Thyroid Hormone Transport into Cellular Tissue

Kent Holtorf, MD[a]

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ABSTRACT

New research is demonstrating that thyroid hormone transport across cellular membranes plays an important role in intracellular triiodothyronine (T3) levels of peripheral and pituitary tissues and is proving to have considerable clinical significance. Reduced T4 and T3 transport into the cells in peripheral tissues is seen with a wide range of common conditions, including insulin resistance, diabetes, depression, bipolar disorder, hyperlipidemia, chronic fatigue syndrome, fibromyalgia, neurodegenerative diseases, migraines, stress, anxiety, chronic dieting and aging, while the intracellular T3 level in the pituitary often remains unaffected. The pituitary has different transporters than every other tissue in the body. The thyroid transporters in the body are very energy dependent and are affected by numerous conditions, including low energy states, toxins and mitochondrial dysfunction, while the pituitary remains unaffected. Because the pituitary remains largely unaffected and is able to maintain intracellular T3 levels while the rest of the body suffers from significantly reduced intracellular T3 levels, there is no elevation in thyroid-stimulating hormone (TSH) despite the presence of wide-spread tissue hypothyroidism, making the TSH and other standard blood tests a poor marker to determine the presence or absence of hypothyroidism. Because the T4 transporter is more energy dependent than the transporter for T3, it is also not surprising that T4 preparations are generally ineffective in the presence of such conditions, while T3 replacement is shown to be beneficial. Thus, if a patient with a normal TSH presents with signs or symptoms consistent with hypothyroidism, which may include low basal body temperature, fatigue, weight gain, depression, cold extremities, muscle aches, headaches, decreased libido, weakness, cold intolerance, water retention, slow reflex relaxation phase or PMS, a combination of both clinical and laboratory assessment, which may include a T3/reverse T3 ratio and the level of sex hormone binding globulin (SHBG), should be used to determine the likely overall thyroid status and if a therapeutic trail of straight T3 or a T4/T3 combination is indicated and not based solely on standard thyroid function tests.

Keywords: Thyroid hormone transport; Membrane transport; T3; T4; TSH; Reverse T3 (RT3); Free T3/reverse T3 ratio; SHBG; Basal body temperature

[a] Corresponding author: 23456 Hawthorne Blvd, Suite 160, Torrance, CA 90505, USA,
E-mail: kholtorf@cox.net

INTRODUCTION

New research is demonstrating that thyroid hormone transport across cellular membranes plays an important role in tissue thyroid levels and is proving to have significant clinical significance. Thus, physicians who evaluate or treat thyroid dysfunction would benefit from an appreciation of this topic. Unfortunately, many physicians are not aware of new developments in the current understanding of thyroid hormone transport, which has resulted in an overreliance on the sole use of standard thyroid blood tests (e.g., thyroid-stimulating hormone (TSH) and T4 levels) to determine the presence or absence of hypothyroidism. This has resulted in the misdiagnosis of many hypothyroid patients as being euthyroid. This overreliance on standard thyroid blood tests and the overconfidence of the diagnostic accuracy of standard thyroid blood tests may be particularly troublesome in the presence of a wide range of common comorbid conditions present in a large percentage of the population.

Serum thyroid levels are, of course, commonly used as an indication of tissue thyroid activity. However, in order to have biological activity, T4 and T3 must cross the cellular membrane from the serum into the target cells. It follows that the activity of these transport processes may have a significant influence on the regulation of biological activity of these hormones. For about two and half decades it has been assumed that the rate and extent of uptake of thyroid hormone into the cells occurs by simple diffusion, which is driven by the concentration gradient of the free hormones in the serum. This "free hormone" or "diffusion hypothesis" was formulated in 1960 and assumes that the serum concentration of free thyroid hormones (free T4 and free T3) will ultimately determine intracellular thyroid hormone concentrations.

However, more recent data has challenged this hypothesized "diffusion" mechanism, showing that the transport of T4 and T3 across the cellular membrane into the cell requires active transport rather than passive diffusion.[1–66] Despite accumulating evidence to the contrary, this misconceived "diffusion hypothesis" continues to be perpetuated among both primary physicians and endocrinologist.

CONDITIONS ASSOCIATED WITH ABNORMAL THYROID TRANSPORT

Since the transport of thyroid hormones into the cell is largely energy dependent, any condition associated with reduced production of the cellular energy (i.e., mitochondrial dysfunction) could also be associated with reduced transport of thyroid hormone into the cell. This can result in cellular hypothyroidism despite having standard blood tests in the "normal" range. Conditions linked with reduced mitochondrial function and impaired thyroid transport include: insulin resistance, diabetes and obesity;[67–70, 71–75]; chronic and acute dieting;[4, 50, 65, 76–83] depression;[71, 84–86] anxiety;[71, 87] bipolar depression;[71, 84, 88, 89] neurodegenerative diseases;[71, 90–94] aging;[71, 72, 95–107] chronic fatigue syndrome;[71, 108, 109] fibromyalgia;[71, 110, 111] migraines;[71] chronic infections;[71] physiologic stress and anxiety;[71, 86] cardiovascular disease;[71, 106, 111–113] inflammation and chronic illness;[71, 114–116] and those with high cholesterol and triglyceride levels.[57, 59, 75, 76, 117] Thus, standard blood tests can be very unreliable if any of these commonly occurring conditions are present.[1, 5, 17, 22, 40, 41, 43, 48, 49, 51, 52, 54, 58–60]

It has also been shown that there are a number of substances that are produced by the body in response to dieting and physiologic stress that can negatively affect thyroid hormone transport.[5, 41] For instance, studies have shown that cell cultures incubated with serum from physiologically stressed or dieting individuals exhibit a dramatic reduction in the uptake of T4 into cells. This reduction correlated with the degree of stress.[41, 42]

It has also been demonstrated that there are a variety of distinct and specific transporters that are necessary for the transport of T4 and T3 into the cell. Furthermore, the transporter for T4 is much more energy dependent (it requires more energy) than the transporter for T3 (see Figure 1).[5, 40, 41, 48, 51, 52, 65] Even slight reductions in cellular energy (i.e., mitochondrial function) can result in dramatic declines in the cellular uptake of T4, while the uptake of T3 appears

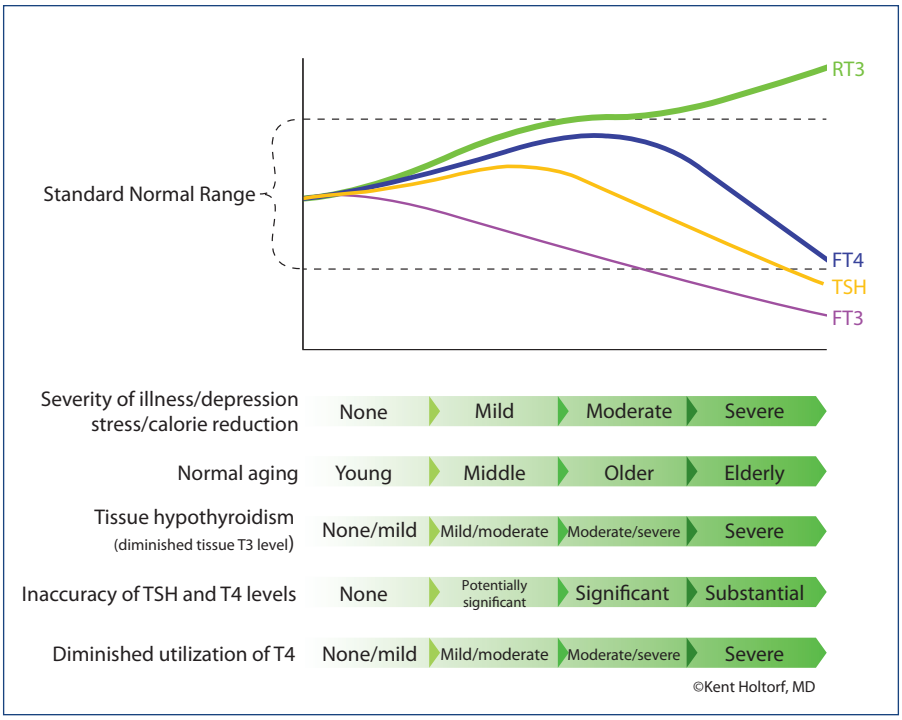

Figure 1: Serum thyroid levels with increasing physiologic stress and aging.

Associated serum thyroid levels with progressively decreasing tissue thyroid levels due to stress, illness, depression, calorie reduction or aging (Why standard blood tests lack sensitivity to detect low thyroid in the presence of such conditions).
Demonstrates why TSH levels lack the accuracy to detect cellular levels and the free T3/reverse T3 ratio is the most accurate method to determine cellular thyroid levels in the presence of physiologic stress, illness, depression or obesity.

to be much less affected.[5, 41, 61, 66] Therefore, the conditions listed above are particularly linked to an impaired transport of T4, resulting in cellular hypothyroidism. When there is reduced transport of T4 or T3 into the cells, the serum T4 and T3 levels increase (less is transported out of the serum). Thus, even though the production of T4 and T3 is diminished in chronic illness, the reduced transport into the cell will tend to raise serum levels, making the serum T4 and T3 remain normal or high-normal (see Figure 2). This is one of the primary reasons that cellular hypothyroidism is not routinely detected by standard serum T4 or T3 levels. A standard TSH level will also not detect such cellular hypothyroidism because the pituitary has completely different transporters that are not energy dependent. Therefore, while the rest of body has impaired thyroid transport, the pituitary experiences increased transport activity.[1, 17, 43, 49, 51, 54, 58–60] Another reason that the standard TSH level may not detect cellular hypothyroidism is that the nuclear thyroid receptors in the pituitary (TR-B2) are different from those in other tissues (TR-a1 and TR-B1). Pituitary receptors can become saturated and turn off TSH while other tissues are lacking thyroid stimulation.[118]

PITUITARY THYROID TRANSPORT DETERMINES TSH LEVELS

The pituitary is different than every cell in the body with its own distinct deiodinases, thyroid transporters, and high affinity thyroid receptors.[1, 17, 43, 49, 51, 54, 58–60] As mentioned previously, the pituitary thyroid hormone transporters are not energy dependent and can thus maintain or increase the cellular uptake of T4 and T3 even in low energy states.[1, 43, 54, 55, 60] This stands in stark contrast with transporters found in other parts of the body that would normally experience significantly reduced transport under similar circumstances.[1, 17, 22, 43, 49, 51, 54, 58–60]

One reason that pituitary thyroid hormone uptake is so resilient may be due to the fact that its T4 and T3 transporters are resistant to various environmental

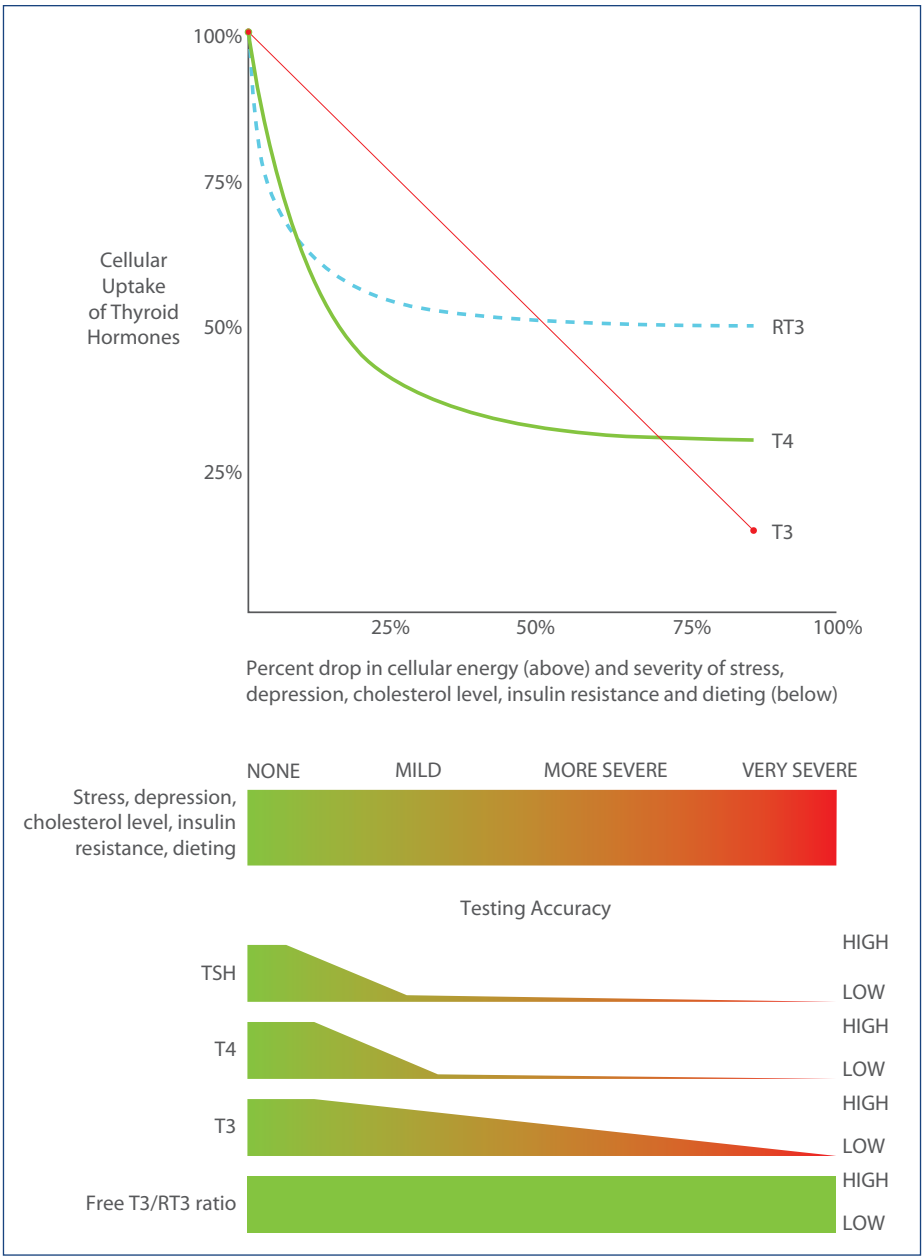

Figure 2: Thyroid transport of cellular energy. Why TSH testing is inaccurate and free T3/RT3 ratio is the best marker for thyroid transport.

Cellular thyroid levels do not correlate with serum levels if uptake into the cells is hindered. This occurs with chronic stress, depression, chronic dieting, diabetes, insulin resistance (obesity) or high cholesterol levels. Thus, with such conditions, TSH, T4 and T3 levels are not accurate measures of intracellular thyroid levels and cannot be used as reliable markers to determine the need for thyroid hormone supplementation. T4 uptake (utilization) drops much faster than T3 utilization as severity increases, making T4 replacement inappropriate for such conditions. Reverse T3 mirrors T4 uptake so high or high-normal reverse T3 is a marker for reduced uptake of T4 into the cell (and to a lesser extent T3) showing that there is a reduced overall tissue thyroid level requiring T3 supplementation (not T4). Utilizing the free T3/reverse T3 ratio does not suffer from the inaccuracies of standard tests and most closely correlates with cellular thyroid levels.

toxins and other substances produced by the body in response to physiologic stress and calorie reduction.[1, 43, 49, 54, 60] Since thyroid hormone uptake in the pituitary is relatively unaffected by outside factors, the presence of intracellular hypothyroidism is not reflected by TSH testing, which is why TSH is a poor

marker for cellular thyroid function in any tissue other than the pituitary.[1, 43, 49, 54, 55, 60] Benzodiazepine medications such as diazepam (Valium®), lorazapam (Atavan®), and alprazolam (Xanax®) are further examples where a given compound can inhibit T3 uptake into the cells of the body, but have no effect on transport of T3 into the pituitary.[60]

St Germain *et al.* investigated the comparison between thyroid hormone transport into the pituitary versus the cells of the rest of the body.[54] The authors demonstrated that the pituitary does not respond to calorie restriction (i.e., dieting) in the same way as the rest of the body. The dramatically reduced serum T4 and T3 levels that accompany dieting are associated with an increase in pituitary T3 receptor saturation (i.e., percentage of activated T3 receptors), which results in a decrease in TSH even when serum thyroid hormone levels were reduced by 50%.[54] Wassen *et al.* also demonstrated the absence of inhibitory effects of chronic caloric deprivation and bilirubin on thyroid hormone uptake by pituitary cells compared to the reduced thyroid transport that occurred in the peripheral tissue (liver).[49]

STRESS

Chronic emotional or physiologic stress can cause a significant reduction of transport of T4 into the cells of the body. For example, Sarne *et al.* added serum from different groups of individuals to cell cultures and measured the amount of T4 uptake from the serum into the cell. Their results showed that the serum from those with significant physiologic stress inhibited the uptake (transport) of T4 into the cell while the serum from the non-physiological stressed had no effect.[4] These results demonstrate that serum T4 levels can be artificially elevated among physiologically stressed individuals, and thus serum T4 and TSH levels are poor markers for tissue thyroid levels in this patient population (see Figure 2).[4] Substances produced by physiologic stress or calorie reduction (e.g., 3-carboxy-4-methyl-5-propyl-2-furan propanoic acid (CMPF), indoxyl sulfate, bilirubin and fatty acids), have been shown to reduce the cellular uptake of T4 by up to 42%, while having no effect on T4 or T3 uptake into the pituitary.[1, 3, 17, 56, 57, 59]

In addition to the above, numerous other studies have linked physiologic stress to reduced cellular uptake of T4 and T3.[42, 62, 63, 114–116] For instance, Arem *et al.* found that significant physiological stress was associated with dramatically reduced tissue levels of T4 and T3 (up to 79%) without a corresponding increase in TSH.[55] The authors also found there was tissue variability in the level of suppression in different tissues, resulting in a significant variation when comparing the T4 and T3 levels in different tissues. This large variation of T4 and T3 levels in different tissues may explain the wide range and variation in individual symptoms of hypothyroidism.[55]

DIETING

In a highly controlled study, Brownell *et al.* found that after repeated cycles of dieting, weight loss occurred at half the rate and weight gain occurred at three times the rate compared to controls with the same calorie intake.[83] Furthermore, severe caloric restriction and weight cycling is shown to be associated with reduced cellular T4 uptake of 25%–50%.[3, 48, 77, 79–81] Therefore, successful weight loss is doomed to failure unless the reduced intracellular thyroid levels are addressed, but, as stated previously, this reduced cellular thyroid level is generally not detected by standard laboratory testing.[3, 56, 57, 75–81]

In a study published in the *American Journal of Physiology-Endocrinology and Metabolism*, Van der Heyden *et al.* studied the effect of calorie restriction (dieting) on the transport of T4 and T3 into the cell.[48] They found that obese individuals in the processes of dieting exhibited a 50% reduction of T4 into the cell and a 25% reduction of T3 into the cell. This is thought to be due to the reduced cellular energy stores as well as increased levels of free fatty acids and non-esterified fatty acids (NEFA) in the serum. This data would help explain why standard thyroid blood tests are not accurate indicators of intracellular thyroid levels. This also explains why it is difficult for obese patients to lose weight; since, as calories are decreased, thyroid utilization is reduced and metabolism drops. Among patients with this type of thyroid hormone transport dysfunction (resulting in

intracellular hypothyroidism) assessing the free T3/reverse T3 ratio can aid in a proper diagnosis, with a free T3/reverse T3 ratio of less than 0.2 being a marker for tissue hypothyroidism (when the free T3 is expressed in pg/mL (2.3–4.2 pg/mL) and the reverse T3 is expressed in ng/dL (8–25 ng/dL)) (see Figure 2).[56, 57, 75–81]

REVERSE T3 (rT3)

TSH and serum T4 levels do not correlate well with intracellular thyroid levels.[119–121] There are competing factors attributing to the serum free T3 levels; reduced T4 to T3 conversion will tend to reduce serum T3 levels while the reduced uptake into the cell tends to increase serum T3 (the T3 transporter is less affected by the low cellular energy than the T4 transporter). Increased rT3 levels are shown to be predominantly due to reduced transport into the cell and not due to increased T4 to rT3 conversion. Because the rT3 and T4 transporters are equally energy dependent, a high serum rT3 is shown to be a marker for reduced uptake of T4 into the cell.[6, 41, 44, 61, 65, 66]

Thus, rT3 is an excellent marker for identifying reduced cellular T4 and T3 levels that would not normally be detected by TSH or serum T4 and T3 tests. As a result, any increase (high or high-normal) of rT3 is not only an indicator of tissue hypothyroidism but also suggests that T4-only replacement would not be considered optimal therapy. While a high rT3 can occasionally be associated with hyperthyroidism, as the body tries to reduce cellular thyroid levels, this can be differentiated on the basis of symptoms and by utilizing the free T3/rT3 ratio, which correlates with intracellular thyroid levels (see Figure 2).[6, 41, 42, 44, 61, 65, 66, 122]

TREATMENT WITH T4

Levothyroxine (T4)-only replacement with products such as Synthroid® and Levoxyl® are the most widely accepted forms of thyroid replacement. This is based on a widely held assumption that the body will convert what it needs to the biologically active form (T3). Based on this assumption, many physicians and endocrinologists believe that the normalization of TSH with a T4 preparation demonstrates adequate tissue levels of thyroid, perpetuated by practice guidelines indicating T4 monotherapy as the standard of care.[123] This assumption, however, had never been directly tested until two studies were published.[124, 125]

The first study investigated whether or not giving T4-only preparations will provide adequate T3 levels in varying tissues. Plasma TSH, T4, and T3 levels and 10 different tissue levels of T4 and T3 were measured after the infusion of 12–13 days of thyroxine. The authors found that the normalization of plasma TSH and T4 levels with T4-only preparations resulted in adequate tissue T3 levels in only a few select tissues types, namely brown adipose tissue, cerebellum and cortex. Almost every other tissue was found to be deficient. This data suggest that the use of T4 therapy (even if given at supra-physiological levels) cannot reasonably achieve normal tissue levels of T3. The authors conclude: "It is evident that neither plasma T4 nor plasma T3 alone permit the prediction of the degree of change in T4 and T3 concentrations in tissues… the current replacement therapy of hypothyroidism [giving T4] should no longer be considered adequate…."[124]

The second study utilizing an experimental model compared plasma TSH, T4 and T3 levels and 13 different tissue levels of T4 and T3 when T4 or T4/T3 treatments were utilized.[125] This study found that a combination of T4/T3 is required to normalize tissue levels of T3, and that the pituitary was able to maintain normal levels of T3 despite the rest of the body being hypothyroid on T4-only preparations. Under normal conditions it was shown that the pituitary will have 7 to 60 times the concentration of T3 when compared to other tissues of the body; and when thyroid levels drop, the pituitary was shown to have 40 to 650 times the concentration of T3 in other tissues. Thus, the pituitary is unique in its ability to concentrate T3 in the presence of diminished serum thyroid levels. Consequently, the pituitary levels of T3 and the subsequent TSH level are poor measures of tissue hypothyroidism, as almost the entire body can be severely hypothyroid despite having a normal TSH level.[125]

The dramatic reduction of T4 cellular uptake that occurs with a wide variety of conditions also

explains why T4 preparations are often associated with poor clinical response (i.e., continued residual symptoms). As stated by Hennemann *et al.* in *Endocrine Reviews*: "Even a small decrease in cellular ATP concentration results in a major reduction in the transport of T4 (and rT3) but only slightly affects T3 uptake."[5] This makes it inappropriate to use T4-only preparations when treating any condition associated with reduced mitochondrial function or ATP production, Thus, it is not surprising that T3 has been shown to be superior in such patient populations.

Fraser *et al.* investigated the correlation between tissue thyroid activity and serum blood tests (TSH, free T4, and T3) and published their results in the *British Medical Journal*. The authors concluded that "The serum concentration of thyroid stimulation hormone is unsatisfactory as the thyrotrophs in the anterior pituitary are more sensitive to changes in the concentration of thyroxin in the circulation than other tissues, which rely more on triiodothyronine (T3)." They found a suppressed or undetectable TSH was not an indication or a reliable marker of over replacement or hyperthyroidism. They state "It is clear that serum thyroid hormone and thyroid stimulating hormone concentrations cannot be used with any degree of confidence to classify patients as receiving satisfactory, insufficient, or excessive amounts of thyroxine replacement… The poor diagnostic sensitivity and high false positive rates associated with such measurements render them virtually useless in clinical practice… Further adjustments to the dose should be made according to the patient's clinical response."[126]

Similar results were observed by Meier *et al.*, who investigated the correlation of TSH and tissue thyroid effect. The authors concluded that "TSH is a poor measure for estimating the clinical and metabolic severity of primary overt thyroid failure... We found no correlations between the different parameters of target tissues and serum TSH." They stated that signs and symptoms of thyroid effect and not the TSH should be used to determine the proper replacement dose.[119]

Alevizaki *et al.* also studied the accuracy of using TSH to determine the proper T4 replacement dose, and found that the use of TSH tests (although common) cannot accurately detect cellular hypothyroidism in the majority of tissues, except for the pituitary. They conclude, "TSH levels used to monitor substitution, mostly regulated by intracellular T3 in the pituitary, may not be such a good indicator of adequate thyroid hormone action in all tissues."[120]

Likewise, Zulewski *et al.* found TSH to be an unsuitable measure of optimal or proper thyroid replacement, as they observed no correlation between TSH and tissue thyroid levels. However, serum T4 and T3 levels had some correlation, with T3 being a better indictor than T4. Based on their data, the authors concluded, "The ultimate test of whether a patient is experiencing the effects of too much or too little thyroid hormone is not the measurement of hormone concentration in the blood but the effect of thyroid hormones on the peripheral tissues [symptoms] ."[121]

In fact, the positive predictive value of TSH (the likelihood that a suppressed TSH indicates over-replacement or hyperthyroidism) has been determined to be 16%. In other words, a suppressed TSH is not associated with hyperthyroidism or over-replacement 84% of the time, making it an inaccurate marker for determining an appropriate thyroid hormone replacement dose.

Additionally, TSH levels become an even worse indicator for an optimal replacement dose in the presence of the following comorbidities: insulin resistance or obesity;[67–70, 71–75] chronic calorie reduction;[4, 50, 65, 76–83] depression;[71, 84–86] bipolar depression;[71, 84, 88, 89] neurodegenerative diseases;[71, 90–94] advanced in age;[71, 72, 95–107] chronic fatigue syndrome;[71, 108, 109] fibromyalgia;[71, 110, 111] migraines;[71] chronic infections;[71] stress or anxiety;[71, 86, 87] heart failure or cardiovascular disease;[71, 106, 111–113] inflammation or chronic illness;[71, 114–116] high cholesterol or triglyceride levels.[56, 57, 59, 75, 76, 79, 117]

SHBG

Sex hormone binding globulin (SHBG) is formed in the liver in response to the tissue level of estrogen and thyroid.[127, 128] Thus, if a patient's estrogen levels are considered to be adequate (natural or replaced), SHBG can be used as a marker for the T3 level

in peripheral tissues. As expected, the SHBG is typically low in individuals with obesity, diabetes and insulin resistance[129–131] due to the reduced transport of thyroid hormones into the cells with these individuals. Women with adequate estrogen levels should have an SHBG above 70 nmol/L and men above 25 nmol/L. If not, the diagnosis of low tissue levels of thyroid should be considered.[127] The SHBG is more useful in women than men because the normal reference range is less broad in men, making it less sensitive and less clinically useful.

In addition to being useful in diagnosing low thyroid in patients, SHBG can also be used to determine the optimal replacement dose or preparation (T4, T4/T3 vs straight T3). Because thyroid replacement is given orally, it must first undergo first pass metabolism in the liver, resulting in significantly higher hepatic levels than in other peripheral tissues. Consequentially, if the SHBG is below 70 nmol/L in women or 25 nmol/L in men who are on thyroid replacement, the rest of body would not be expected to have adequate thyroid levels. Additionally, if the SHBG does not significantly increase with replacement, this demonstrates the likelihood of a peripheral resistance to thyroid hormones.[128]

CURRENT BEST METHOD TO DIAGNOSIS

While a normal TSH cannot be used as a reliable indicator of global tissue thyroid effect, even a minimally elevated TSH (above 2 mU/L) demonstrates that there is a diminished intra-pituitary T3 level and is a clear indication (except in unique situations such as a TSH-secreting tumor) that the rest of the body is suffering from inadequate thyroid activity because the pituitary T3 level is always significantly higher than the rest of the body.[1, 17, 43, 49, 51, 54, 58–60] Additionally, the most rigorously screened individuals for absence of thyroid disease have a TSH below 2 to 2.5 mU/L.[132, 133] Thus, treatment should be considered in any symptomatic person with a TSH greater than 2 mU/L. As discussed, a free T3/rT3 ratio below 0.2 is a useful indicator of low tissue thyroid levels.[6, 41, 42, 44, 61, 65, 66, 122] Additionally, a relatively low SHBG,[127, 128–131] a slow reflex relaxation time,[134] a low resting metabolic rate (metabolism),[135] and a low basal body temperature[135, 136] can also be useful indicators of low tissue thyroid levels and can aid in the diagnosis of tissue hypothyroidism.[127, 128–131]

CONCLUSION

The most important determinant of thyroid activity is the intra-cellular level of T3, and a major determinant of the intracellular T3 level is the activity of the cellular thyroid transporters.[1–66] Reduced thyroid transport into the cell is seen with a wide range of common conditions, including insulin resistance, diabetes, depression, bipolar disorder, hyperlipidemia (high cholesterol and triglycerides), chronic fatigue syndrome, fibromyalgia, neurodegenerative diseases (Alzheimer's, Parkinson's and multiple sclerosis), migraines, stress, anxiety, chronic dieting and aging.[1–43, 46, 48, 50–52, 57, 59, 65, 67, 68, 71–117] The high incidence of reduced cellular thyroid transport seen with these conditions makes standard thyroid tests a poor indicator of cellular thyroid levels in these patient populations.

The pituitary has different transporters than every other tissue in the body; the thyroid transporters in the body are very energy dependent and are affected by numerous conditions while the pituitary is minimally affected. Because the pituitary remains largely unaffected, there is no elevation in TSH despite wide-spread tissue hypothyroidism. This explains why TSH is an inaccurate marker for tissue T3 levels for a variety of patients.[1, 3, 4, 17, 22, 43, 49, 51, 54, 58–60]

Reduced thyroid transport results in an artificial elevation in serum thyroid levels (especially T4), making this a poor marker for tissue thyroid levels, as well.[5, 40, 41, 48, 51, 52, 61, 65, 66] Rather, an elevated or high-normal rT3 along with symptoms is shown to be a reliable marker for reduced transport of thyroid hormones and an indication that a person has low cellular thyroid levels despite having normal TSH, free T4, and free T3 levels (see Figure 2).[6, 32, 41, 44, 61, 65, 66, 137–182]

The intracellular T3 deficiency seen with these conditions often results in a vicious cycle of worsening symptoms that usually goes untreated because

standard thyroid tests look normal. Additionally, it is not surprising that T4 preparations are generally ineffective in the presence of such conditions, while T3 replacement is shown to be beneficial, with potentially dramatic results.[70, 72–74, 87–89, 93, 104–112, 122, 124, 183–205] In the presence of such conditions, it should be understood that significant intracellular hypothyroidism may remain undiagnosed by standard blood tests. On the basis of the data presented here, the free T3/rT3 ratio and a low SHBG, along with signs and symptoms, including basal body temperature and the reflex relaxation phase, appear to be a more appropriate method for assessing the presence of hypothyroidism and determining whether supplementation with T3 (rather than T4 only) should be considered in a particular patient.

Thus, if a patient with a normal TSH presents with symptoms consistent with hypothyroidism, including fatigue, weight gain, depression, cold extremities, muscle aches, headaches, decreased libido, weakness, cold intolerance, water retention or PMS, a combination of both clinical and laboratory assessment should be used to determine the likely overall thyroid status and if a therapeutic trial of straight T3 or a T4/T3 combination is indicated.

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