# The Diagnosis and Treatment of Hypothyroidism: A Patient's Perspective

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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, sleep apnoea and diabetes 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 investigations 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. Free T3 (FT3), which is significantly more biologically active than FT4, is largely ignored. Clinical evaluation has been largely superseded by TSH and FT4 tests, which will be shown later to be inadequate.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/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].

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 [4]. 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 [5 - 9].

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 [10].

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

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.[11] TSH should not be used to determine the medication dosage.

The above abstract should provide general information adequate to encourage a potential hypothyroid patient to engage in a discussion about following the preceding suggestions and if more detailed information is sought give a copy of all 38 pages to their doctor.

The following is a detailed review of those suggestions, along with supporting scientific evidence needed to answer questions from doctors and inquisitive patients who want to delve deeper. However, it 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 [12]. 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 [13]. 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 [14, 15] 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, diabetes, coma and in extreme cases even death.

## How Is Hypothyroidism Currently Diagnosed?

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; those symptoms can be specific as well as non-specific. However, there are some symptoms that occur far more frequently in hypothyroid patients than normal patients and they have an important role in diagnosis.

Unfortunately, published guidelines give clear direction that consideration of symptoms has been largely superseded by supposedly sensitive thyroid function tests [1, 2]. Diagnosis currently relies almost completely on a TSH test and a follow-up FT4 test compared to reference ranges. However the guidelines state that:

> "A guideline is not intended to take the place of physician judgment in diagnosing and treatment of particular patients".

They also state that:

> "We encourage medical professionals to use this information in conjunction with their best clinical judgment."

These statements are essentially ignored in favour of almost total reliance on the TSH and FT4 tests. If diagnosis really required nothing further in the way of additional knowledge of the patient or good judgement, it could be done more effectively by a computer; however, as will be shown, this is clearly not the case.

## Review of Current Diagnostic Practices

Current diagnostic practices have been found to be inadequate through the experience of many millions of hypothyroid patients 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 control appears to be much more complex than previously thought with important implications for diagnosis and treatment of thyroid disease [16]. The actual response from each of these areas will vary widely from one individual to another. In effect, each person has his own thyroid process parameter values at which he feels normal.

   Several scientific studies have shown that reference ranges based on the specific thyroid test results of individuals were approximately half those of population ranges. This applies to all thyroid tests [17 - 25]. So, trying to identify abnormality by comparing an individual's TSH, FT4, or FT3 test result to the much wider reference range for the entire population can be very misleading [5, 26] Furthermore, the current upper range limit for TSH, calculated from group data, 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 [5, 26 - 28].

   No matter what reference range is used, TSH doesn't tell us what we need to know about the thyroid status in a given person.

2. Group studies have shown that TSH, particularly within the reference range, does not even correlate well with the biologically active thyroid hormones, FT4 and FT3 [29], and has negligible correlation with tissue thyroid effects and resulting symptoms, which are the patient's prime concern [4 - 9].

3. Hypothyroidism results from diminished body functions due to inadequate metabolism of thyroid hormone at the tissue level throughout the body. However, as shown in Figure 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 several other causes:

a. A dysfunction of the hypothalamus/pituitary system resulting in inadequate stimulation of the thyroid gland by TSH (central hypothyroidism).

b. Inadequate conversion of the pro-hormone 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. "RT3 is an excellent marker for reduced cellular T4 and T3 levels not detected by TSH or serum T4 and T3 levels." [30]. "There is also evidence of RT3 binding to membrane receptors and producing hypo-metabolic effects." [11]

d. A tendency for FT3, the biologically active thyroid hormone shown to correlate best with symptoms, to diminish with age, sometimes resulting in hypothyroid symptoms that are frequently overlooked as just being age related [31, 32].

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 [30].

f. Deficiencies in the confounding variables shown in Figure 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 where TSH is not suppressed despite elevated circulating concentrations of thyroid hormones.

So the bottom line is that hypothyroidism has a wide range of potential causes, and it occurs when one or more of these conditions results in inadequate tissue thyroid effects, with consequent diminished body functions. As shown in Figure 1, the number of intervening process variables and confounding variables between tissue thyroid effects and a TSH test precludes good correlation between the two, thus rendering TSH inadequate as the primary diagnostic tool [16, 33 - 37].

4. When a serum TSH test exceeds the reference then a FT4 test usually 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. The validity of that reference range is thus a major concern [26, 38].

   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 [39, 40, 41]. Instead those ranges are locally established in the small series of 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 TSH range to identify hypothyroidism even contaminates ranges established for FT4 and FT3. In addition, as previously discussed, trying to identify abnormality by comparing individual test results to group reference ranges can be very misleading [26 - 28].

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".

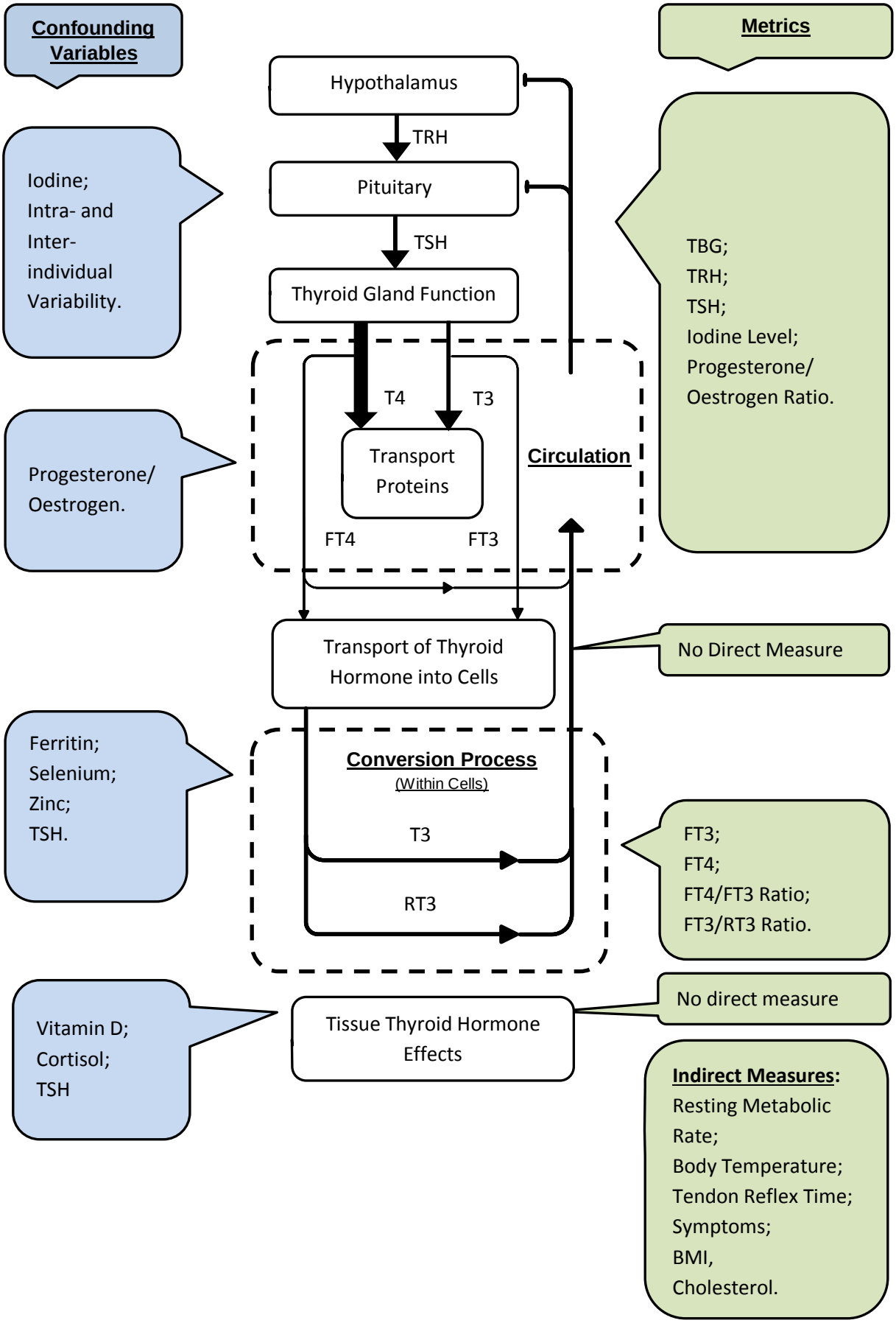
In another section it is stated,

> "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.

Coupled with the tendency of thyroid patients to downplay their symptoms, these flawed diagnostic procedures have resulted in an enormous number of 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 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 tissue thyroid effects. From that process view we can select and evaluate surrogate measures that, in conjunction with the knowledge and clinical judgment of the doctor, will result in more effective diagnoses. In fact, laboratory data must not be interpreted without knowledge of the patient history and clinical examination.

## Figure 1. Processes and Variables Affecting Tissue Thyroid Effects



## Review of Figure 1

As mentioned previously there 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, but these so-called individual set points may be significantly different from one individual to another [5, 16 -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.

As shown in Figure 1, there is a conversion process that determines the balance between 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.

Then there is another process that actively transports thyroid hormone across the cellular membrane. This is not simply a result of diffusion; it is also affected by a number of variables [33].

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 [42 - 44].

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. As shown in Figure 1, the only likely upstream candidates for the indirect measurement of tissue thyroid effects are TSH, FT4, FT3 and RT3. Due to all the intervening processes, and confounding variables, that come between TSH and tissue thyroid effects, and TSH having been discounted as an accurate diagnostic measure of euthyroidism in the previous analysis discussion, TSH does not meet the requirements of a primary diagnostic.

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" [35]. They also demonstrated in the same study that:

a) 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, and that

b) RT3 inversely correlates with physical performance scores and the T3/RT3 ratio is a useful indicator of tissue levels of thyroid hormone [6].

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.” [30]

A study of the correlation of thyroid function tests on a composite score of typical hypothyroid symptoms concluded that they correlated best with urine FT3, but significant variability was not accounted for by FT3 alone [34].

Having only a relatively few upstream measures indicative of tissue thyroid levels and effects we have to consider downstream candidates. These include resting metabolic rate, body mass index, and cholesterol levels. From experience and scientific information, the best of these candidates to use as diagnostics are tendon reflex time and 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]. This may become even more useful now that objective tests for measuring tendon reflex time in milliseconds have been developed.

Furthermore, a composite list has been developed of signs and symptoms, 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 [10].

## 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 adequate to raise 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]. In addition, due to their flawed ranges as 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, 38. 44]. 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 [31. 44]. If cortisol is low in the range, lower levels of FT4 and FT3 may be effective, as discussed below. 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 [45].

2. If signs and symptoms are significant, but biochemical abnormalities are minor, then an ultrasound test of the thyroid gland may reveal characteristic trauma from Hashimoto's Thyroiditis or reduced/inadequate thyroid volume.

3. Given adequate evidence of hypothyroidism, the patient should be started on a therapeutic trial of thyroid medication. There is much controversy about the current medication of choice, which is synthetic levothyroxine (L-T4) [46]. 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 [36, 37, 47]. Further dose adjustment should be guided individually by relief of symptoms and tolerance of the medication dosage.

4. While L-T4 mono therapy works for many hypothyroid patients, there are others who require the addition of L-T3 to feel well. “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” [48]. 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 [25, 49- 52], and

   b. those that did find a measurable improvement and participants liked it better [53 - 58].

   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, when 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" [44, 59 - 62]. 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 triiodothyronine (T3) and the incomplete resolution of hypothyroid symptoms" [63, 64].

5. 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 [65].

   Given this recognition 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 [44]. 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 [66]. This underscores the necessity for individualised treatment strategies.

   In summary L-T4 monotherapy remains the treatment of 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 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 (MACE) [67, 68].

6. When adding L-T3 to a hypothyroid patient's medication, is should be noted that the conversion tables available 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 [1, 69, 70].

7. It should be noted that L-T3 medication doses should best be split in half for a morning and early afternoon dose [71]. Since L-T3 reaches peak effect in 3 to 4 hours, and then drops off, this split dose provides a more consistent effect over the full day. In addition, the guidelines [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 [72].

8. Since each person has their own thyroid process levels that provide the needed tissue thyroid effect, as discussed above, specific target values for thyroid function tests do not apply to individuals. Thyroid hormones should be prescribed as needed to eliminate the symptoms and signs of hypothyroidism without producing any symptoms or signs of thyroid hormone excess. Given the variation in the dose response and apparent FT3 – TSH dissociation under LT4, FT4 and FT3 tests are the most valuable tests for monitoring a patient's progress with increasing doses of thyroid medication [58 - 60]. 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.

9. 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 [16, 73, 74].

   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 [75, 76]. The conversion of T4 into T3 becomes inefficient whereas RT3 accumulates [77]. 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 [78]. 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" [78].

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 [78].

10. It should be noted that when taking adequate thyroid medication, the TSH level in an L-T4 treated patient is frequently suppressed below the reference range [79 - 81]. 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 no longer stimulating natural thyroid hormone production, or is suppressed, will serum thyroid levels reflect further increases in thyroid medication [37].

    Concerns that suppressed TSH without concomitant elevation of free thyroid hormones will cause osteoporosis are unfounded [82 - 86]. "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 [87]. 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 [88, 89].

11. 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 [90 - 92]. Dose adequacy should then be assessed and adjusted as needed, with relief of symptoms being the main concern. While severe grave 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 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 a treated collective on L-T4 treatment. This phenomenon, which has been long known to practitioners, has recently been documented by large clinical studies [47, 58, 93].

12. Hypothyroid patients are frequently too low in the ranges for Vitamin D and ferritin, as previously identified for testing [94, 95]. Since fatigue is one of the main symptoms of hypothyroidism, B12 should also be tested, and all three optimised. Recommendations for the target levels for 25-hydroxy vitamin D differ among various guidelines; it should be 50ng/mL according to the Vitamin D council [96], those for ferritin should be above 100ng/mL [97], and B12 should best be above 500pg/ml [98].

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

13. 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 [99].

14. 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.

15. Diabetes type 1 is more prevalent as a second autoimmune disorder in patients with autoimmune thyroid disease [100]. 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 [101]. 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.

16. 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

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| ATA | American Thyroid Association |
| Athyreotic | Absence or functional deficiency of the thyroid gland |
| BMI | Body Mass Index |
| Co-factors | Any of various organic or inorganic substances necessary to the function of an enzyme. |
| Confounding Variable | 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. |
| DHEA | 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. |
| Euthyroid | The state of having normal tissue thyroid levels and effects, so that there are neither hypo nor hyper symptoms. |
| Homeostasis | The property of a system in which variables are regulated so that internal conditions remain stable and relatively constant |
| L-T3 | Liothyronine (synthetic T3) |
| L-T4 | Levothyroxine (synthetic T4) |
| MACE | Major Adverse Cardiac Events |
| NDT | Natural Desiccated Thyroid |
| NHANES | National Health and Nutrition Examination Survey |
| RMR | Resting Metabolic Rate |
| RT3 | Reverse T3 |
| Sprue | A chronic form of Malabsorption Syndrome |
| TBG | Thyroxine-Binding Globulin |
| TG-ab | Thyroglobulin Antibodies |
| TPO-ab | Thyroid Peroxidase Antibodies |
| TRH | Thyroid Release Hormone |
| TSH | Thyroid Stimulating Hormone |

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   *"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".*

5. Hoermann R, Midgley JEM. TSH Measurement and its Implications for Personalised Clinical Decision-Making. J Thyr R, 2012; Article 1D 438037

   *"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."*

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   *"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 the T3/RT3 ratio is currently the best indicator of tissue levels of thyroid."*

7. Ehrenkranz J, Bach PR, Snow GL, Schneider A, Lee JL, Ilstrup S, et al. Circadian and Circannual Rhythms in Thyroid Hormones: Determining the TSH and Free T4 Reference Intervals Based Upon Time of Day, Age, and Sex. 201525(8):954-61

   *"TSH levels vary diurnally by up to approximately 50% of mean values, with more recent reports indicating up to 40% variation on specimens performed serially during the same time of day."*

8. Gerber M. Epidemic Hypothyroidism Part 1 of 2 for doctors,

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   *"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."*

9. Skinner GRB, Holmes D, Ahmad A, Davies JA, Benitez J, Clinical Response to Thyroxine Sodium in Clinically Hypothyroid but Biochemically Euthyroid Patients J Nutr Environ Med 2000;10 (2):115-124

   *Purpose: To examine clinical response to thyroid replacement therapy in patients considered to be clinically hypothyroid but with normal thyroid biochemistry.*

   *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). Patients were treated with 25 mcg day - 1 thyroxine sodium for 1 week followed by 50 mcg day -1 for 6 weeks and an increase thereafter of 25 mcg at 6 week intervals until the patient was clinically euthyroid. Clinical response was adjudged by improvement or disappearance of clinical features of hypothyroidism; thyroid chemistry was estimated in 41 patients at 6-12 months following institution of thyroid replacement.*

   *Results: There was improvement or disappearance of all 16 clinical features in 30 patients (22%) and in over 12 features in 106 patients (76%), with a decrease in the mean number of clinical features from 13.3 - 0.18 before treatment to 3.0 - 0.23 following treatment over a minimum follow-up period of 6 months. Energy*

*loss and poor memory and concentration were most responsive to treatment while reduction in tongue size and weight gain improved in 57% and 24% of patients respectively. 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.*

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*"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."*

| Symptoms and Signs* | Sensitivity (%) | Specificity (%) | Positive Predictive Value (%) | Negative Predictive Value (%) |
|---|---|---|---|---|
| Ankle Reflex | 77 | 93.5 | 92.2 | 80.3 |
| Dry Skin | 76 | 63.8 | 67.7 | 72.7 |
| Cold Intolerance | 64 | 65.0 | 64.6 | 64.4 |
| Coarse Skin | 60 | 81.2 | 76.1 | 67.0 |
| Puffiness | 60 | 96.3 | 94.2 | 70.7 |
| Pulse Rate | 58 | 42.5 | 50.2 | 50.3 |
| Sweating | 54 | 86.2 | 79.6 | 65.2 |
| Wt. Increase | 54 | 77.5 | 70.6 | 62.8 |
| Paraesthesia | 52 | 82.5 | 74.8 | 63.2 |
| Cold Skin | 50 | 80.0 | 71.4 | 61.5 |
| Constipation | 48 | 85.0 | 76.2 | 62.0 |
| Slow Movement | 36 | 98.7 | 96.5 | 60.7 |
| Hoarseness | 34 | 87.5 | 73.1 | 57.0 |
| Hearing | 22 | 97.5 | 89.8 | 52.6 |

**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.*

11. 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) CR1-7

*"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."*

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14. Shoman M. When Endocrinologists Briefly Narrowed the TSH Reference Range.

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

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*"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."*

16. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Homeostatic control of the thyroid–pituitary axis: perspectives for diagnosis and treatment. Front Endocrinol. 2015 18(6):1-17

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*"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…A condition with abnormal serum TSH but with serum T4 and T3 within laboratory reference ranges is labelled subclinical thyroid disease. Our data indicate that the distinction between subclinical and overt thyroid disease (abnormal serum TSH and abnormal T4 and/orT3) is somewhat arbitrary. 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."*

18. Nagayama I, Yamamoto K, Saito K, Kuzuya T, Saito T. Subject-based Reference Values in Thyroid Function Tests. Endocr J 1993;40:557-62

*"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."*

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*"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 latter consists of circadian and seasonal differences although there are indicators of a genetically determined starting point. 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."*

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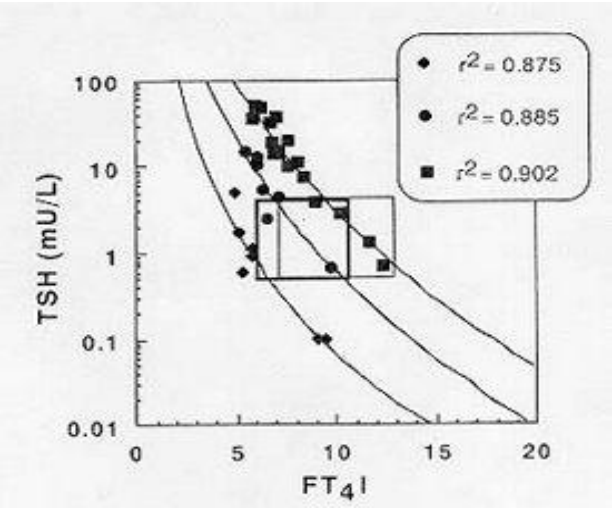
Fig. 6-7. "Correlation of the serum concentration and the free thyroxine index (FT4I) in three individuals given increasing doses of L-T4." Although there is excellent correlation of individual results, the diagram clearly shows the significant difference in inter-individual results of TSH and FT4 Index among just 3 patients.

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*"Intra-and inter individual 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".*

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*"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."*

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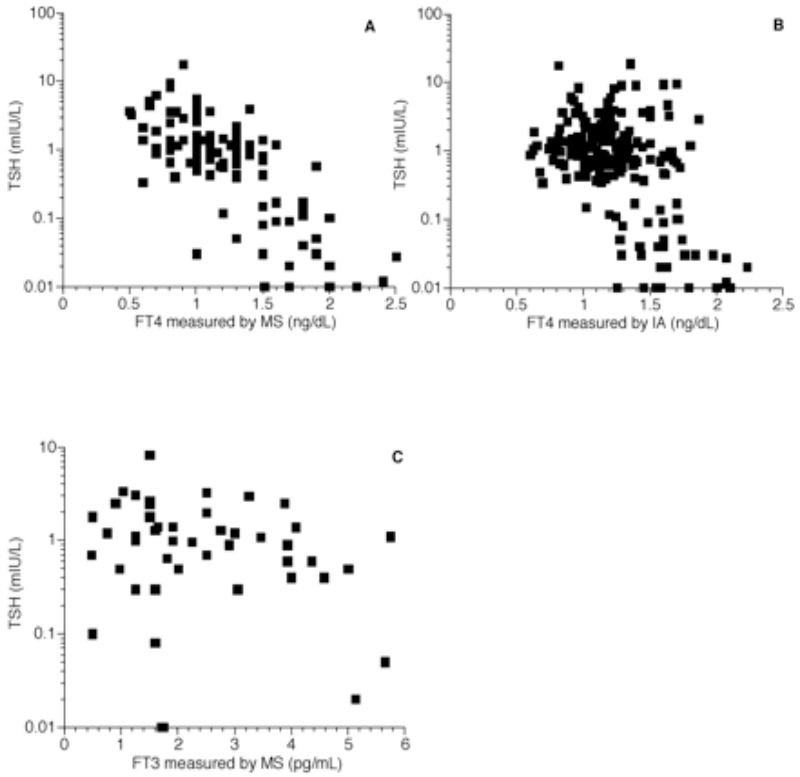


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*"Thus, a high reverse T3 demonstrates that there is either an inhibition of reverse T3 uptake into the cell and/or there is increased T4 to reverse T3 formation. These always occur together in a wide range of physiologic conditions and both cause 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".*

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*"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".*

35. Meier C, Trittiback P, Fuflielmetti M, Staub J, Muller B. Serum Thyroid Stimulating Hormone in Assessment of Severity of Tissue Hypothyroidism in Patients with Overt Primary Thyroid Failure: Cross Sectional Survey, BMJ 2003;326(7384):311-12

*"We found no correlations between the different parameters of target tissues and serum TSH. Our findings are in accordance with a cross sectional study showing only a modest correlation between TSH and the percentage of positive hypothyroid symptoms and data showing discordant responses between the pituitary and peripheral target tissues in patient treated with L-triiodothyronine. We assume that secretion of TSH is driven by maximal stimulation with no further increase occurring with greater severity of hypothyroidism. Therefore, the biological effects of thyroid hormones at the peripheral tissues - and not TSH concentrations - reflect the clinical severity of hypothyroidism."*

36. Frasier WD, Biggart EM, O'Reilly D St J, Gray HW, McKillop JH, Thomson JA. Are Biochemical Tests of Thyroid Function of any Value in Monitoring Patient Receiving Thyroxine Replacement? BMJ 1986;293(6550):808-10

*"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 hypothyroid 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

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*"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."*

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http://dx.doi.org/10.1055/s-0034-1398616

*"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".*

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"*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 assesses 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*."

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http://www.ncbi.nlm.nih.gov/pubmed/15705921

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*"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".*

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*"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".*

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http://www.ncbi.nlm.ni.gov/pubmed/23539727

*"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".*

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*"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".*

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*"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."*

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*"An L-T4 related FTTSH 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, and further encourage further study of this important issue."*

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*"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 levothyroine 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".*

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*"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."*

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*"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."*

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*"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. "*

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

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*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."*

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*Although monotherapy with levothyroxine is the standard of care for hypothyroidism, not all patients normalise serum T3 levels with many advocating for combination therapy with levothyroxine and liothyronine. The later could be relevant for a significant number of patients that remain symptomatic on monotherapy with levothyroxine, despite normalization of serum TSH levels."*

*"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 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."*

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## 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 patient 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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