On the Relative Ineffectiveness of TSH-Normalizing T4 Therapy

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In the treatment of primary hypothyroidism, guidelines issued by some organizations advise merely normalizing the TSH, reducing it to any value within the reference range. However, many studies show that this approach often produces little improvement in symptoms or in the risk of diseases associated with hypothyroidism. For this reason, some organizations and experts recommend titrating T4 doses to reduce the TSH to low values within the reference range. The data indicate that once-daily oral T4 therapy differs from endogenous thyroid hormone production in several ways that can cause the degree of TSH-lowering to be excessive relative to the thyroid hormone effects in most tissues. Lacking an objective test that can reliably assess thyroid hormone sufficiency in all tissues of the body with thyroid replacement, dosing must be guided not by a "normal" TSH but the free thyroid hormone levels, by physiological indicators of thyroid hormone effect, and ultimately by the patient's subjective and objective clinical response.

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Introduction

The current approach to treating primary hypothyroidism is based upon the assumption that serum TSH level and all peripheral tissues respond to once-daily oral levothyroxine (T4) and/or triiodothyronine (T3) therapy in exactly the same way that they respond to physiological T4 and T3 production by the thyroid gland. It is thus believed that primary hypothyroidism is adequately treated when the TSH is "normalized" with a given dose of oral T4. By extension, a low TSH on oral T4 therapy is believed to have the same physiological implications as a similarly low TSH caused by endogenous production. This reliance upon the TSH to guide therapy is not supported by the scientific literature. The TSH level represents the affect of oral therapy on one organ only—the anterior pituitary. Yet its secretion of TSH is affected by several factors that do not operate in other tissues. Serum free T4 (FT4) and free T3 (FT3) levels are a more direct indicator of the efficacy of oral thyroid replacement therapy. However, the practice of clinical medicine requires acknowledging the complexity of human physiology and the necessity of titrating therapy not according to a serum hormone level but according to the patient's objective and subjective response to therapy.

There already exists a tacit recognition of the relative ineffectiveness of TSH-normalizing T4 therapy. One authoritative source has called for a TSH target of less than 2.0 mU/L.(1) Other researchers have called for low TSH targets based on the need to normalize parameters such as weight gain(2) and cardiac risk factors including lipids.(3) Some prominent thyroidologists have admitted that it sometimes necessary, and does not appear harmful, to suppress the TSH with T4 therapy in some patients.(4) However, in the absence of an explanation for such a significant change in practice, and given the

persistence of official guidelines calling for merely normalizing the TSH,(5) most clinicians continue to prescribe only enough T4 to lower the TSH to within its reference range (usually <5mU/L). Believing they have thus restored "euthyroidism", they conclude that the patient's persistent symptoms are due to some other cause such as depression, chronic fatigue syndrome, or fibromyalgia. In stark contrast, some patients may be made hyperthyroid by attempts to reduce the TSH to within the reference range.(6) A rigorous clinical evaluation of treated hypothyroid patients by experienced clinicians revealed that the 95% reference range of the TSH of those who were rendered clinically euthyroid (the treatment reference range) varied from <0.1 to 19.7mU/L.(7) Such data emphasize the need for individualized clinical dosing rather than adherence to a TSH-based algorithm.

Language is a part of this problem as the broad reference ranges (RRs) are merely statistical ranges including 2 standard deviations from the mean. They encompass 95% of all persons tested; not of carefully screened populations. The RRs arbitrarily label only the highest and lowest 2.5% of the entire population as "abnormal". The RRs are inappropriately referred to as "normal" or "euthyroid" ranges, implying that they are physiological optimums as determined by clinical research. On the contrary, there is abundant evidence in the literature that lower FT4 and FT3 levels within their RRs are associated with symptoms and with various biochemical disorders, diseases, and health risks when compared to higher levels within the RRs. (8,9,10,11,12,13,14,15,16,17.18,19,20,21,22,23,24) Consider the extensive literature on the symptoms, metabolic abnormalities, and increased risk of diseases associated with subclinical primary hypothyroidism.[25,26,27,28,29] Since TSH is not a thyroid hormone, what

this body of evidence indicates is that lower FT4 and/or FT3 levels within the RR are harmful compared with higher levels within the RRs.

The evidence against the practice of just normalizing the TSH with T4 therapy in all patients is herein presented and an explanation for its frequent ineffectiveness is offered. Concerns about the safety of partial or complete TSH-suppression with T4 therapy are discussed.

TSH-Normalizing T4 Monotherapy Often Does not Restore T3 levels or Euthyroidism

If TSH-normalizing T4 therapy constituted adequate treatment, then a majority of studies would demonstrate that it produces biochemical and clinical indices identical to those of healthy controls. However, a large study revealed that patients on thyroxine with a "normal" TSH (0.1-6.0 mU/L) displayed significant impairment in psychological well being compared to controls of similar age and sex.(30) In another study, hypothyroid patients on T4 had decrements in health status, psychological function, working memory, and motor learning compared to euthyroid controls.(31) Treatment of hypothyroid and subclinical hypothyroid patients with an avg. of 103 ± 27.5mcg/day of T4 lowered the TSH to 1.9±1.5mU/L but produced lower T3 values, higher hypothyroid index scores, and higher BMIs than in the euthyroid controls.(9) Patients with treated primary hypothyroidism were found to have an increased risk of cardiovascular morbidity.(32) Patients who receive TSH-normalizing T4 therapy after thyroid ablation gain weight (avg. 4kg), whereas those who receive TSH-suppressive therapy do not.(33) Patients on long-term TSH-normalizing T4 therapy were found to have 21% greater fat mass and

lower T3 levels than controls.(34) Patients on TSH-normalizing doses of T4 or T4 plus T3 had much worse scores than euthyroid controls on various measures of mentation and mood.(35)

The serum FT3 does reflect the amount of T4-to-T3 conversion throughout the body and the exposure of all tissues to the active thyroid hormone via the serum. A clue to the ineffectiveness of T4 therapy is the fact that it in low doses, it usually lowers the FT3 level, and in high doses often fails to raise the serum FT3 to the midpoint of the 95% population RR. TSH-normalizing T4 therapy produces abnormally low T3/T4 ratios and typically does not restore serum T3 concentrations to those of controls.(36,37) T4 is a prohormone, although it may have some direct actions of which we are not aware. T3 has a 10-to-20 fold greater affinity for the thyroid hormone nuclear receptor.(38,39) The liver and kidneys, and possibly other organs also are dependent upon serum T3 rather than T4-to-T3 conversion. So it is sensible to presume, until proven otherwise, that restoring euthyroidism requires maintaining optimal T3 levels both in the serum and within in all tissues. This goal is not routinely achieved with TSH-normalizing T4 therapy. On T4 therapy, T4 levels are significantly higher than controls while T3 levels are lower.(40) The effects of T4 and T3 therapy on various tissues were revealed in an elegant series of experiments performed on rats. The investigators determined both serum and tissue levels of T4 and T3 during continuous infusions of various combinations of the two hormones. A T3-only infusion failed to restore T3 levels in all tissues—illustrating the necessity of T4 and peripheral T4-to-T3 conversion.(41) A continuous T4-only infusion also failed to restore serum and tissue T3 levels to those of controls until T4 levels were raised into the supraphysiological range and TSH was suppressed.(42) The addition of T3 to a T4

infusion in the same ratio produced by the rat's thyroid gland (1:6) allowed a normalization of both serum and tissue levels of both hormones without suppressing the TSH.(43) The human thyroid produces T3 and T4 in a lower 1:14 ratio,(44) but otherwise the findings should apply to our species.

Patients with untreated primary hypothyroidism were much less symptomatic if their FT3 was within the RR rather than below the range.(45) In patients with subclinical hypothyroidism, a subreplacement T4 dose of 85mcg (range 50-125) lowered the TSH from 12.8 to 3.1mU/L, raised the FT4 from low-RR to just above mid-RR, and further lowered the total T3, which before therapy was already below the mid-point of the RR.(46) In a study of TSH-suppressive T4 therapy (avg. TSH 0.03mU/L), the FT4 was 66% higher but the total T3 levels were identical to those of healthy controls whose average TSH was 1.36mU/L. These patients had no symptoms of hyperthyroidism despite the sub-RR TSH.(47) A group of patients treated with T4 and a group of untreated hypothyroid patients had identical 24-hour urine FT3 levels.(48) Patients with subclinical hypothyroidism had elevated lipid levels compared with controls. The difference was not eliminated until the patients were treated with enough T4 to reduce the TSH to below the RR.(49) In a study of elderly hypothyroid patients with coronary artery disease, it was found that a daily dose of 100mcg T4 or less allowed progression of coronary atherosclerosis in 6 of 6 patients, while doses of 150mcg or higher stopped progression in 5 of 6 patients.(50) Again, the explanation can be found in the FT3 levels. Serum FT3 levels in the lower tertile of the RR have been associated with a 50% greater risk of severe atherosclerosis than those in the highest tertile.(51)

Untreated patients with subclinical hypothyroidism had TSH levels of 3.5–10mU/L and FT4 and FT3 levels slightly lower than healthy controls. Even relatively aggressive T4 therapy that lowered the TSH to 1.5mU/L (avg. dose 100mcg/day) did not produce a higher FT3 level than in the placebo group of similar patients.(52) Given that there was no improvement in the treatment group compared to placebo, the authors concluded that there is no cognitive impairment in subclinical hypothyroidism. An alternative conclusion is that TSH-normalizing T4 therapy does not provide sufficient thyroid replacement to produce physiological euthyroidism, and that the failure to raise the T3 level may be significant marker of under-replacement.

Increasing the dose of T4 given to hypothyroid patients on TSH-normalizing T4 therapy suppressed their TSH levels from mid-RR to low-RR but had no effect at all on patient's symptoms and did not cause any symptoms of overdosage. T3 levels were not reported. The authors concluded that merely normalizing the TSH to any point within the RR is sufficient.(53) An alternative conclusion is that TSH-normalizing T4 therapy is equally ineffective at any TSH level within the RR. Indeed, a careful study of T4 dosing and TSH responses to TRH found that patients felt better when their TSH was suppressed below the RR, their FT4 and FT3 were in the upper half of their RRs, and their T4 dose was 50mcg greater than that required to normalize their TSH response to TRH.(54) Some claim that patients who feel better on TSH-suppressive doses of T4 are experience an thyrotoxic euphoria. However, there is abundant evidence from the literature on endogenous clinical and subclinical hyperthyroidism indicated that people do not feel better when they are even mildly hyperthyroid.

The inability of TSH-normalizing T4 therapy to raise FT3 levels or produce laboratory or clinical euthyroidism has led some investigators to recommend adjusting T4 therapy based upon the T3 level.(55,56) From the data in the studies quoted above, one can conclude that the dose of T4 needed to raise the FT3 of patients with hypothyroidism or subclinical hypothyroidism to at or above those of controls is generally greater than 100mcg/d and generally requires suppression of the TSH to below its RR (to <0.5mU/L). Since merely normalizing the TSH with T4 constitutes insufficient treatment in many if not most patients, we must reinterpret every study, review paper, textbook, and clinical practice utilized the assumption that TSH-normalizing T4 therapy produces euthyroidism.

Why TSH-Normalizing T4 Therapy is Often Ineffective

The hypothalamic-pituitary (HP) feedback control system evolved to react to thyroid hormones being produced continuously by the thyroid gland, not to unphysiological once-daily oral T4 therapy. The bulk of the evidence indicates that the HP system is excessively suppressed by once-daily T4 therapy. The following phenomena are sufficient to explain the ineffectiveness of oral T4 therapy that is titrated to merely normalize the TSH:

1. Compared to continuous thyroidal T4 and T3 production, the temporary peak levels produced by once-daily oral therapy cause an excessive suppression of HP responsiveness that lasts more than 24 hours.
2. Higher levels or activity of the deiodinase D2 in the HP system convert T4 to T3 more efficiently there than in other tissues, producing excessive suppression of TSH secretion by peak T4 levels during T4-only oral therapy.

3. The lower TSH on T4 therapy reduces T3 production by the thyroid gland.
4. The lower TSH on T4 therapy reduces T4 to T3 conversion throughout the body.
5. The relatively high FT4 level required to compensate for #3 and #4 directly suppresses D2 deiodinase activity in the periphery, inhibiting T4 to T3 conversion within various tissues.
6. With aging, the HP sensitivity and TSH secretion in response to low FT4 levels are reduced. This should also cause excessive TSH suppression with age at any given T4 dose.
7. T4 can be over-converted to reverse T3, instead of T3, thereby reducing the effectiveness of T4-only replacement therapy.

Let us consider these points in depth. Endogenous T4 and T3 production are essentially constant over 24hrs, whereas oral dosing delivers the entire day's hormone into the circulation within a couple hours. With once-daily T4 therapy, studies have shown that peak FT4 levels are 13% to 31% higher than trough levels.(57,58,) These peaks cause associated peaks in HP T3 levels due to T4 to T3 conversion (see below). Does such a T3 spike in the pituitary produce an excessive and prolonged suppression of TSH production? In rats, rapid T3 infusions suppressed the TSH levels for 7 hours, whereas rapid infusions of T4 suppressed the TSH for over 22 hours.(59) During once-daily oral T3 therapy in humans, T3 levels varied between peaks of 350ng/dL 2 hrs. post dose and 100ng/dL after 24 hr. (RR: 70-150ng/dL), yet the TSH did not vary significantly over the same 24 hr. period. Likewise, no variation was seen in the TSH with once-daily oral T4.(60) The data in human oral dosing indicate that either the TSH is insensitive to peak levels, or that it is sensitive and is suppressed by the peak levels for the following 20

hours or so. The latter is the better assumption based upon the rat data mentioned above and on studies in human beings.

Why would the TSH remained suppressed long after a temporary spike in thyroid hormone levels? Humans, like other omnivores and carnivores, have always ingested thyroid hormone, often in massive doses, by eating the thyroid glands, livers, and kidneys of other animals. It is reasonable to expect that the HP system and thyroid metabolism would have adapted to cope with this occasional excess thyroid hormone ingestion in order to avoid hyperthyroidism and its increased caloric requirements.(61)

A second cause of excessive TSH suppression on T4 therapy is the fact that the HP axis is more sensitive to circulating T4 than to T3. This was illustrated in a study of T4 and T3 monotherapies in patients with severe primary hypothyroidism. Once daily therapy with 200mcg T4 produced average 24hr. T4 levels around 9mcg/dL, well within the RR (5-11mcg/dL); yet lowered the basal TSH of patients from 45 to 4.3mU/L. On the contrary, a 50mcg daily dose of T3 (with a similar clinical effect) produced average 24hr. T3 levels of 186ng/dL, well above the upper RR limit of 150ng/dL, yet this supraphysiological T3 level only lowered the TSH from 77mU/L to only 11.8 mU/L.(62) Another study similarly found that T3 monotherapy normalizes many important measures of thyroid sufficiency at lower doses than are needed to normalize the TSH.(63) T4 has the dominant effect on TSH secretion because the pituitary and brain rapidly convert T4 to T3, whereas the rest of the body is more dependent on T3 levels.(64) The best explanation of this effect is that there are higher levels or activity of the deiodinase D2 in the central nervous system and pituitary gland than in other tissues.So the HP system converts T4 to T3 more efficiently than most other tissues in the body. This higher

conversion rate causes oral T4 therapy to suppress the TSH more efficiently than it restores euthyroidism in other tissues. If the opposite were true, if D2 activity in the pituitary were low relative to other tissues, then normalization of TSH production would only be achieved when circulating T3 levels had returned to control levels or higher,(65) and we have seen that this is not the case. In hypothyroid patients serum levels of T3, T4 and FT4 did not change after a single ingestion of 50mcg T4, while the TSH level dropped by 25 to 50%.(66) The heart appears to be another site of very active T4-to-T3 conversion as systolic time intervals are associated with T4 and TSH levels but not T3 levels.(67) Highly active T4-to-T3 conversion in the pituitary helps to explain why oral T4 therapy suppresses TSH output but fails to raise the serum FT3 levels or restore whole-body euthyroidism..

This excessive suppression of TSH output by short and long-term T4 therapy lowers T3 levels by two mechanisms: it reduces endogenous thyroidal T3 secretion and it suppresses peripheral T4-to-T3 conversion. The role of TSH in the latter case was the subject of two papers. The first documented that there are higher T3/T4 ratios in primary hypothyroidism (high TSH) compared to the lower T3/T4 ratios seen in central hypothyroidism (low TSH). In the patients studied, serum T3 values in primary hypothyroidism were double those in central hypothyroidism.(68) Since approximately 75% of T3 in the serum is produced peripherally from T4-to-T3 conversion(69), and the T4 levels were comparable in the primary and central hypothyroidism patients, this positive correlation between TSH and T3 strongly suggests causation. To further investigate this hypothesis, a study was performed on thyroidectomized dogs receiving T4 replacement. TSH-injections raised serum T3 levels to a peak at 12 hours and

simultaneously lowered T4 levels.(70) This was a direct demonstration that TSH stimulates T4 to T3 conversion in a mammal. In hypothyroid infants 6 hours after T4 administration, serum T4 levels were elevated and the TSH and serum T3 were reduced.(71) As most T3 in the serum results from peripheral T4-to-T3 conversion, this result implies that the lower TSH levels reduced T4-to-T3 conversion. Patients with suprasellar lesions have little or no TSH production. For their resulting hypothalamic obesity, supraphysiological T3 supplementation has been found to be superior to T4.(72) This effect is understandable if the absence of TSH reduces peripheral T4-to-T3 conversion to such an extent as to render T4 monotherapy less effective.

It also appears that higher FT4 levels with T4-only therapy directly suppress peripheral T4-to-T3 conversion, an effect that is independent of TSH. D2 in skeletal muscle is the source of ~72% of peripheral T3 production.(73) D2 is suppressed by higher FT4 levels and induced by lower levels, whereas D1 in the liver and kidneys is induced by higher and suppressed by lower FT4 levels.(74) This would explain why increases in already supraphysiological levels of T4 do not produce proportionate increases in FT3 levels.([75])

Another problem in using the TSH range as a therapeutic target is the possibility that the patient has some degree of HP dysfunction. The clinician frequently encounters symptomatic patients with TSH levels in the lower third of the RR accompanied by FT4 and/or FT3 levels that are also in the lower third of their ranges. This combination implies a subclinical secondary hypothyroidism. Any T4 or T3 therapy will easily suppress the TSH below its RR. Also, most people diagnosed with subclinical or overt hypothyroidism are middle-aged adults. It has been shown that the HP response to a given low T4 level declines markedly with age, beginning in the

third decade of life (see Table).(76) By extension, the aging HP system is probably less responsive to "low-normal" levels also. Therefore we should expect that with increasing age, TSH secretion will be more easily suppressed with T4 therapy, potentially resulting in undertreatment if a "normal" TSH is the only guide to therapy.

In many patients with primary hypothyroidism or subclinical hypothyroidism, the TSH can be "normalized" (lowered to some point within the RR) with doses of only 25 to 50mcg T4, well below an average full replacement dose for a 70kg person of around 145mgc/day.(77) Such sub-replacement T4 doses run the risk of reducing endogenous T3 production and T4-to-T3 conversion by known mechanisms. There are no studies demonstrating the restoration of all parameters of euthyroidism with such low doses, indeed, there are no studies demonstrating the restoration of complete euthyroidism at any TSH-normalizing T4 dose.

With oral T4 therapy, the combination of the effects of peak T4 levels, increased D2 activity in the pituitary relative to other tissues, reduced TSH, reduced thyroidal T3 production, reduced peripheral T4-to-T3 conversion, and reduced HP function together are sufficient explanation for why T4 therapy that merely normalizes the TSH often does not restore whole-body euthyroidism.

Overall Conclusions based on the T3/T4 Substitution Studies

Most editorials on the implications of the many T3/T4 substitution studies (78,79,80,81,82,83,84,85,86,87,88) conclude that there's no benefit to substituting T3 for some of the T4 dose and no reason to change existing T4-only treatment guidelines. However, a careful review of the extant studies on the use of combinations of T4 and T3

shows that the addition of T3 offers distinct advantages. (Analysis of individual studies available upon request) The primary flaw in most of the studies was that the TSH was kept within the reference range; dosing was not optimized according to clinical response. Thus all the objections stated above to merely normalizing the TSH apply. T3/T4 therapy generally produced a greater improvement in hypothyroid symptoms scales at any given TSH level. At any given TSH level, and even when the TSH rose to some degree on T3/T4 combinations, the T3/T4 combination therapy produced a better subjective sense of well-being as indicated by the patient preference for combination therapy. Adding T3 to the current T4 dose often improved mood. This finding is supported by numerous studies of T3 in depression.(89,90,91,92,93,94) The studies did show that patients on TSH-normalizing doses of T4 frequently have much higher symptoms scores than controls, as discussed previously.

Arbitrary substitutions of varying amounts of T3 for T4 without TSH-based adjustment sometimes produced under- and over-replacement in a significant number of patients, causing negative symptoms. The TSH level was reliably affected by T3 substitution—if the TSH rose with combination therapy it generally indicated reduced overall thyroid hormone effect. TSH levels that were below the RR often yielded optimal clinical effects with T3/T4 combination therapy just as with T4 therapy. Some patients, however, did not tolerate low or undetectable TSH levels on either kind of therapy.

The studies did not support the contentions that T3 therapy is dangerous or causes problems due to the fluctuations in T3 levels on oral replacement. No deleterious effects were noted with T3 substitution—other than those related to general thyroid dose increases or over-replacement. No studies supported the idea that fluctuations in T3 from

once or twice daily oral therapy have negative effects. The studies supported the hypothesis that the addition of T3 to T4 therapy can have benefits for many patients—and perhaps for all with careful individualization of doses of both hormones. Most importantly, the studies are a clear illustration of the fact that there is no substitute for individual adjustment of either T4 or T3/T4 combinations to achieve optimal clinical effects. Since the thyroid makes T3 and T4, and in the light of these studies, combination replacement should be considered superior to unphysiological T4-only therapy until proven otherwise.

Conclusion

Oral T4 therapy differs in several significant ways from endogenous thyroid gland hormone production. The hypothalamic-pituitary axis does not respond to oral thyroid hormone replacement in the same way that it does to endogenous production. The TSH is overly suppressed by oral T4 therapy and tissue and serum levels of T3 are not restored. There is no evidence of harm with physician-monitored TSH-suppressive T4 therapy. Therefore T4 replacement therapy cannot be guided by the non-supplemented TSH reference range. The evidence presented here indicates that adequate thyroid hormone replacement with T4 therapy often requires some degree of TSH suppression. Therefore a new approach to the monitoring of thyroid replacement therapy is required; one based upon optimal serum levels of both FT4 and FT3, upon physiological parameters, and most importantly, upon the clinical response of the patient.

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