The Diagnosis and Treatment of Hypothyroidism:  
A Patient’s Perspective

Authors: Mel Rowe, Rudolf Hoermann, Peter Warmingham

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Correspondence to peter@warmingham.plus.com

The authors have teamed up in an attempt to bring the patient and doctor perspective together. Their brief biographies can be found at the end of this article.

Abstract

Hypothyroidism is caused by inadequate supply of, or response to, thyroid hormones throughout the body. Hypothyroidism is the number one endocrine system problem and it affects hundreds of millions around the world. People with hypothyroidism typically suffer from a lack of energy and many other symptoms including cold intolerance, dry skin, weight gain, constipation, slow movement/speech, low sex drive, and dry, thinning or coarse hair. When the hypothyroid condition is not adequately diagnosed and treated, more severe problems such as high cholesterol, cardiac issues, obesity, joint and muscle pain, gradual hearing loss, reproductive system disorders, depression, periodontal problems, carpal tunnel syndrome or sleep apnoea will eventually appear; in extreme cases it may even result in coma or death.

Due to the non-specific nature of some symptoms, and the tendency of patients to downplay them, the possibility of hypothyroidism is often overlooked by both patients and doctors. When sufficient symptoms are present to warrant further investigation doctors will, in accordance with existing guidelines \(^1\), \(^2\) order a test for Thyroid Stimulating Hormone (TSH), the pituitary hormone that stimulates the output of hormone from the thyroid gland. If the TSH result is within the reference range, hypothyroidism is usually discounted. If TSH exceeds the range, and the follow-up test for the thyroid hormone Free T4 (FT4) is within the range, then hypothyroidism is also usually discounted. Patients are told that their test results are ‘normal’ and that their symptoms must be due to something else. Thyroid hormone Free T3 (FT3), which is significantly more biologically active than FT4, is largely ignored. Thus clinical evaluation has been largely superseded by TSH and FT4 tests, which will be shown later to be inadequate. For these reasons, the extent of undiagnosed and/or inadequately treated hypothyroidism is huge and frequently unrecognised. This is reflected in the American Thyroid Association’s (ATA) estimate that 20 million Americans have some form of thyroid disease and that up to 60% are unaware of their condition \(^3\). Surveys have also shown that a majority of thyroid patients are not satisfied with their treatment. Current treatment protocol with levothyroxine does not restore their quality of life to a level observed in the normal population according to a large recent study \(^4\).

In addition to the problems discussed above, patients have not had easy access to the basic information necessary to realise that their symptoms are not normal, and to understand what
testing and evaluation should be done. Doctors are not adequately informed on the benefit of combining clinical evaluation with biochemical tests. These issues also adversely affect communication and cooperation between patients and doctors. Finally, although there are exhaustive scientific studies on all facets of hypothyroidism, no concise, comprehensive information for improved diagnosis and treatment, supported with scientific evidence, has been available to either group.

The intent of this paper is to meet the needs of both parties with the following suggestions for more effective diagnosis and treatment:

1. The current diagnostic protocol based on TSH followed by FT4 is ineffective in reliably diagnosing a large proportion of hypothyroid patients and should be amended.

2. Diagnosis must include a review of the full medical history of the patient.

3. Diagnosis should include an evaluation of the patient’s signs and symptoms, since they reflect both thyroid status and the patient’s concerns.

4. Symptomatic testing and case finding should include FT4, FT3, arguably reverse T3 (RT3), TSH, TPOab, TG ab (only if TPO ab is negative and TSH is high), cortisol, vitamin D, vitamin B12 and ferritin. Interpretation of the test results is discussed in the Recommended Diagnostic and Treatment Procedures section.

5. If signs and symptoms are present, an ultrasound examination of the thyroid gland should be carried out, irrespective of the severity of biochemical abnormalities.

6. If hypothyroidism is diagnosed, the patient’s FT4 and FT3 levels should be increased enough to eliminate signs/symptoms of hypothyroidism without creating signs/symptoms of hyperthyroidism. TSH should not be relied on to determine the medication dosage.

The above abstract should provide general information adequate to encourage a potential hypothyroid patient to discuss the above suggestions with their doctor. If agreement on these suggestions requires further review and discussion, the full paper provides a thorough discussion and extensive scientific evidence adequate to answer related questions from both doctors and inquisitive patients who want to delve deeper. Note that this does not constitute medical advice nor is it meant to provide specific medical recommendations.
Extent and Severity of Hypothyroidism

Hypothyroidism occurs at a much higher frequency than widely recognised. The National Health and Nutrition Examination Survey (NHANES III) survey concluded from their data base of 17,353 patients that 9.2% had “clinically significant thyroid disease” based on biochemical criteria \(^5\). That number included both hypothyroid and hyperthyroid patients; however hyperthyroid patients frequently end up hypothyroid after ablative therapy. In addition, in the large scale Colorado Thyroid Disease Study 9.5% of results exceeded the upper range limit for TSH \(^4\). Within those percentages of biochemically hypothyroid patients there will be some that are not clinically hypothyroid. By the same token, some of the people having TSH within range will be clinically hypothyroid.

Further evidence of the magnitude of thyroid problems comes from an ATA estimate that “20 million Americans have some form of thyroid disease” and that “up to 60% are unaware of their condition” \(^3\). It was also noted that “women are 5 to 8 times more likely than men to have thyroid problems” \(^3\).

When these estimates are considered together with two surveys showing that over 50% and 75% of patients are not satisfied with their treatment \(^15,16\) it is easy to see that hypothyroidism is a huge problem, with serious implications. In addition to literally hundreds of hypothyroid symptoms that cause untold misery, inadequately diagnosed/treated hypothyroidism can lead to more serious problems such as high cholesterol, cardiac issues, depression, chronic fatigue, obesity, carpal tunnel syndrome, joint and muscle pain/aches, gradual hearing loss, reproductive system disorders, periodontal disease, coma and in extreme cases even death.

Review of Current Diagnostic Practices

The all important question is how to reliably diagnose a patient as either hypothyroid, euthyroid, or hyperthyroid. Patients usually go to their doctors because of symptoms: Symptoms can be specific as well as non-specific; however, there are symptoms that occur far more frequently with hypothyroidism, and they have an important role in diagnosis. Unfortunately, published guidelines \(^1,2\) give clear direction that consideration of symptoms has been largely superseded by supposedly sensitive thyroid function tests. So patients are diagnosed predominantly by TSH and, if needed, a FT4 test.

This practice has been found to be inadequate through the experience of many millions of hypothyroid patients, extensive scientific evidence, and evaluation by many thyroid experts around the world for the following basic reasons (note that more detailed information from supporting scientific evidence is included in the References section):

1. The output from a normal thyroid gland is essentially a result of the TSH 'signal' from the pituitary in response to a Thyrotropin Releasing Hormone (TRH) 'signal' from the hypothalamus, and in response to serum FT4 and FT3 levels: in other words a control loop. The hypothalamic-pituitary-thyroid feedback loop appears to be much more complex than previously thought with important implications for diagnosis and treatment of thyroid disease \(^17\). The actual response from each of these areas will vary widely from
The Diagnosis and Treatment of Hypothyroidism

one individual to another. In effect, each person has their own thyroid process parameters with which they feel normal.

Several scientific studies have confirmed that "normal" ranges based on specific thyroid test results of individuals were approximately half those of population based reference ranges. The latter are reported by laboratories. This applies to all thyroid tests 18-26. So, trying to identify abnormality by comparing an individual's TSH (or FT4, FT3) test result to the much wider reference range derived from a group of patients can be very misleading 18-26.

Also, the current upper range limit for TSH is usually around 4 mIU/L, although it varies among different laboratories and in its interpretation by doctors. The upper limit has been purposely set even higher than would be expected from the normal distribution, in order to avoid excessive false positive diagnoses, and instead may result in excessive false negative diagnoses 6. In addition, when TSH is the sole diagnostic, treatment is usually withheld unless the TSH level is above 10 mIU/L, which is well above the reference range.

No matter what conventional reference range is used, TSH is not a reliable marker of an individual’s euthyroid status 5-12, 18-26.

2. Group studies have shown that other than in overt hypothyroidism, TSH does not correlate well with the biologically active thyroid hormones, FT4 and FT3 30, nor with tissue thyroid effects and the resulting symptoms, which are the patient’s prime concern 5-12.

3. When a serum TSH test exceeds the laboratory reference range, further evaluation with an FT4 test follows. If the FT4 test falls within its reference range (which has somehow become accepted as 'normal'), this is classified as subclinical thyroid dysfunction and treatment is usually withheld unless TSH exceeds 10 mIU/L. Thus the validity of the FT4 reference range is a major concern 27-31, along with the questionable reference range for TSH, as previously reviewed in 1 above.

Unfortunately the ranges for FT4 (and also FT3) are not well standardised among different test machine manufacturers, generally validated, or based on large databases of healthy adults with no thyroid pathology 32-34. Instead those ranges are locally established from test data available at any given laboratory, excluding only data from patients assumed to have thyroid issues based on the flawed TSH range. Clinically hypothyroid patients with TSH within the reference range, people with hidden pathologies such as undiagnosed central hypothyroidism or autoimmune disease, and patients taking thyroid medication can all be included in the database.

So using the flawed concept of a population based TSH range to diagnose thyroid dysfunction even contaminates ranges established for FT4 and FT3 and further adversely affects diagnosis. In addition, as previously discussed, trying to identify abnormality by comparing individual FT4/FT3 test results to group reference ranges can be misleading 6, 18-26.
4. Hypothyroidism results from diminished body functions due to inadequate metabolism of thyroid hormone at the tissue level throughout the body. However, as shown in Fig. 1, hypothyroidism is not only caused by an underactive thyroid gland resulting from autoimmune system disorder (primary hypothyroidism due to Hashimoto's Thyroiditis) or prior ablative therapy, but can also be the result of the following additional causes not readily identified by routine diagnostic practice.

a) Dysfunction of the hypothalamus/pituitary system resulting in inadequate stimulation of the thyroid gland by TSH (central hypothyroidism). Note also that central hypothyroidism is frequently overlooked by relying solely on TSH screening.

b) Inadequate conversion of the prohormone T4 to the biologically active T3 (conversion failure).

c) Excess conversion of T4 to Reverse T3 (RT3), a biologically inactive 'mirror image' version of T3. Thus, "RT3 is an excellent marker for reduced cellular T4 and T3 levels not detected by TSH or serum T4 and T3 levels" 35. There is also evidence of RT3 binding to membrane receptors 36,37 and producing hypo-metabolic effects 38.

d) A tendency for FT3, the biologically active thyroid hormone, to diminish with age, sometimes resulting in hypothyroid symptoms that are frequently overlooked as just being age related 39. Another source concluded that, "in male subjects, negative relationships were observed between aging and serum concentration 40.

e) Deficiencies in variables which affect transport of serum thyroid hormone into the organs and cells of the body, so that serum thyroid levels sometimes do not adequately reflect tissue thyroid levels 35,41.

f) Deficiencies in the confounding variables shown in Fig. 1 that affect how available thyroid hormone is metabolised at the cellular level (tissue thyroid effects).

g) Decreased end organ responsiveness or impaired sensitivity to thyroid hormone, mostly due to genetic syndromes of thyroid hormone resistance (THR) where TSH is not suppressed despite elevated circulating concentrations of thyroid hormones 42.

In summary, current diagnostic practice predominantly follows published guidelines 1,2 that prescribe laboratory tests for TSH and FT4 in which the results are compared to population based reference ranges. Although not usually recognised and applied, the guidelines also state,

“Treatment decisions must be based on the independent judgment of health care providers and each patient's individual circumstances. A guideline is not intended to take the place of physician judgment in diagnosing and treatment of particular patients”.

In another section it is stated,
“We encourage medical professionals to use this information in conjunction with their best clinical judgment”.

Unfortunately in most cases clinical evaluation of the individual is ignored in favour of biochemical evaluation with TSH and FT4 tests compared to group reference ranges (with all the inherent flaws previously discussed). This is a violation of both common sense and basic mathematical principles. If diagnosis and treatment required no further knowledge about the patient, or good judgment, it could be done more effectively by a computer.

Coupled with the tendency of thyroid patients to downplay their symptoms, these flawed diagnostic procedures have resulted in an enormous number of misdiagnosed/ inadequately treated hypothyroid patients. Worse still, untreated hypothyroidism will eventually cause even more serious problems, as previously mentioned. So from the perspective of a patient we need to recognise potential hypothyroid symptoms and better communicate our concerns to doctors. Doctors in turn need to recognise that the currently prevalent diagnostic practice, without knowledge of patient history and clinical examination, has severe limitations, and that there is a better approach that is supported by scientific evidence.

To that end Figure 1 is intended to clearly show the major processes and confounding variables that affect the desired outcome: adequate tissue thyroid effects. Except in cases of markedly elevated levels of TSH, the interactions of those intervening processes and variables prevent good correlation between TSH/FT4 and tissue thyroid effect, thus negating their use as primary diagnostic tools. This necessitates that we select and evaluate other surrogate measures that, in conjunction with the knowledge and clinical judgment of the doctor, will result in more effective diagnoses.
1. Processes and Variables Affecting Tissue Thyroid Effects

**Confounding Variables**
- Iodine; Intra and Inter Individual Variability; Ageing
- Progesterone/Oestrogen; TBG
- Ferritin; Selenium; Zinc; TSH; Iodine; See Reference 84
- Vitamin D; Cortisol; TSH; THR

**Metrics**
- TBG; TRH; TSH; Iodine; Progesterone/Oestrogen Ratio
- No Direct Measure
- FT3; FT4; FT3/FT4 Ratio; FT3/RT3 Ratio
- No Direct Measure
- Indirect Measures: Resting Metabolic Rate; Body Temperature; Tendon Reflex Time; Signs/Symptoms; BMI; Cholesterol

**Conversion Process**
- (Within Cells)
- T3
- RT3

**Circulation**
- FT4
- FT3

**Transport of Thyroid Hormone into Cells**

**Hypothalamus**
- TRH

**Pituitary**
- TSH

**Thyroid Gland Function**
- T4
- T3

**Transport Proteins**
- FT4
- FT3

**Tissue Thyroid Hormone Effects**
Review of Figure 1

As shown in Figure 1, there are numerous processes and variables that affect the desired outcome: adequate tissue thyroid effects. The first level is a control loop that circulates round the thyroid gland, the hypothalamus, and the pituitary. Under normal conditions this results in an output of T4, T3 and TSH that meets the individual’s need for thyroid hormone; however, these so-called individual set points may be significantly different from one individual to another.\(^{18-26}\)

The thyroid gland releases two hormones, T4 and T3, into the circulation. The larger portion of the secreted hormone is T4, and T3 makes up only a small part. Both hormones are largely bound to transport proteins (thyroxine-binding globulin (TBG), albumin and transthyretin) when entering the blood stream. The minute fraction which is actually unbound is termed FT3 and FT4. Only the free hormones are biologically active, and FT3 is far more active than FT4.

Thyroid hormones are then actively transported across the cellular membrane. This is not simply a result of diffusion of serum thyroid hormone, it is also affected by a number of variables.\(^{41}\)

As shown there is a conversion process that determines the balance among FT4, FT3 and RT3 at the tissue and serum levels. While FT4 is the predominant extracellular thyroid hormone, T3 is the main intracellular thyroid hormone. This means that T4 is converted into T3, and hence biologically activated, on entry into the cells. The conversion process is affected by a number of confounding variables including levels of iodine, selenium, ferritin, zinc, and even TSH and LT4 dose.

Finally, at the cellular level the process that metabolises thyroid hormone and creates the overall tissue thyroid effect throughout the body is affected by co-factors such as Vitamin D, cortisol, and TSH.\(^{46-48}\) Thyroid hormone resistance (THR) is also occasionally encountered.

So not only are there several thyroid related processes that are inherently different among individuals, there are also a number of confounding variables that affect the final response to thyroid hormone at the cellular level (tissue thyroid effects). Since the tissue thyroid levels/effects cannot be directly measured, indirect measures must be used instead. From the metrics shown in Figure 1, the most likely upstream candidates for the indirect measurement of tissue thyroid effects are TSH, FT4, FT3 and RT3, as reviewed in the following:

a) Researchers have concluded that “the biological effects of thyroid hormones at the peripheral tissues - and not TSH concentrations - reflect the clinical severity of hypothyroidism and the lack of euthyroidism”\(^5\).

b) FT4 levels show only a weak correlation with tissue thyroid effects, so FT4 is inadequate as a primary diagnostic for thyroid status.\(^5,7,10\)
c) RT3 inversely correlates with physical performance scores and the T3/RT3 ratio is a useful indicator of tissue levels of thyroid hormone 7.

d) From another study it was concluded that, “reverse T3 is an excellent marker for reduced cellular T4 and T3 levels not detected by TSH or serum T4 and T3 levels.” 35

e) Another study concluded that a composite score of typical hypothyroid symptoms correlated best with urine FT3, but significant variability was not accounted for by FT3 alone 43.

So having only a relatively few upstream measures that are even indicative of tissue thyroid levels and effects, we have to consider the identified downstream candidates. From experience and scientific information, the best of those candidates to use as diagnostics are tendon reflex time and other signs/symptoms. As stated in the guidelines, “early as well as recent studies strongly correlate the degree of hypothyroidism with ankle reflex relaxation time, a measure rarely used in current clinical practice today” 1. Tendon reflex time may become even more useful for evaluating thyroid status now that objective tests have been developed for accurate measurement in milliseconds.

Also, a composite list of signs and symptoms has been developed, including tendon reflex time, which can give a valuable estimate of the individual severity of metabolic hypothyroidism”. The composite score correlates equally well or better with parameters reflecting tissue hypothyroidism than did circulating thyroid hormone or TSH. From this study, positive predictive values and negative predictive values, along with sensitivity and specificity values, are included for each symptom, showing their relevance to diagnosis 11.

**General Recommendations for Diagnostic and Treatment Procedures**

It should be noted that a doctor cannot diagnose with perfect certainty, even based on medical history, signs and symptoms as well as test results. Every diagnosis is basically a probability theory; it has a degree of uncertainty associated with it. For hypothyroidism, the ultimate test of the theory includes a successful trial of thyroid replacement therapy. If symptoms improve with thyroid medication that adequately increase the FT4 and FT3 levels, then the diagnosis is tentatively supported.

1. Diagnosis should result from a comprehensive review of all patient evaluations, starting with a full medical history of the patient. This may identify a family history of hypothyroidism, an unusual susceptibility for infections, a traumatic injury to the thyroid area, the fluoridation of local water supplies, iodine deficiency, an age related effect on FT3 levels, and other clues. Signs and symptoms should be a main consideration. Some validated methodology has been included 10-12.

2. Due to their flawed ranges previously discussed, FT4 and FT3 in the lower half of their range should be regarded as potential indicators of hypothyroidism. Also RT3 in the upper part of its range, with a FT3 in the lower part of its range should be considered as indicative of hypothyroidism. FT4 and FT3 should also be interpreted in relation to each other 31, 40, 48. Typically, both FT4 and FT3 are best in the upper half of their ranges. If the FT4 is below mid-range, then FT3 should be in the upper end of its range, or as
needed to assure thyroid sufficiency \(^{36, 45}\). In case of beginning thyroid failure TSH tends to rise and the FT3/FT4 ratio is adjusted according to the TSH-standardized FT4 production \(^{46}\). This means that FT3, FT4 and TSH cannot be treated as independent variables. They must be viewed as interrelated, supporting relational, not absolute stability \(^{31, 45-49}\).

3. If cortisol is low in the range, lower levels of FT4 and FT3 may be effective. If cortisol is above range, FT4 and FT3 may need to be higher in the range. TSH is useful only in the identification of overt primary hypothyroidism (TSH >10 mIU/L, FT4 below range) and for distinguishing between primary and central hypothyroidism. Importantly, the use of all thyroid tests, particularly FT3, may be compromised in the presence of more severe non-thyroidal comorbidity such as infection (pneumonia, sepsis), trauma, malignancy, heart failure, myocardial infarction, chronic renal failure, liver cirrhosis, and diabetic ketoacidosis \(^{50}\).

4. If signs and symptoms are present, an ultrasound examination of the thyroid gland should be carried out.

5. Given adequate clinical and biochemical evidence of hypothyroidism, the patient should be started on a therapeutic dose of thyroid medication adequate to raise thyroid hormone levels and determine the effect on patient symptoms. Since each person has their own thyroid process levels to maintain the needed tissue thyroid effect, specific target values for thyroid functions tests do not apply to individuals. If the diagnosis of hypothyroidism is confirmed, then thyroid hormone replacement should aim at eliminating the signs and symptoms of hypothyroidism without producing any signs or symptoms of thyroid hormone excess. Given the variation in dose response and apparent FT3-TSH dissociation under LT4, FT4 and FT3 tests and their ratio are the most valuable tests for monitoring a patient's progress with increasing doses of thyroid medication \(^{51-53}\). Patients just want to feel normal. If they become overdosed there are unwanted effects such as palpitations, irritability, sweating, insomnia, and shaky hands. These can be reversed by reduction of thyroid medication. The long term implications from under treatment are frequently greater than the short term effects of over treatment which can be rapidly identified and corrected.

6. There is ongoing controversy about the current medication of choice, which is synthetic levothyroxine (L-T4) \(^{51-53, 55}\). Certainly L-T4 is easier to administer, since it has a half-life of about seven days, and can be taken only once a day. However, the human thyroid gland produces T4 to T3 in a ratio of about 13:1 by weight, and the additional T3 that is needed must come from conversion of T4 in various body tissues. Dosages should be adjusted according to symptoms first and FT4 and FT3 second. It is totally ineffective to dose a hypothyroid patient to just bring the TSH level within the reference range determined using group test data \(^{40-42, 49-55}\). Further dose adjustment should be guided individually by relief of symptoms and tolerance of the medication dosage.

7. While L-T4 mono therapy works for many hypothyroid patients, there are others who require the addition of L-T3 to feel well. This has also recently been confirmed by a large Danish study demonstrating that quality of life in hypothyroid patients with autoimmune
thyroiditis on LT4 treatment did improve but not to a level observed in a healthy population. Although earlier meta-analyses failed to find clear benefit in treatment of hypothyroid individuals with combination L-T4 and L-T3, continued interest in such approaches to replacement therapy is warranted due to methodological deficiencies in the majority of the prior studies. Other studies of combination L-T4 and L-T3 treatment have fallen into two basic categories:

a. those that found no measurable effects, but a majority of participants liked it better, and
b. those that confirmed a measurable improvement and participants liked it better.

In addition to the studies of the effect of substituting L-T3 for a portion of the prior L-T4 dosage, there are other studies of the effect on FT3 to FT4 ratios compared to control groups using only L-T4 medication. In many studies it was concluded that the ratio of FT3 to FT4 was lower in thyroxine-treated patients than the euthyroid control group, and that FT3 levels were significantly lower in L-T4 treated than untreated non-hypothyroid autoimmune thyroiditis, despite lower TSH and higher FT4 levels in the treated group. Also, the roles of the iodothyronine deiodinases have "come into question as they have been implicated in both an inability to normalise serum levels of FT3 and the incomplete resolution of hypothyroid symptoms."

8. Due to the persistence of symptoms in some hypothyroid patients treated with L-T4 and with normal serum TSH, the European Thyroid Association (ETA) established a task force to investigate a list of relevant topics. With the long history of the ETA supporting the treatment of hypothyroidism with L-T4 with the aim of bringing the TSH within range, it is very revealing that the task force recognised the same problems discussed above. As a result they continued to promote L-T4 monotherapy as the preferred approach, but opened the door to combination L-T4 plus L-T3 therapy as an experimental approach in certain circumstances that they outlined. So the task force finally recognised that there are circumstances that call for combination therapy, whilst spelling out the necessary carefully controlled conditions.

Given current evidence the question is no longer if there really are hypothyroid patients that need L-T3 as well as L-T4 therapy, but how many are there and how best to diagnose and treat them. One promising approach may arise from a recent study that showed considerable variation in the biochemical response to L-T4 treatment and documented a relationship to conversion efficiency. In this respect, the ratio of FT3 to FT4 may offer a simple and inexpensive means of estimating conversion efficiency and guiding the addition of T3 to the treatment regime. Genetic testing for the polymorphism in the DIO2 gene could also play a future role in identifying subject with varying abilities to convert T4 into T3 and differing treatment requirements. This underscores the necessity for individualised treatment strategies.

In summary L-T4 monotherapy remains the primary treatment choice due to its long half-life and the convenience of a single daily dose, and the assumption that T4 is largely converted to T3 as needed. However, there is rapidly accumulating evidence that L-T4 monotherapy does not invariably assure adequate levels of FT3, even when the...
The Diagnosis and Treatment of Hypothyroidism

medication dose is adjusted to bring FT4 and TSH back within their respective reference ranges. Some hypothyroid patients find this inadequate and report continuing hypothyroid symptoms. If treated adequately with a combination L-T4 plus L-T3 therapy, numerous studies show that a majority of those patients prefer that to L-T4 monotherapy. Several studies have also identified possible causes for the lack of normalisation of T3 under L-T4 monotherapy. In particular, athyreotic patients may frequently fall into this category.

In addition to the direct benefit of achieving adequate FT3 levels, some studies have concluded that low FT3 levels are risk factors for artery calcification and major adverse cardiac events \(^\text{72, 73}\).

9. When adding L-T3 to a hypothyroid patient's medication, it should be noted that available conversion tables wrongly show that 100 mcg of L-T4 = one grain of NDT = 25 mcg of L-T3. This implies that 100 mcg of L-T4 is equivalent to 25 mcg of L-T3, a ratio of 4 to 1. If that were the case then one grain of NDT would be equivalent to only 75 mcg of L-T4, since it contains 39 mcg of T4 and 9 mcg of T3 (39 + (9 times 4) = 75). Furthermore, studies have reported that the correct ratio of T4 to T3 is closer to 3 to 1; consequently one grain of NDT is equivalent to only 66 mcg of L-T4 \(^\text{74, 75}\).

10. It should be noted that higher L-T3 medication doses should best be split in half for a morning and early afternoon dose \(^\text{76}\). Since L-T3 reaches peak effect in 3 to 4 hours, and then drops off, this split dose may provide a more consistent effect over the full day. In addition, the guidelines \(^\text{1, 2}\) recommend that “blood for assessment of serum FT4 should be collected before dosing because the level will be transiently increased by up to 20% after Levothyroxine (L-T4) administration”. For the same reason, L-T3 medications should be deferred until after the blood draw for FT3 testing in order to avoid false high results \(^\text{76, 77}\).

11. Reverse T3 (RT3) is a normal result of conversion of T4 to T3. Under some conditions, including L-T4 medication in some patients, excessive RT3 will be produced, along with less T3. RT3 and other non-classical thyroid hormones have long been regarded as inactive degradation products and their important physiological roles have only recently emerged \(^\text{78, 79}\).

Excess RT3 indicates a conversion problem, not a direct thyroid deficiency. It can be part of an exaggerated and prolonged stress response as characterised by elevated cortisol levels, which, in turn, inhibit the 5-deiodinase enzyme type 1 and conversion of T4 into T3 \(^\text{80, 81}\). The conversion of T4 into T3 becomes inefficient whereas RT3 accumulates \(^\text{82}\). The latter can be considered as ‘toxic waste’ that persists even after the normalisation of the stress response because the imbalance of RT3/T3 itself may continue to inhibit the 5-deiodinase enzyme type 1.

The elevation of RT3 appears to be transient in most healthy people. There are however reports that link patients suffering from a range of hypothyroid symptoms to prolonged elevated RT3 levels \(^\text{83}\). These patients may respond favourably to treatment, although many experts do not accept ‘RT3 dominance theory’ and will refuse to treat this condition.
Other postulated causes of reverse T3 dominance include a broad spectrum of abnormalities such as: “Leptin resistance; Inflammation (NF kappa-B); Dieting; Nutrient deficiencies such as low iron, selenium, zinc, chromium, vitamin B6 and B12, vitamin D and iodine; low testosterone; low human growth hormone; Insulin dependent diabetes; pain; stress; environmental toxins; free radical load; haemorrhagic shock; liver disease; kidney disease; severe or systemic illness; severe injury’, surgery; toxic metal exposure”

Successful treatment usually entails first correcting any identifiable cause and then symptomatically reducing T4 excess and gradually increasing T3 levels until RT3 approaches the middle of its range and Free T3 the upper part of its range.

12. The aim of dose determination for a patient should be to get the patient on the required or optimum dose as quickly as possible. Dose and timing may vary by individual needs. In an otherwise healthy patient the initial dose can be higher, whereas a patient with a history of cardiac problems may need more gradual and careful titration of the L-T4 dose under close clinical supervision.

Major determinants would be the presence of a residual thyroid gland or the size of the remnant, with athyreotic patients requiring a higher dose, and the weight or BMI of the patient. Some sets of rules have been proposed which may serve as an initial crude estimate to predict the final dose, which would equal the starting dose in unproblematic situations. Dose adequacy should then be assessed and adjusted as needed, with relief of symptoms being the main concern. While severe symptoms and free thyroid hormones may respond more quickly - within a month or so - achievement of final symptomatic relief may take several months, as time is needed for the body to heal. As for TSH, it takes 6 to 8 weeks after initiation of treatment or change of the L-T4 dose until it reaches equilibrium levels with the peripheral hormones. Intermediate measurements are therefore of little value.

Contrary to widespread practice, TSH should not be relied on as the dominant determinant of treatment success or main gauge of dose adequacy; the equilibria established in a healthy population do not equally apply and are therefore not transferable to patients taking replacement thyroid hormone. This phenomenon, which has been long known to practitioners, has recently been documented by large clinical studies.

13. Studies have shown that when taking adequate thyroid medication, the TSH level in a treated patient is frequently suppressed below the reference range. A suppressed TSH level means that the patient has become hyperthyroid only if there are hyper symptoms due to excessive levels of FT4 and FT3. In addition, serum thyroid hormone levels are a sum of both natural thyroid hormone and thyroid medication. As medication dosages are increased the production of both TSH and natural thyroid hormone is diminished. As a result, equilibrium serum levels are not increased with small starting doses of thyroid medication. Only when TSH is suppressed enough to no longer stimulate natural thyroid hormone production, will serum thyroid levels reflect further increases in thyroid medication.
Concerns that suppressed TSH without concomitant elevation of free thyroid hormones will cause osteoporosis are unfounded. "Thyroid hormone does not cause bone loss; it simply affects metabolism and therefore the rate of the current bone formation or loss." Bone loss or formation is related to combined effects of "sex steroid, DHEA (see glossary), Vitamin D, and growth hormone levels." The solution is to correct other deficiencies rather than to maintain sub-optimal thyroid hormone levels. For instance, bone effects have been recognised mainly in postmenopausal women where there is a strong influence and modulatory role of oestrogens.

It should be mentioned that TSH also has a direct positive anti-resorptive effect on bone which is independent of the action of thyroid hormones and further adds to the complexity of the interaction.

14. Nutritional influences should also be considered. Severe iodine deficiency that may cause hypothyroidism is rarely present in developed countries, and unnecessary iodine supplementation is to be avoided in patients with thyroid autoimmune disease. However, there is some evidence that patients with Hashimoto’s thyroiditis may benefit from supplementing selenium to mitigate their autoimmune response. Hypothyroid patients are frequently too low in the ranges for Vitamin D and ferritin, as previously identified through testing. Since fatigue is one of the main symptoms of hypothyroidism, B12 should also be tested, and all three optimised. Although recommendations for the target levels for 25-hydroxy vitamin D differ among various guidelines, it should be at least 50ng/mL according to the Vitamin D council. From other sources, ferritin should be above 100ng/mL, and B12 is best above 500pg/ml.

(Note: Variations may apply by condition, gender, age and method used).

15. A number of medical conditions such as comorbidities with autoimmune thyroiditis (Sprue) or hypothyroid state itself, drugs and food that may affect absorption of externally administered thyroid hormones should be taken into consideration.

16. The response to a given hormone level as defined by measuring thyroid hormones in the circulation may be subject to variation and modification by various influences that determine the thyroid hormone tissue effects. Those influences may be genetic, but also include age, body weight, environmental temperature, toxic chemicals and many others.

17. Diabetes type 1 is more prevalent as a second autoimmune disorder in patients with autoimmune thyroid disease. The same is true for Addison’s disease. Hence, a morning cortisol measurement and blood sugar should be obtained. Even a low normal thyroid function has been linked to a higher risk of type 2 diabetes. Also, in patients with type 2 diabetes insulin sensitivity may vary with thyroid function and therefore adjustment of treatment may be necessary with changing thyroid function.

18. Central or secondary hypothyroidism is frequently part of a more complex hypothalamic or pituitary disorder. This requires a complete evaluation and biochemical testing of all pituitary hormones and dependent organs. In case of suspected or proven cortisol
deficiency of either central or adrenal origin, it is important to defer any thyroid hormone replacement until prior adequate correction of hypocortisolism.

Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATA</td>
<td>American Thyroid Association</td>
</tr>
<tr>
<td>Athyreotic</td>
<td>Absence or functional deficiency of the thyroid gland</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>Co-factors</td>
<td>Any of various organic or inorganic substances necessary to the function of an enzyme.</td>
</tr>
<tr>
<td>Confounding Variable</td>
<td>A confounding variable is a variable, other than the independent variable that you’re interested in, that may affect the dependent variable. This can lead to erroneous conclusions about the relationship between the independent and dependent variables.</td>
</tr>
<tr>
<td>DHEA</td>
<td>Dehydroepiandrosterone, one of two anabolic steroids produced by the inner layer of the adrenal cortex, is the most abundant circulating steroid hormone in humans. The other anabolic steroid produced by the adrenal gland is androstendione.</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>The state of having normal tissue thyroid levels and effects, so that there are neither hypo nor hyper symptoms.</td>
</tr>
<tr>
<td>Homeostasis</td>
<td>The property of a system in which variables are regulated so that internal conditions remain stable and relatively constant</td>
</tr>
<tr>
<td>L-T3</td>
<td>Liothyronine (synthetic T3)</td>
</tr>
<tr>
<td>L-T4</td>
<td>Levothyroxine (synthetic T4)</td>
</tr>
<tr>
<td>MACE</td>
<td>Major Adverse Cardiac Events</td>
</tr>
<tr>
<td>NDT</td>
<td>Natural Desiccated Thyroid</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>RMR</td>
<td>Resting Metabolic Rate</td>
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</tbody>
</table>
The Diagnosis and Treatment of Hypothyroidism

RT3  Reverse T3
Sprue  A chronic form of Malabsorption Syndrome
TBG  Thyroxine-Binding Globulin
TG-ab  Thyroglobulin Antibodies
THR  Thyroid Hormone Resistance
TPO-ab  Thyroid Peroxidase Antibodies
TRH  Thyroid Release Hormone
TSH  Thyroid Stimulating Hormone

References


   “Many aspects of HRQL improved during the first six months of LT4 therapy, but full recovery was not obtained. Our results may help clinicians inform patients about expected clinical treatment effects.”

“We found no correlations between the different parameters of target tissues and serum TSH. ……Therefore, the biological effects of thyroid hormones at the peripheral tissues - and not TSH concentrations - reflect the clinical severity of hypothyroidism”.


“We conclude that advances in assay techniques have unduly promoted TSH measurement to its current role as an exclusive statistical estimate in its own right and the most important single parameter in thyroid function testing, thereby optimizing both convenience and cost. However, the predominant use of TSH as a statistical parameter has some severe shortcomings that limit its clinical usefulness in a given patient. A revision may be needed to reconcile TSH measurement with the challenge of not only evidence-based medicine but personalised medicine.”


“This study demonstrates that TSH and/or T4 levels are poor indicators of tissue thyroid levels and thus, in a large percentage of patients, cannot be used to determine whether a person has normal thyroid levels at the tissue level. This study demonstrates that RT3 inversely correlates with physical performance scores and the T3/RT3 ratio is currently the best indicator of tissue levels of thyroid.”


“Observations on this cohort, in summary, demonstrate that the reference interval for TSH varies significantly by age, sex, time of day, and ethnicity.”


“Due to the lack of correlation of TSH and tissue thyroid levels, as discussed, a normal TSH should not be used as the sole reason to withhold treatment in a symptomatic patient.”…….Consequently, serum T4 levels oftentimes do not correlate with tissue T3 levels and, as with the TSH, the serum T4 level is often misleading and an unreliable marker of the body’s overall thyroid status.”

*Design: Practice-based open intervention study; control group used for baseline laboratory values only*

*Materials and Methods: Clinical response to thyroxine (T4 only) was examined in 139 patients who were considered hypothyroid by 16 recognised criteria but whose free thyroxine (FT4) and thyroid stimulating hormone (TSH) fell within 95% laboratory reference intervals (133 patients) or whose FT4 or TSH fell within these intervals (6 patients). Clinical response correlated with the level of thyroid replacement but not significantly with pre-treatment or post-treatment levels of FT4 and TSH nor with duration of illness or treatment.*


“The study found the clinical score and ankle reflex time correlated well with tissue thyroid effect but the TSH has no correlation with the tissue effect of thyroid hormones. The ankle reflex itself had a specificity of 93% and a sensitivity of 77%, making both the measurement of the reflex speed and clinical assessment a more accurate measurement of tissue thyroid effect than the TSH.”

<table>
<thead>
<tr>
<th>Symptoms and Signs*</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle Reflex</td>
<td>77</td>
<td>93.5</td>
<td>92.2</td>
<td>80.3</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>76</td>
<td>63.8</td>
<td>67.7</td>
<td>72.7</td>
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<tr>
<td>Cold Intolerance</td>
<td>64</td>
<td>65.0</td>
<td>64.6</td>
<td>64.4</td>
</tr>
<tr>
<td>Coarse Skin</td>
<td>60</td>
<td>81.2</td>
<td>76.1</td>
<td>67.0</td>
</tr>
<tr>
<td>Puffiness</td>
<td>60</td>
<td>96.3</td>
<td>94.2</td>
<td>70.7</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>58</td>
<td>42.5</td>
<td>50.2</td>
<td>50.3</td>
</tr>
<tr>
<td>Sweating</td>
<td>54</td>
<td>86.2</td>
<td>79.6</td>
<td>65.2</td>
</tr>
<tr>
<td>Wt. Increase</td>
<td>54</td>
<td>77.5</td>
<td>70.6</td>
<td>62.8</td>
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<tr>
<td>Paraesthesia</td>
<td>52</td>
<td>82.5</td>
<td>74.8</td>
<td>63.2</td>
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<tr>
<td>Cold Skin</td>
<td>50</td>
<td>80.0</td>
<td>71.4</td>
<td>61.5</td>
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</tbody>
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The Diagnosis and Treatment of Hypothyroidism

<table>
<thead>
<tr>
<th>Symptoms and Signs*</th>
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<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>48</td>
<td>85.0</td>
<td>76.2</td>
<td>62.0</td>
</tr>
<tr>
<td>Slow Movement</td>
<td>36</td>
<td>98.7</td>
<td>96.5</td>
<td>60.7</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>34</td>
<td>87.5</td>
<td>73.1</td>
<td>57.0</td>
</tr>
<tr>
<td>Hearing</td>
<td>22</td>
<td>97.5</td>
<td>89.8</td>
<td>52.6</td>
</tr>
</tbody>
</table>

*Two signs (cold intolerance and decreased pulse rate) showed positive and negative predictive values below 70% and were, therefore, excluded from the new score.

For clinical judgement, add 1 point to the sum of symptoms and signs present in women younger than 55 years. Hypothyroid, more than 5 points; euthyroid, less than 3 points; intermediate, 3-5 points.

12. Najarian T, Rowsemitt CN. Hypothyroidism, Particularly Associated with Weight Loss: Evaluation and Treatment based on Symptoms and Thyroid Hormone Levels. Thyroid science 2011;6(6) CR17

“But we will never argue for the dominance of a lab test when signs and symptoms are available. In considering thyroid lab values, we must also be cognizant of known biochemical variants such as receptor and transporter abnormalities which may cause a lab result to be at odds with the signs and symptoms.”


“A large proportion of the U.S. population unknowingly have laboratory evidence of thyroid disease, which supports the usefulness of screening for early detection.”


“The Prevalence of elevated TSH levels (normal range, 0.3-5.1 mIU/L) in this population was 9.5%, and the prevalence of decreased TSH levels was 2.2%. Symptoms were reported more often in hypothyroid vs. euthyroid individuals, but individual symptom sensitivities were low.”
15. Shoman M. When Endocrinologists Briefly Narrowed the TSH Reference Range.

http://thyroid.about.com/cs/testsforthyroid/a/newrange.htm

A survey of over 1000 thyroid patients found that more than 50% were not satisfied with their treatment.


“In 1996, I began tracking patient(s?) 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% continued to suffer from common hypothyroid symptoms.”


http://journal.frontiersin.org/article/10.3389/fendo.2015.00177/full

“Homeostatic principles conjoin all thyroid parameters into an adaptive context, demanding a more flexible interpretation in the accurate diagnosis and treatment of thyroid dysfunction.”


“High individuality causes laboratory reference ranges to be insensitive to changes in test results that are significant for the individual. The width of the individual 95% confidence intervals were approximately half that of the group for all variables. For the same degree of thyroid function abnormality, the diagnosis depends to a considerable extent on the position of the patient’s normal set point for T4 and T3 within the laboratory reference range.”


“The data indicate that conventional reference values are insensitive when compared to subject-based reference intervals in assessing the thyroid status of a given subject.”
20. Andersen S, Brun NH, Pedersen KM, Laurberg P. Biologic Variation is Important for Interpretation of Thyroid Function Tests. Thyroid 2003;13(11):1069-78

“Large variations exist in thyrotropin (TSH) and thyroid hormones in serum. The components of variation include pre analytical, analytical, and biologic variation. This is divided into between-and within-individual variation. The ratio of within-to between-individual variation describes the reliability of population-based reference ranges. This ratio is low for serum TSH thyroxine (T4) and triiodothyronine (T3) indicating that laboratory reference ranges are relatively insensitive to aberrations from normality in the individual.”

21. Franklyn J, Shephard M. Evaluation of Thyroid Function in Health and Disease. In: Thyroid Disease Manager


Fig. 6-7. “Correlation of the serum concentration and the free thyroxine index (FT4I) in three individuals given increasing doses of L-T4.”

Comment: Although there is excellent correlation of individual results, the diagram clearly shows the significant difference in inter-individual results of TSH and FT4 Index among just 3 patients.

The inter-individual variability negates any effort to distinguish what is normal when comparing individual test results to a reference range determined from a large group of patients

“TSH, FT3, and FT4 showed a significant intra-individual biological variation. The utility of population-based reference intervals for TSH would be of limited use”.


“Intra-and interindividual components of biological variation have been determined for total thyroxin (TT4), free thyroxin (FT4), total triiodothyronine (TT3), free triiodothyronine (FT3), and thyrotropin (TSH)……The marked degree of individuality demonstrated for all hormones indicates that, if conventional population-based reference ranges are used uncritically, major changes in hormone concentration may not be correctly identified for some patients because observed values continue to lie with the reference range”.


“Variations of FT4 and FT3 in each subject were narrow and approximately one third of normal reference ranges.”


“The diagnosis of abnormalities of thyroid function is generally based on the measurement of thyroid hormones and TSH in blood. The recommended reference ranges for serum T4 and T3 as well as TSH are quite wide as the result of large differences in thyroid function tests in healthy persons. It has been proven that the inter-individual variation is small compared with the variation between individuals.”


“The results showed that, within an individual, thyroid hormone concentrations are maintained within narrow limits. …..This high degree of individuality implies that rigorous comparison of thyroid hormone results against a population-based “normal range” can be potentially misleading.”

“The question arises as to how clinicians can practically assess the validity of the reference range they employ apart from relying on this having been well established by the manufacturer or laboratory institution in the first place. …

In the present study, we used an indirect method to evaluate the reference range of TSH post hoc in a fairly large retrospective sample.”


“This paper provides the reader with an overview of our current knowledge of hypothalamic-pituitary-thyroid feedback from a cybernetic standpoint. “


“The current evidence on lowering or increasing the upper limit of the TSH reference interval is reviewed and the need to individualize levothyroxine treatment in patients with elevated TSH levels is discussed. “

30. Jonklaas J, Kahric-Janicic N, Soldin OP, Soldin SJ. Correlations of Free Thyroid Hormones Measured by Tandem Mass Spectrometry and Immunoassay with Thyroid-Stimulating Hormone across Four Patient Populations. Clinical Chemistry 2009;55:1380-1388 (Figure reproduced with permission from the American Association for Clinical Chemistry). Correlations of Free Thyroid Hormones Measured by Tandem Mass Spectrometry and Immunoassay with Thyroid-Stimulating Hormone across 4 Patient Populations

"Frequent divergencies between composite multivariate reference limits and a combination of separate univariate reference intervals suggest that statistical analytic techniques may heavily influence thyroid disease classification. This challenges the validity of the conjoined roles of TSH currently employed as both a sensitive screening test and a reliable classification tool for thyroid disease."


"The results showed that the most discrepant TSH assays (G and C) differed by an average of 39%, …"

35. Holtorf KT. National Academy of Hypothyroidism, Thyroid Hormone Transport

https://www.nahypothyroidism.org/thyroid-hormone-transport/#reverseT3

“Thus, a high reverse T3 demonstrates that there is either an inhibition of reverse T3 uptake into the cell and/or there is increased T4 to reverse T3 formation. These always occur together in a wide range of physiologic conditions and both cause reduced intracellular T4 and T3 levels and cellular hypothyroidism. Thus, reverse T3 is an excellent marker for reduced cellular T4 and T3 levels not detected by TSH or serum T4 and T3 levels. Because increased rT3 is a marker for reduced uptake of T4 and reduced T4 to T3 conversion, any increase (high or high normal) in rT3 is not only an indicator of tissue hypothyroidism but also that T4 only replacement would not be considered optimal in such cases and would be expected to have inadequate or sub-optimal results. A high reverse T3 can be associated with hyperthyroidism as the body tries to reduce cellular thyroid levels, but this can be differentiated by symptoms and by utilizing the free T3/reverse T3 ratio, which is proving to be the best physiologic marker of intracellular thyroid levels”.


“Moreover, comparatively higher concentrations of T3 were needed to displace either radio-labeled T4 or rT3, suggesting that T3 was binding to both the T4 and rT3 sites with lower affinity.”


40. Suzuki S, Nishio S, Takeda T, Komatsu M. Gender-specific regulation of response to thyroid hormone in aging. Thyroid Research 2012 5:1

41. Visser TJ. Cellular Uptake of Thyroid Hormones

http://www.thyroidmanager.org/chapter/cellular-uptake-of-thyroid-hormones

"During the last three decades it has become clear that thyroid hormones (THs) are transported into cells by specific carrier-mediated uptake mechanisms. Before that time, it was thought that crossing the plasma membrane of tissue
cells is a matter of simple diffusion as THs are lipophilic compounds which can easily pass the lipid bilayer of the plasma membrane. There is now a vast literature showing that this is apparently not the case. In fact, diffusion probably plays a minor role, if any, in TH transport across the plasma membrane.”


“A further need for precaution is based on evidence that individuals exposed to EDCs may carry that body burden for their entire lives in the case of long-lived chemicals; that even short-lived chemicals may induce changes that are permanent; and that some actions of EDCs are observed in an individual’s offspring.”


“The score of these 8 main symptoms is a reliable expression of their illness in 97% of hypothyroid patients. 24 h urine free T3 correlates better with the clinical status of hypothyroid patients (R2 = 0.30) than serum T4-RIA (R2 = 0.12), and even better than T4-RIA/TBG (R2 = 0.19). Other investigators were unable to find any correlation between serum thyroid stimulating hormone (TSH) or serum free T4 and thyroid symptoms”.

“The determination of Free T3 in 24 hour urine collection provides a logical and practical answer to the many clinicians who are anxiously looking for laboratory confirmation of their clinical diagnosis in thyroid disease”.


“Measurements of serum concentrations of total thyroxine, analogue free thyroxine, total triiodothyronine, analogue free triiodothyronine, and thyroid stimulating hormone, made with a sensitive immunoradiometric assay, did not, except in patients with gross abnormalities, distinguish euthyroid patients from those who were receiving inadequate or excessive replacement. These measurements are therefore of little, if any, value in monitoring patients receiving thyroxine replacement.”

Of 148 patients attending an outpatient clinic, 148 were classified by their clinical status by 4 qualified consultants with experience in thyroid disease. Of those 108 were classified as euthyroid and from biochemical testing, their TSH ranged from 0.1 to 19.7. The TSH for 22 patients classified as hyperthyroid ranged from 0.1 to 14.4. The TSH for the 18 patients classified as hypothyroid ranged from 0.1 to 123.5
45. Warmingham P. Effect of Exogenous Thyroid Hormone Intake on the Interpretation of Serum TSH Test Results, 2010(May)


“Hypothyroid patients whose thyroid hormone replacement dose is being regulated against the TSH reading alone are being maintained in an under-treated state and are correct to assert that they feel better on a higher dose. Therefore, hypothyroid patients should not have their thyroid hormone dosages set by reference to their TSH readings.”

46. Macejová D1, Ondková S, Brtko J. Vitamin D3 Affects Expression of Thyroid Hormone Receptor Alpha and Deiodinase Activity in Liver of MNU-treated Sprague-Dawley Rats. Gen PhysiolBiophys 2009;28:363-70


“These findings suggest that the thyroid gland and peripheral tissues are integrated in the physiological process of T3 homeostasis in humans via a feed-forward TSH motif …”

“As T3 is largely created intracellularly and contributes to the circulating T3 pool following its active transport across the plasma membrane reduced T3 levels in the circulation are likely to reflect T3 deficiency within the bulk of the T3 producing tissues. Experimental studies in the rat, discussed above, and the high dissatisfaction rate with the current L-T4 standard treatment patients expressed in many trials point in the same direction”.


“Homeostatic equilibria (set points) in healthy subjects are less variable and do not follow a pattern of random variation, rather indicating signs of early and progressive homeostatic control across the euthyroid range. In the event of imminent thyroid failure with a reduced FT4 output per unit TSH, conversion efficiency increases in order to maintain FT3 stability. “

“It is clear that the name “NTI” during critical illness refers to a syndrome with different faces. Some of it is good and some of it may be bad, depending on the timing and the context. “


http://www.endocrineconnections.org

“An L-T4 related FT4TSH disjoint was also apparent; some patients with fully suppressed TSH failed to raise FT3 above the median level. These findings imply that thyroid hormone conversion efficiency is an important modulator of the biochemical response to L-T4; FT3 measurement may be an additional treatment target; and L-T4 dose escalation may have limited success to raise FT3 appropriately in some cases.”

“Our clinical data on homeostatic regulation, further supported independently by theoretical modelling, at least cast doubt on an “autoregulated” and guaranteed optimum tissue supply of T3 by L-T4 treatment, ”


“FT4 levels are significantly higher and FT3 levels were significantly lower (p<.001 in both cases) in levothyroxine treated athyreotic patients than in matched euthyroid controls. Among the levothyroxine treated patients 15.2% had lower serum FT3 and 7.2% had higher serum FT4 compared to euthyroid controls. ......A more physiological treatment than levothyroxine mono therapy may be required in some hypothyroid patients”.


“By group comparison and confirmation by more individual TSH-related regression, FT3 levels were significantly lower in L-T4 treated vs untreated non-hypothyroid autoimmune thyroiditis, despite lower TSH and higher FT4 levels in the treated group.”
The Diagnosis and Treatment of Hypothyroidism

“Equilibria typical of the healthy state are not invariant, but profoundly altered, for example, by L-T4 treatment.”


“TSH level is not an optimal marker of adequate thyroid hormone replacement therapy in all hypothyroid patients. In the future, the use of other more sensitive peripheral markers of thyroid hormone action at tissue levels might help clinicians to personalize the treatment of thyroid hormone deficiency.”


“Total deiodinase activity was positively correlated with TSH in untreated subjects. However, deiodinase activity was significantly altered and the correlation was lost under increasing L-T4 doses. Ninety-five per cent confidence intervals for the Ft3 and FT4, when assessed in defined TSH concentration bands differed significantly for L-T4 treated compared with untreated patients. Higher doses were often needed to restore FT3 levels within its reference range.”


“Although earlier meta-analyses failed to find clear benefit in treatment of hypothyroid individuals with combination T4 and T3 continued interest in such approaches to replacement therapy is warranted due to methodological deficiencies in the majority of the prior studies. New insights into deiodinase polymorphisms may explain differences in both tissue and relative individual clinical responses to treatment.”


“Patients preferred combined LT4/LT3 therapy to usual LT4 therapy, but changes in mood, fatigue, well-being, and neurocognitive functions could not satisfactorily explain why the primary outcome was in favor of LT4/LT3 combination therapy.”


“In our analysis 78% rated subsequent AT treatment as superior while in the prospective study of unselected hypothyroid patients [17] a 48.0% preference for AT compared to L-T4 mono therapy was reported”.


“In conclusion, the results of this pharmacology, proof-of-concept study indicate that replacement therapy of hypothyroidism with L-T3, compared with L-T4 causes weight loss and favorable changes in the lipid profile without appreciable side effects”.


“DTE therapy did not result in a significant improvement in quality of life; however, DTE caused modest weight loss and nearly half (48.6%) of the study patients expressed preference for DTE over L-T”.


“This community-based study is the first evidence to indicate that patients on thyroxine replacement even with a normal TSH display significant impairment in psychological well-being compared to controls of similar age and sex. In view of the large numbers of people on thyroxine replacement, we believe that these differences, although not large, could contribute to significant psychological morbidity in a substantial number of individuals.”


“However, a significant minority of patients only achieve the desired sense of well-being if serum TSH is suppressed. Furthermore, patients rendered hypothyroid following treatment of thyrotoxicosis and taking a dose of T4 which maintains a normal TSH, gain more weight than those who do not become hypothyroid. Studies in hypothyroid rats suggest that it is only possible to restore universal tissue euthyroidism using a combination of T3 and T4. In patients in whom long-term T4 therapy was substituted by the equivalent combination of T3 and T4 scored better in a variety of neuropsychological tests. It appears that the treatment of hypothyroidism is about to come full circle.”


“Among 17 scores on tests of cognitive performance and assessments of mood, 6 were better or closer to normal after treatment with thyroxine plus triiodothyronine. Similar, among 15 visual-analogue scales used to indicate mood and physical status, the results for 10 were significantly better after treatment with thyroxine plus triiodothyronine.”


“When comparing scores of QOL and depression on T4 mono therapy versus T4/T3 combination therapy, significant differences were seen in 7 out of 11 amores, indicating a positive effect related to the combination therapy. Forty-nine percent preferred the combination and 15% monotherapy.”


“Studies in hypothyroid rats show that, when infused with a combination of thyroxine (T4) plus triiodothyronine (T3) to normalise thyrotropin (TSH), euthyroidism in all organs is only ensured when T4 and T3 are administered in a ratio as normally secreted by the rat thyroid. As substitution with T4 only results in an abnormal serum T4/T3 ratio, it is also possible that in humans euthyroidism does not exist at the tissue level in many organs, considering that iodothyronine metabolism in the human and the rat share many similar mechanisms. .......In the study reported her we show that treatment of hypothyroid subjects with a combination of T4 plus slow-release T3 leads to a considerable improvement of serum T4 and T3 values, the T4/T3 ratio and serum TSH as compared to treatment with T4 only.”

67. Liewendahl K, Helenius T, Lamberg BA, Mahonen H, Wagar G. Free Thyroxine, Free Triiodothyronine, and Thyrotropin Concentrations in
Hypothyroid and Thyroid Carcinoma Patients Receiving Thyroxine Therapy. 
ActaEndocrinol (Copenh), 1987;116(3):418-24

“Forty-one of 56 operated thyroid carcinoma patients on suppressive therapy (mean thyroxine dose 214 micrograms/day) had raised FT4 concentrations, whereas the FT3 concentration was elevated in only one patient. There was a large difference in mean FT4 values for hypothyroid and thyroid carcinoma patients, whereas the difference in mean FT3 values was small, suggesting a decreased peripheral conversion of T4 to T3 with increasing concentrations of FT4. ……As a single test, serum TSH is therefore not very useful for the assessment of adequate thyroxine dosage in patients with primary hypothyroidism”.


“Once heralded as the pathway underpinning adequate thyroid hormone replacement therapy with levothyroxine, the role of these enzymes has come into question as they have been implicated in both an inability to normalise serum levels of triiodothyronine (T3) and the incomplete resolution of hypothyroid symptoms.”


“Now that the mechanism underlying the inability of levothyroxine mono therapy to universally normalise serum T3 in patients with normal serum TSH concentrations is understood, it is important that future investigations into the clinical significance of a low serum T3 concentration or high T4:T3 ratio are done. High quality randomised controlled clinical trials are also justified to establish whether patients with the ThrS92Ala D2 polymorphism have a unique response to combination therapy.”


“It appears that some patients are unable to convert the ingested L-T4 into an adequate amount of T3. The insufficient peripheral T3 production cannot be appropriately corrected by increasing L-T4 dose. …….. Because of tissue heterogeneity, pituitary TSH secretion may not reflect what happens in other target tissues, and therefore serum TSH alone may not be a good marker for the adequacy of thyroid hormone replacement. Theoretically thyroid hormone replacement therapy should aim not only at normalization of serum TSH but also at normalization of serum free T4, free T3 and free T4/free T3 ratio”.

“Our results require replication but suggest that commonly inherited variation in the DIO2 gene is associated both with impaired baseline psychological well-being on T4 and enhanced response to combination T4/T3 therapy, but did not affect serum thyroid hormone levels.”


“FT3 levels are associated with coronary artery calcification scores and the incidence rate of MACE (Major Adverse Cardiac Events) in patients with suspected coronary artery disease. A low FT3 level is considered as an important risk factor of high calcification scores and MACE (Major Adverse Cardiac Events).”


“In a large cohort of euthyroid men and women, FT4 and FT3 levels within the normal range were inversely associated with the risk of all-cause mortality and cancer mortality, particularly liver cancer mortality.”


“Using the average SD50 for the two T3 regimens (37 mug/day), the calculated relative potency indicates that oral T3 is 3.3 times as potent as oral T4, a value in reasonable agreement with the value previously estimated with a calorigenic end-point.”


“The therapeutic substitution of L-T3 for L-T4 was achieved at approximately 1:3 ratio.”
76. Jonklaas J, Burman KD. Daily Administration of Short Acting Liothyronine is Associated with Significant Triiodothyronine Excursions and Fails to Alter Thyroid-Responsive Parameters. Thyroid 2016;thy.2015.0629.

“Once daily dosing of liothyronine at doses of 30-45 mcg did not return serum TSH to the values seen during levothyroxine therapy. There were significant excursions in serum total and free T3 concentrations with once daily therapy. “


“Our data suggests that despite chronic combined T3/T4 therapy, wide peak-to-trough variation in fT3 levels persists.”

78. Senese R, Cioffi F, de Lange P, Goglia F. Thyroid: Biological Actions of “Nonclassical” Thyroid Hormones. J Endocrinol 2014;221:R1-12

“The overall nongenomi processes, emerging as important accessory mechanisms in TH actions, have been observed at the plasma membrane, in the cytoplasm and cytoskeleton, and in organelles. “


“T2 might be a valuable indicator of T3 metabolism, and its elevations in NTIS could explain why patients with low-T3 syndrome substituted with T4/T3 don’t benefit of exogenous TH administration.”


“Acute endocrine adaptations are directed toward providing energy and substrates for the vital fight-or-flight response in a context of exogenous substrate deprivation. Distinct endocrine and metabolic alterations characterize the chronic phase of critical illness, which seems to be no longer solely beneficial and could hamper recovery and rehabilitation.”

81. Maia AL, Goermann IM, Meyer ELS, Wajner SM. Type 1 Iodothyronine Deiodinase in Human Physiology and Disease: Deiodinases: the Balance of Thyroid Hormone. J Endocrinol 2011(5);209:283-97

“The iodothyronine deiodinases catalyze the removal of an iodine residue from the pro-hormone thyroxine (T4) molecule, thus producing either the active form
triiodothyronine (T3; activation) or inactive metabolites (reverse T3; inactivation). Type I deiodinase (D1) catalyzes both reactions. “

82. Chopra IJ. A study of Extrathyroidal Conversion of Thyroxine (T4) to 3,3',5-Triiodothyronine (T3) in Vitro. Endocrinology101:453-63


84. Reverse T3 Dominance.


In addition to the effect of high cortisol, “other causes of reverse T3 dominance include: leptin resistance, inflammation (NF kappa-B), dieting, nutrient deficiencies such as low iron, selenium, zinc, chromium, Vit B6 and B12, Vit D and iodine, low testosterone, low human growth hormone, insulin dependent diabetes, pain, stress, environmental toxins, free radical load, hemorrhagic shock, liver disease, kidney disease, severe or systemic illness, severe injury, surgery, toxic metal exposure.”


“A 1.5- and 1.3-mg/kg dosage calculation based on actual weight is currently the best estimation for levothyroxine replacement therapy after thyroidectomy.”


“The current standard of weight-based thyroid replacement fails to appropriately dose underweight and overweight patients. Body mass index can be used to more accurately dose thyroid hormone using a simple formula.”

87. Di Donna V, Santoro MG, de Waure C, Ricciato MP, Paragliola RM, Pontecorvi A, Corsello SM. A New Strategy to Estimate L evothyroxine Requirement After Total Thyroidectomy for Benign Thyroid Disease. Thyroid 2014;24:1759-64

“A new correlation between optimal dose and presurgical levels of fT3 and mean corpuscular volume was observed.”

“Disruption of key elements in the hypothalamic-pituitary-thyroid axis as well as the deiodinase system in animals suggest that maintaining a stable serum T3 within normal range is a biological priority. At the same time, an analysis of a large number of hypothyroid patients maintained on levothyroxine replacement therapy indicate that monotherapy restores serum TSH levels without normalizing serum T3 in a portion of patients. The clinical relevance of a relatively lower serum T3 is unknown. “

89. Shimon I, Cohen O, Lubetsky A, Olchovsky D. hyrotropin Suppression by Thyroid Hormone Replacement Is Correlated With Thyroxine Level Normalization In Central Hypothyroidism. Thyroid 2002;12(9):823-7

“Plotting measurements of TSH against FT4 for 6 individuals with central hypothyroidism showed different regression slope for each patient. Suppression of TSH by thyroid replacement to levels below .1 mU/L predicted euthyroidism in 92% of cases, compared to 34% when TSH was above 1 mU/L (p<.0001). In conclusion in central hypothyroidism baseline TSH is usually within normal values, and is further suppressed by exogenous thyroid hormone as in primary hypothyroidism, but to lower levels. Thus insufficient replacement may be reflected by inappropriately elevated TSH levels, and may lead to dosage increment. “


“Suppressed TSH levels were associated with elevated FT4 levels in 37.5% of patients and normal FT4 levels in 62.5%”


“Our study indicated that a moderately TSH-suppressive dose of L-T4 is required to achieve the preoperative native serum T3 levels in postoperative L-T4 therapy. “


“This study suggests that at slightly suppressing TSH doses, LT4 therapy has no adverse effects on BMD in both pre- and postmenopausal women, while having an efficacy on nodule size comparable with that reported using an LT4 schedule able to maintain TSH near or below the assay sensitivity limit.”

“We found no consistent evidence that low TSH a sensitive biomarker of excess thyroid hormone, was associated with low BMD or accelerated bone loss in older ambulatory women.”


“There was no difference in bone metabolic markers and incidence of vertebral deformity between the groups. These prospective and cross-sectional data suggest that long-term levothyroxine therapy using suppressive doses has no significant adverse effects on bone.”


Of 63 identified studies, 31 studies reported no effects of levothyroxine on bone mineral density, 23 studies showed partial beneficial or adverse, and 9 studies overall adverse effects. A significant dose-response was not found. There was a tendency towards peripheral cortical bone loss, suggesting a site-specific effect. In adolescents, men, and premenopausal women evidence for levothyroxine influence was weaker than in postmenopausal women. However, also findings in postmenopausal women remained unclear. The extent and etiology of underlying thyroid diseases also contributed to inconsistent results. Further, controversial results were due to substantial heterogeneity of studies. Above all, studies were limited by moderate quality, small size, and inadequate control for confounders. Based on current studies there is insufficient evidence about effectiveness of levothyroxine on bone mineral density.”


“In this patient population, the reduction in bone mineral density due to thyroxine is small. It is unlikely to be of clinical significance and should not on its own be an indication for reduction of thyroxine dose in patients who are clinically euthyroid.

97. Lindner, H.

http://hormonerestoration.com/files/ThyroidPMD.pdf

“Thyroid hormone does not cause bone loss, it simply increases metabolism and therefore the rate of the current bone formation or loss. Most older women
are losing bone due to their combined sex steroid, DHEA, Vitamin D, and growth hormone deficiencies. The solution is not life-long hypothyroidism, but the correction of their other deficiencies.”

98. Bassett JHD, Williams GR. Role of Thyroid Hormones in Skeletal Development and Bone Maintenance. Endocr Rev 2016;Feb;er20151106.

“The skeleton is an exquisitely sensitive and archetypal T3-target tissue that demonstrates the critical role for thyroid hormones during development, linear growth, and adult bone turnover and maintenance.”


“low TSH levels per se did not diminish bone quality, supporting the hypothesis that levels of TSH alone might not be associated with osteoporosis “


“Chronic high iodine intake has been associated in various studies with increased frequency of autoimmune thyroiditis. …

“Selenium supplementation may be useful in autoimmune thyroid diseases, though, while usually well-tolerated, it should not be universally recommended, and it is also likely to be helpful for those with low Se status and autoimmunity.”


“The prevalence of vitamin D insufficiency in HT cases (148 of 161, 92%) was significantly higher than that observed in healthy controls (102 of 162, 63%, p < 0.0001).”

103. Vitamin D Council:

http://www.vitamindcouncil.org/about-vitamin-d/testing-for-vitamin-d/?gclid=Clynofnx1MwCFQmqaqodqMEMvQ


Food, dietary fibre and espresso coffee interfere with the absorption of levothyroxine. Malabsorptive disorders reported to affect the absorption of levothyroxine include coeliac disease, inflammatory bowel disease, lactose intolerance as well as Helicobacter pylori (H. pylori) infection and atrophic gastritis. Many commonly used drugs, such as bile acid sequestrants, ferrous sulphate, sucralfate, calcium carbonate, aluminium-containing antacids, phosphate binders, raloxifene and proton-pump inhibitors, have also been shown to interfere with the absorption of levothyroxine.”


“Actual diagnosis of PAS involves serological measurement of organ-specific autoantibodies and subsequent functional testing.”

108. Chaker L et al.: Study Links Low Thyroid Function to Greater Odds of Type 2 Diabetes | Endocrine Society. 98th Annual Meeting of the American Endocrine Society 2016;4;1-3 (Abstract).
About the Authors

Professor Dr Rudolf Hoermann, MD PhD

Rudolf received his MD and PhD from the University of Munich, Germany and is a board certified Internist and Endocrinologist. His training included a fellowship with Harvard University, Boston, USA. During his career Rudolf has worked in various positions at leading universities in Germany. He has also headed the Department of General Medicine, Gastroenterology and Endocrinology at Klinikum Luedenscheid, a major teaching hospital for ten years. He is a member of numerous medical societies.

Rudolf's ongoing interest in thyroidology and extensive experience in basic and clinical research is documented by the authorship or co-authorship of more than 100 articles or reviews in peer-reviewed journals, numerous book sections, and many international scientific presentations.

M L Rowe:

Mel has been a hypothyroid patient for fifty years. For most of that time he was inadequately tested and undiagnosed. He has a BS and MS in Engineering, spent thirty five years in automotive manufacturing, and been extensively trained in the Design of Experiments and Statistical Analysis, all greatly facilitating his research into hypothyroidism over the last six years.

Upon finding the MedHelp Thyroid Forum years ago, Mel learned of the importance of Free T3 on tissue thyroid effects, including symptoms, so enabling him to optimise his FT3 level and feel better than he could even remember. In repayment he spends time daily researching hypothyroidism and helping other thyroid patients from around the world.

Mel came to recognise the need for clear and concise information on the inadequacy of current testing and treatment of hypothyroidism, and recommendations for improvement that could be easily understood and pursued by patients. During his researches he was greatly impressed by scientific studies by his co-authors. That prompted ongoing discussion and eventually a partnership invaluable to the development and completion of this paper.

P S Warmingham BSc MIET:

In 1972 Peter gained a BSc Honours degree in Electrical and Electronic engineering. He completed forty six years of service with Rolls Royce as an electronics engineer. For the last ten years before retiring in 2011, he worked on reliability assessments of electrical equipment used in safety-critical instrumentation and control systems.

In 1995, Peter began researching first fibromyalgia and later hypothyroidism, becoming involved with local and national self-help groups, and joined Thyroid UK in 2003. Peter has had articles published in the Fibromyalgia Association UK’s magazine, Thyroid UK’s newsletter and website, the East Midlands Fibromyalgia Support Group’s newsletter and the Environmental Issues Forum (EIF) newsletter.

In 2010, Dr John Lowe published Peter’s article on the interpretation of TSH results in the on-line journal Thyroid Science, prompting the initial responses from both Rudolf and Mel which eventually lead to the three of them to collaborating on the writing of this article.
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