum half- life, and low cost". [1] It is essential that patients be educated to always take their thyroid hormone (pork or synthetic) on an empty stomach with only water. It is best to avoid other medications, vitamins, food or drink (even black coffee) for 30-60 minutes.

Controversy!:

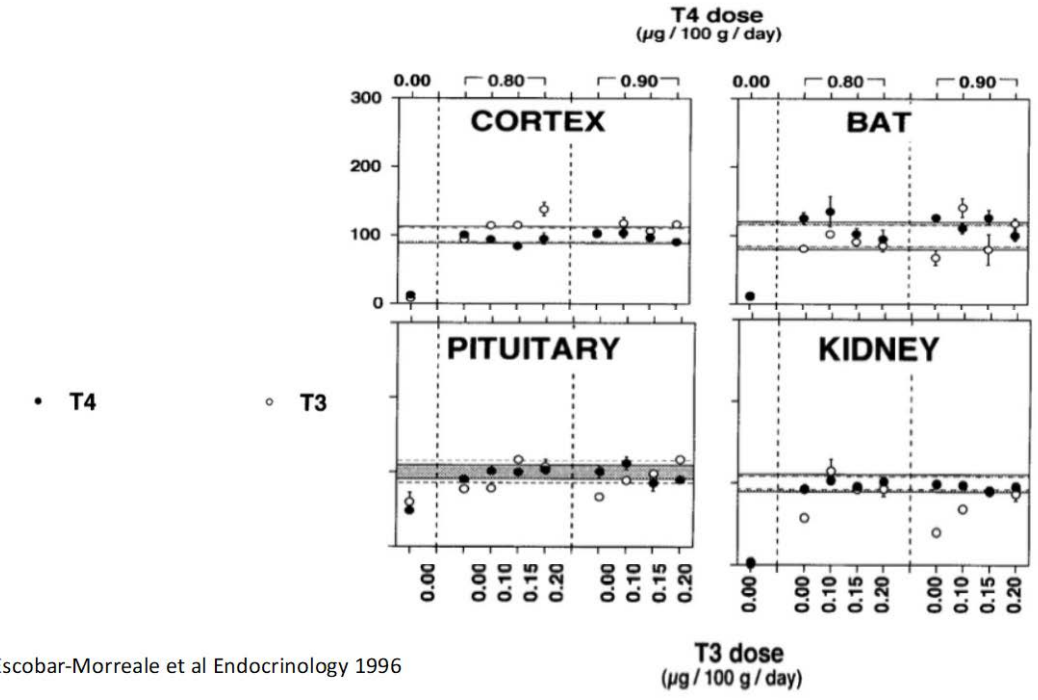
Despite the attainment of a normal TSH level with supplementation, many hypothyroid patients continue to complain of "hypothyroid" symptoms. Case-controlled studies in the UK and Norway showed a significant percentage of individuals on levothyroxine had an increase in psychiatric "caseness" despite having a normal TSH when compared to control groups.[8-10] This difference may apply to as many as 5-10% of treated patients. The precise reason for these persistent symptoms despite "adequate" replacement therapy is unknown.

Certainly, it is possible that the treatment dissatisfaction experienced by so many individuals may not be explained by the thyroid hormone level per se. The "awareness" of having a chronic disease may lead to a reduction of perceived quality of life.[11] Additionally, since most hypothyroidism is related to autoimmunity, the presence of one such disorder in a patient may signal the presence of others. In fact, as many as 14% of patients with Hashimoto's may have an additional identifiable autoimmune disease.[12] Rheumatoid arthritis is the most common coexistent autoimmune disease, followed closely by pernicious anemia. It has also been speculated that some of the symptoms may be related to thyroid-specific autoimmunity. One study from Austria detected a higher incidence of fatigue and other symptoms in women with higher TPO concentrations, although another study from England did not.[13, 14] Perhaps the problem lies in the use of TSH as a target. Prior to the development of sensitive assays for TSH, hypothyroid extracts were used to ameliorate the "symptoms of hypothyroidism." It wasn't until the 1980s that TSH level as a therapeutic target of thyroid hormone replacement became the standard of care.[8] The result was many patients saw significant reductions in their daily doses of levothyroxine. Another argument is that perhaps the target range is too large. The range of TSH in the general population is rather broad: 0.4 to 4.5 mIU/L. The intra-individual variation is generally a lot less. Thus, perhaps a treated TSH at 4 mIU/L would not be felt as "adequate" by an individual whose native TSH would be closer to 1 mIU/L. To test this hypothesis, Walsh et al performed a double-blind, crossover study targeting three levels of TSH by adjusting levothyroxine dosage. At each visit, participants answered a battery of physical and mental wellbeing questionnaires. These surveys included validated somatic and mental health questionnaires such as SF-36 and GHQ-28. In addition, a more thyroid-specific symptoms questionnaire, the TSQ, was administered.

Questionnaire/Instrument		TSH level (mU/L)			P-value
		2.0-4.8	0.3-1.99	<0.3	
Visual Analog	Gen Wellbeing	36.5 +/- 3.7	40.0 +/- 3.0	40.0 +/- 1.9	0.79
SF-36	Physical Summ	42.3 +/- 0.8	42.5 +/- 0.6	42.3 +/- 0.7	0.97
	Mental Summ	51.2 +/- 0.8	49.1 +/- 1.0	48.9 +/- 1.0	0.31
GHQ-28	Total	16.6 +/- 1.6	18.3 +/- 1.4	19.6 +/- 1.7	0.49
TSQ (Thy Symptom Ques)		12.5 +/- 0.7	13.0 +/- 0.6	13.6 +/- 0.8	0.65
Treatment Satisfaction		0.7 +/- 0.2	0.8 +/- 0.1	0.8 +/- 0.1	0.77

Walsh JP et al J Clin Endocrinol Metab 2006

Ultimately, no significant differences were detected between high and low dose levothyroxine therapy, challenging this assertion.[15]



Escobar-Morreale et al Endocrinology 1996

Based on this data, there is inadequate proof that treating an individual to a TSH in the lower reference range (i.e. < 0.3 mIU/L vs 4 mIU/L) improves quality of life or "thyroid symptoms." In the 1990s, Escobar-Morreale and colleagues demonstrated in mouse models that levothyroxine monotherapy was not sufficient to achieve normal T3 levels in all tissues. In fact, it required a combination of T3 and T4 replacement to attain this.[16]

It has long been recognized that patients treated with LT4 monotherapy have relatively higher circulating T4 levels and lower T3 levels compared with controls. [17] Further, considering the Escobar-Morreale data, tissue-specific levels of T3 may be abnormal even in the setting of normal TSH values. One potential mechanism to explain this phenomenon lies in the process of thyroid hormone activation. DiO2 (type 2 deiodinase) is widely expressed in the body and the CNS. Its expression, however, is variable depending on the tissue. In the presence of T4, the expression half-life of DiO2 is approximately 20 minutes. When T4 is scarce, this half-life extends for hours. DiO2 is eliminated via ubiquitination, a process stimulated by T4. Thus, T4 indirectly regulates its own activation. This process is not uniform however. Utilizing rodent models, Gullo et al demonstrated that while in the periphery, the T4-mediated ubiquitination process is rapid, the hypothalamus is less affected by this process.[17] In other words, in the hypothalamus, either DiO2 is not as readily ubiquitinated or has a vigorous deubiquitination process. As a result, thyroid hormone signaling in the hypothalamus may be more robust, hence suppressing TSH, while other tissues are functioning in a relatively hypothyroid state.

T3/T4 combination therapy:

This data sparked a new debate in the thyroid community regarding the benefit of adding T3 (pharmacologically, liothyronine) to levothyroxine in the replacement of thyroid hormone in

hypothyroid individuals. In 1999, Bunevicius et al randomized 33 patients in a crossover fashion to T4 monotherapy or T3/T4 combination therapy. 50 mcg of T4 of the patient's maintenance LT4 dose was substituted with 12.5 mcg of LT3 to perform the combination. In the end, combination therapy prevailed when judged according to the Visual Analogue Scale for mood and physical symptoms.[18]

Since 1999, several studies have been published comparing T3/T4 combination therapy to T4 monotherapy. Most, have not been able to repeat the findings of the Bunevicius study. Unfortunately, the available studies have been mostly small sample sizes (only 3 studies with > 100 patients), with differing ratios of T3 and T4 that utilized variable endpoints and inhomogeneous populations. Hypothyroid patients can be a heterogeneous cohort in that some require full replacement doses whereas others less. Also, patients with an intact gland may still have endogenous T3 production while an athyreotic patient would derive all T3 from deiodination of T4.

A recent meta-analysis of seven RCTs showed no significant advantages of combination therapy on quality of life parameters. There was also no significant benefit of combination therapy on fatigue, weight or serum lipids. [19]

Seven studies investigated patient preference. Interestingly, despite lack of objective differences by way of questionnaires, more people preferred combination therapy than monotherapy. This data has been utilized by both sides of the argument! In the six crossover studies, 48% of patients preferred combination therapy vs 25% preferring monotherapy. Someone arguing against the use of combination therapy might add in the 27% of individuals that had no preference. There, it's 52 to 48. All settled, right?!!

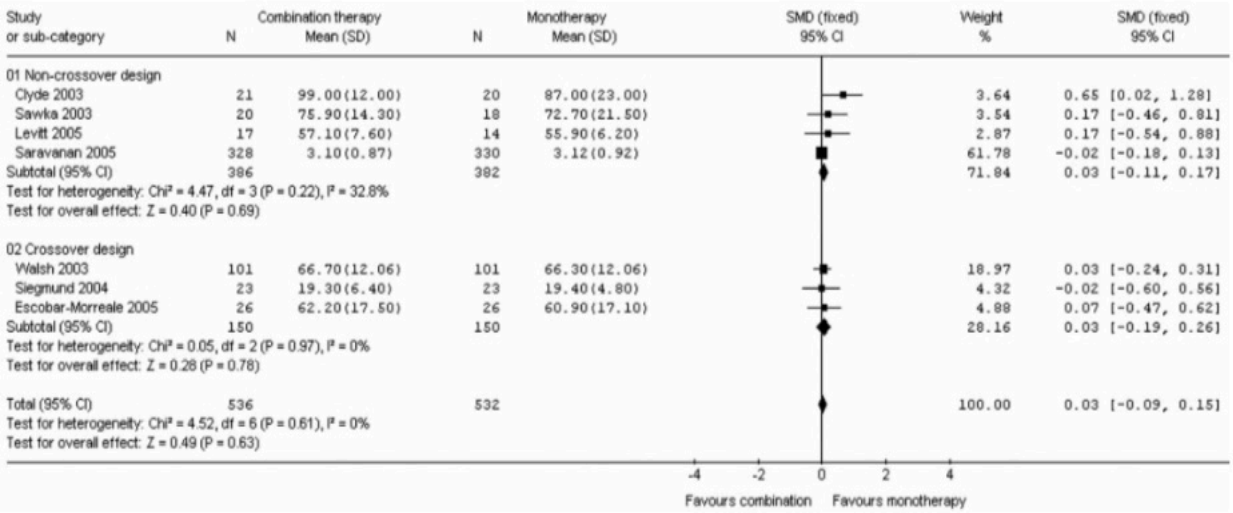


FIG. 3. The effect of the combination therapy *vs.* monotherapy on quality of life.

Grozinski-Glasberg J Clin Endocrinol Metab 2006

Another common argument in favor of combination therapy has been that some individuals may not convert T4 to T3 as readily as others. A search for polymorphisms in the DiO2 gene that might account for lower quality of life scores was conducted by Panicker et al. [9] A statistically significant association was identified in one single nucleotide polymorphism (SNP), Thr92Ala. The investigators utilized the largest combination trial to date, the Weston T3/T4 trial with a study population of 697 participants.[20] Subjects homozygous for the minor allele scored significantly lower quality of life measures at baseline, and responded more favorably to combination therapy at three and twelve-month time points relative to the wild types and heterozygotes. Interestingly, there were no significant differences in TSH, free T4 and free T3 levels related to genotype. The SNP occurs in the region of the enzyme which is ubiquitinated, a potential explanation for these differences.

How to convert to synthetic T3/T4 combination from levothyroxine:

Both the American and European Thyroid Associations state that in patients with persistent "hypothyroid" symptoms despite normal blood work, T3/T4 combination could be initiated on an "experimental basis." [1, 21]

The ETA guidelines give more detail as to how one might accomplish this experiment. They provide 4 different "recipes" for determining optimum T3 and T4 doses when converting from a single daily dose of LT4. The challenge with the mathematical equations is that LT3 is only available in 5, 25 and 50 mcg tablets. These pills are very small and a challenge to split. The purpose for these calculations is to mimic normal human T4/T3 ratios (~14:1).

LT4 Dose:	**100 mcg**	**125 mcg**	**150 mcg**	**200 mcg**
LT3 Dose	5 mcg	5 mcg – 7.5 mcg	7.5 mcg	10 mcg
LT4 Dose	88 mcg	100 mcg	125 mcg	175 mcg
LT4:LT3 Ratio	17.6: 1	20:1 – 13.3:1	16.6:1	17.5: 1

Adapted from Wiersinga et al Eur J Endocrinol 2012

The above is a reference chart aimed to try to simplify the process of conversion.

Desiccated pork thyroid vs LT4 monotherapy:

Despite much interest by patient groups and social media, there has only been one published head to head trial of desiccated pork thyroid (DTE) and levothyroxine in the treatment of hypothyroidism. Hoang et al conducted a randomized double-blind crossover study using desiccated porcine thyroid product vs levothyroxine. Seventy patients stable on LT4 for 6 months were enrolled and randomized to desiccated porcine thyroid (Armour®) vs levothyroxine (Synthroid®) for 16 weeks then crossed over to the opposite treatment. At the conclusion, there were no differences in thyroid symptoms or neurocognitive measurements. While on the DTE, patients lost 3 lbs. on average. Like the T3/T4 combination trials above, 49% preferred the DTE therapy vs 19% who preferred LT4. The rest, of course, had no preference. [22]

Risk of overtreatment:

Overtreatment of patients with thyroid hormone has well-documented adverse effects on the cardiovascular system and bone health, specifically atrial fibrillation and osteoporosis. TSH levels <0.1 mIU/L in patients on levothyroxine is associated with a four-fold increased risk of atrial fibrillation. The risk of osteoporosis in postmenopausal women is also substantially increased particularly when TSH values are < 0.1 mIU/L. Whether lesser levels of TSH suppression are significant cardiovascular or skeletal risk factors remains uncertain. Nevertheless, providers must exercise caution in avoiding overtreatment with thyroid hormone, particularly in the elderly. [1]

Effect of thyroid hormone replacement on weight:

An important public service announcement is in order here: *Plain and simple, thyroid hormone replacement does not cause weight loss.* Many patients expect, largely due to the iniquities of social media, their weight to be dramatically reduced once they are treated for hypothyroidism. Further, many believe despite normal thyroid hormone levels, their weight gain is somehow due to hypothyroidism. If their provider would simply increase the dose of their thyroid hormone replacement (DTE, T4 or T3/T4) they would find it easier to lose weight. Walsh et al conducted a cross-over study of 56 hypothyroid patients with 8 week periods achieving three different target TSH levels (2.8, 1 and 0.3 mIU/L). There was no change in weight at any level of TSH despite increased T4 and T3 levels at each decrement of TSH.[15]

Providers should also observe the Walsh and Hoang studies that showed no meaningful reduction in weight with escalating doses of thyroid hormone or whether the replacement consisted of DTE or synthetic human thyroid hormone. The risk of cardiovascular and skeletal complications with overtreatment should outweigh any attempt to promote weight loss via thyroid hormone supplementation.[15, 22]

Back to our Patient:

To recap, we have a 48-year-old woman who has had a total thyroidectomy. She has a normal TSH of 2.2 mIU/L and normal Free T4 of 1.3 ng/dL on LT4 112 mcg daily. She complains of several symptoms that can be seen in hypothyroidism yet she is euthyroid based on her labs. The initial approach to this patient should include a thorough history (including lifestyle) and physical examination to exclude non-thyroidal etiologies for her symptoms. A careful review of

concomitant medications, sleep habits and mental health should occur. Additional focused laboratories or polysomnography may be required. Treatment of possible non-thyroidal sources of the patient's symptoms should take priority.

If no other etiology is identified or treatment of comorbidities is completed without symptom resolution, perform an "experiment" of combination synthetic T3/T4 for 3-6 months. This would be preferable to desiccated pork thyroid for product consistency and such that a human T3/T4 ratio could be achieved.

Conclusions:

Hypothyroidism is a common clinical scenario, affecting up to 15-20% of the adult US population, particularly women. Practitioners in every discipline need to have familiarity with the symptoms and the management of hypothyroidism.

In a simplistic view, thyroid hormone is an essential hormone utilized by virtually every cell type for the regulation of gene expression. The importance of thyroid hormone to normal physiology is illustrated by the stable serum levels and tight homeostatic control of thyroid hormone release.

There is no acceptable treatment for hypothyroidism apart from thyroid hormone replacement. Practitioners have several options available to accomplish this with desiccated pork thyroid and synthetic human hormones (levothyroxine and liothyronine). Any thyroid hormone must be taken in the proper fashion: empty stomach, water only (not black coffee), no other foods, vitamins or medications for at least 30 minutes. Consider that last statement underlined twice, no, three times!

Controversy lies in the ideal choice of thyroid hormone replacement regimen. Levothyroxine monotherapy (LT4) remains the treatment of choice for most hypothyroid patients. The

symptoms of “hypothyroidism” are nonspecific and those that display them with normal thyroid serum levels usually have another etiology. There may be a minority, however (possibly due to gene polymorphisms in T4 to T3 conversion) that require combination therapy. If attempted, this is best accomplished with synthetic human thyroid hormones dosed according to normal human ratios, not pig ratios.

Much more research is needed to evaluate the benefits and risks of combination T3/T4 therapy. Such investigations should be done with careful consideration of genetic polymorphisms, the underlying etiology of hypothyroidism and the measure by which improvement is measured.

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