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Thyroid Hormone Transport

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Thyroid hormone transport is an extremely important topic. It must be clearly understood by any physician who hopes to accurately evaluate an individual's thyroid status and to appropriately treat thyroid dysfunction. Unfortunately, only a small fraction physicians and endocrinologists understand even the basics of thyroid transport, because what they have learned in medical school and continue to be taught regarding this topic is incorrect. When one understands the physiology involved with thyroid hormone transport, it becomes clear that standard blood tests, including the TSH and T4 levels, cannot be used to accurately determine intracellular and tissue thyroid level in the presence of a wide range of common conditions, including chronic and acute dieting, anxiety, stress, insulin resistance, obesity, diabetes, depression and bipolar disorder, hyperlipidemia (high cholesterol and triglycerides), chronic fatigue syndrome, fibromyalgia, neurodegenerative diseases (Alzheimer's, Parkinson's and multiple sclerosis), migraines, cardiomyopathy, and aging.

Serum thyroid levels are, of course, commonly used as an indication of cellular thyroid activity. In order to have biological activity, the T4 and T3 must, however, cross the cellular membrane from the serum into the target cells. It follows that the activity of these transport processes may have an important influence on the regulation of biological activity of the thyroid hormones. For about two and half decades it was assumed that the uptake of thyroid into the cells is by simple diffusion and that the driving force for this diffusion is the concentration of the free hormones in the serum. This "free hormone" or "diffusion hypothesis" was formulated in 1960 and assumes the concentration of free hormones (free T4 and free T3) in the serum determines the rate and extent of uptake into the cell and thus intracellular thyroid hormone concentration.

This hypothesis and mechanism of thyroid uptake into the cell has been shown to be totally incorrect (1-43). It has clearly been shown that the rate-limiting (most important) step in the determination of thyroid activity is the rate of thyroid hormone transport into the cell (5,20,41,44,45) and that this transport has nothing to do with diffusion, but rather it is energy requiring active transport (1-43,45,46,47,48-64,65,66,67). The incorrect "diffusion hypothesis," however, continues to be taught in medical school and is believed to be true by most physicians and endocrinologists ([see thyroid transport graph](#) ^[1]).

Conditions associated with abnormal thyroid transport

It is important to note that because this transport of thyroid hormones into the cell is energy dependent, any condition associated with reduced production of the cellular energy (mitochondrial dysfunction) will also be associated with reduced transport of thyroid into the cell, resulting in cellular hypothyroidism despite having standard blood tests in the "normal" range. Conditions associated with reduced mitochondrial function and impaired thyroid transport include: insulin resistance, diabetes and obesity (68,69,70,71,106); chronic and acute dieting (4,51,66,72,112,113,114,115,116,117,118); diabetes (69,73,74,75,76); depression (73,77,78,79); anxiety (73,80); bipolar depression (73,77,81,82); neurodegenerative diseases (73,83,84,85,86,87); aging (73,74,88-100); chronic fatigue syndrome (73,101,102); fibromyalgia (73,103,104); migraines (73); chronic infections (73); physiologic stress and anxiety (73,79); cardiovascular disease (73,99,104,105,108); inflammation and chronic illness (73,109,110,111); and those with high cholesterol and triglyceride levels (58,60,72,106,107). Thus, standard blood tests can be very unreliable if any of these commonly occurring conditions are present (1-107).

The exact cause of the inhibition of the transport of thyroid is unknown, but it is clear that there are a number of substances that are produced by the body in response to dieting and physiologic stress that negatively effect thyroid hormone transport (5,41). This is clearly shown by studies where cell cultures are incubated with the serum from physiologically

stressed or dieting individuals; there is shown to be a dramatic reduction of the uptake of T4 by the cells that correlates with the degree of stress (41,42).

Additionally, it has been clearly shown that there are different transporters that are specific and necessary for the transport of T4 and T3 into the cell where they have their effect. The transporter for T4 is much more energy dependent (it requires more energy) than the transporter for T3 (see figure 1) (5,40,41,49,52,53,66). Even slight reductions in cellular energy (mitochondrial function) results in dramatic declines in the uptake of T4 while the uptake of T3 is much less affected (5,41,62,67). Thus, the conditions listed above have, in particular, an impaired transport of T4 that results in cellular hypothyroidism. This cellular hypothyroidism is not detected by serum T4 levels because the less T4 transported into the cell and the lower the cellular level of T4, the higher the serum T4 level. The TSH will also not detect such cellular hypothyroidism because the pituitary has completely different transporters that are not energy dependent and increase transport activity, while the rest of body has impaired thyroid transport ([see thyroid transport graph](#) ^[1]).

Pituitary thyroid transport determines TSH levels

As discussed previously, the pituitary is different than every cell in the body with different deiodinases and different high affinity thyroid receptors. It is also shown to have unique thyroid transporters that are different than those in the rest of the body (1,17,43,50,52,55,59,60,61). The pituitary thyroid hormone transporters are shown not to be energy dependent and will maintain or increase the uptake of T4 and T3 in low energy states, while this is not the case for transporters in other parts of the body that have significantly reduced transport (1,17,22,43,50,52,55,59,60,61).

The transporters for T4 and T3 in the pituitary are also not inhibited by numerous environmental toxins and substances produced by the body during physiologic stress and calorie reduction that inhibit thyroid transport into other cells in the body, including bilirubin and fatty acids. Thus, the reduced uptake of T3 and T4 and subsequent intracellular hypothyroidism that occurs throughout the body from numerous conditions stated above is not reflected by TSH testing because thyroid uptake in the pituitary cells is not effected, making the TSH a poor marker for cellular thyroid in any tissue other than the pituitary (1,43,55).

Even common medications, including benzodiazepines such as diazepam (Valium), lorazepam (Atavan) and alprazolam (Xanax), are shown to inhibit T3 uptake into the cells of the body but have no effect on transport of T3 into the pituitary (61).

This difference in pituitary thyroid transport was investigated by Germain et al. This study demonstrated that with calorie restriction (dieting), pituitary T3 content is independent of the rest of the body. The dramatically reduced serum T4 and T3 levels seen with dieting are associated with an increase in pituitary T3 receptor saturation (percent of activated T3 receptors), which results in a decrease in TSH even when serum levels were reduced by 50% (55).

Studies show that numerous conditions are associated with reduced transport of thyroid into the cells, which can lead to dramatic cellular hypothyroidism and symptoms that are not detected by standard blood tests because the TSH will be normal and serum T4 may actually increase due to reduced uptake into the cells (54). Most physicians and endocrinologist are unaware of the importance of the difference of this rate-limiting step in cellular thyroid activity in the pituitary and the rest of the body. Physicians are often quick to declare a person with numerous symptoms of low thyroid as having "normal" thyroid function based on a normal TSH and T4 level.

Wassen FS et al states in the Journal of Endocrinology that "These observations lend further support to the view that thyroid hormone transport into the pituitary is regulated differently than that in the liver (50)." As stated, the T4 level may be high normal. This high-normal T4 and low-normal TSH often leads an endocrinologist to erroneously make a diagnosis of "normal" or "high-normal" thyroid level while a patient is in fact suffering from low cellular thyroid levels ([see thyroid transport graph](#) ^[1]).

Stress

Chronic emotional or physiologic stress can cause the significant reduction of T4 into the cells of the body while the pituitary is unaffected. A study published in the Journal of Clinical Endocrinology and Metabolism studied the effect of adding serum from different groups of individuals to cell cultures and measured the amount of T4 uptake from the serum into the cell. The study found that the serum from those with significant physiologic stress inhibited the uptake (transport) of T4 into the cell while the serum from non-physiological stress had no effect, demonstrating that serum T4 levels are artificially elevated in physiologically stressed individuals and that serum T4 and TSH levels are poor markers for tissue thyroid levels in stressed individuals (4).

A number of studies have shown that significant physiologic stress reduces cellular uptake T4 and T3 by up to 50% (63,64,109,110,111). Arem et al found that with significant physiological stress, tissue levels of T4 and T3 were dramatically reduced by up to 79% without an increase in TSH. Additionally, when comparing the T4 and T3 levels in different tissues in different individuals, there is significant variation. This large variation of T4 and T3 levels in different tissues (not reflected by TSH or serum T4 and T3 levels) explains the wide range of symptoms that are due to tissue specific hypothyroidism not reflected or detected by standard blood tests, including TSH and T4 (56).

A confirming study published in the Journal of Clinical Endocrinology and Metabolism also found that serum from non-stress individuals had no effect on T4 cellular uptake, while those with significant physiologic stress had up to a 44% reduction in T4 uptake into the cell (42). It was shown that the free T3/reverse T3 ratio was the most accurate marker for reduced cellular uptake of T4 (42).

A number of substances have been identified that are produced in response to physiologic stress or calorie reduction. These include 3-carboxy-4-methyl-5-propyl-2-furapropanoic acid (CMPF), indoxyl sulfate, bilirubin and fatty acids (1,3,57,58,60). The addition of these substances to cell cultures in concentrations comparable to those seen in patients results in a 27%-42% reduction in cellular uptake of T4 but has no effect on T4 or T3 uptake into the pituitary (1,17,57,58,60) ([see thyroid transport graph](#) ^[1]).

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 (118). Chronic and yo-yo dieting, frequently done by a large percentage of the population, is shown to be associated with reduced cellular T4 uptake of 25%-50% (3,49,112,114,115,116). Successful weight loss is doomed to failure unless the reduced intracellular thyroid levels are addressed, but this reduced cellular thyroid level is generally not detected by standard laboratory testing unless a free T3/reverse T3 ratio is done.

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 (49). It was found that dieting obese individuals had a 50% reduction of T4 into the cell and a 25% reduction of T3 into the cell due to the reduced cellular energy stores, demonstrating that in such patients standard thyroid blood tests are not accurate indicators of intracellular thyroid levels. This also demonstrates why it is very difficult for obese patients to lose weight; as calories are decreased, thyroid utilization is reduced and metabolism drops. This will, however, not be detected by standard TSH, T4 and T3 testing (a free T3/reverse T3 can aid in the diagnosis of reduced uptake of thyroid hormones and intracellular hypothyroidism). Additionally, there are increased levels of free fatty acids in the serum with chronic dieting, which further suppresses T4 uptake into the cells and further cellular hypothyroidism (106,72,57,58,114).

Many overweight individuals fail to lose weight with dieting. While it is always assumed they are doing a poor job of dieting, it has been shown, however, that chronic dieting in overweight individuals results in increased levels of NEFA, which suppresses T4 uptake into the cells (3). This suppressed T4 uptake results in reduced intracellular T4 levels and

subsequent T4 to T3 conversion and a reduced metabolism (3,112,114,115,116) ([see thyroid transport graph](#) ^[1]).

Reverse T3

TSH and serum T4 levels fail to correlate with intracellular thyroid levels. Additionally, the free T3 will also tend to be less accurate with reduced cellular energy. This artificial elevation of T3 due to be reduced uptake into the cell is generally offset by a reduced T4 to T3 conversion due to reduced uptake and T4 and subsequent conversion to T3, making T3 a more accurate marker than the TSH or T4 with physiologic stress. Also, the transporter for reverse T3 (rT3) is similar to T4 in that it is energy dependent and has the same kinetics as the T4 transporter (6,41,45,62,66,67). This property (among others) makes it the most useful indicator of diminished transport of T4 into the cell (45).

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 ([see Diagnosis of low thyroid due to stress & illness Graph](#) ^[2]).

Treatment

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, most physicians and endocrinologists believe that the normalization of TSH with a T4 preparation demonstrates adequate tissue levels of thyroid. This assumption, however, had never been directly tested until two studies were published (119,120). 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.

This study demonstrated that the normalization of plasma TSH and T4 levels with T4-only preparations provide adequate tissue T3 levels to only a few tissues, including the pituitary (hence the normal TSH), but almost every other tissue will be deficient. This study demonstrated that it is impossible to achieve normal tissue levels of T3 by giving T4 only preparations unless supra-physiological levels of T4 are given. 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...(119)."

The second study compared the plasma TSH, T4 and T3 levels and 13 different tissue levels of T4 and T3 when T4 or T4/T3 preparations were utilized (120). This study found that a combination of T4/T3 is required to normalize tissue levels of T3. The study found 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 of other tissues of the body; and when thyroid levels drop, the pituitary was shown to have 40 to 650 times the concentration of T3 of other tissues. Thus, the pituitary is unique in its ability to concentrate T3 in the presence of diminished thyroid levels that are not present in other tissues. Consequently, the pituitary levels of T3 and the subsequent level of TSH are poor measures of tissue hypothyroidism, as almost the entire body can be severely hypothyroid despite having a normal TSH level (120).

These studies add to the large amount of medical literature demonstrating that pituitary thyroid levels are not indicative of other tissues in the body and showing why the TSH level is a poor indicator of a proper thyroid dose. These studies also demonstrate that it is impossible to achieve normal tissue thyroid levels with T4 preparations such as Synthroid and Levoxyl. It is no surprise that the majority of patients on T4 preparations will continue to suffer from symptoms of hypothyroidism despite being told their levels are "normal." Patients on T4 only preparations should seek out a physician who is well-versed in the medical literature and understands the physiologic limitations and inadequacy of commonly used thyroid preparations.

The dramatic reduction of T4 cellular uptake with a wide variety of conditions (T3 being less affected) also explains why T4 preparations are often associated with poor clinical response and continued residual symptoms that the unknowing physician assumes is not due to low thyroid, because serum levels look "good" if the physician does not understand the potential effects of reduced thyroid hormone transport. As stated by Hennemann G 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 if treating any condition associated with the following: reduced mitochondrial function or ATP production, which includes insulin resistance, diabetes and obesity (68,69,70,71,106); chronic and acute dieting (4,51,66,72,112,113,114,115,116,117,118); diabetes (69,73,74,75,76); depression (73,77,78,79); anxiety (73,80); bipolar depression (73,77,81,82); neurodegenerative diseases (73,83,84,85,86,87); aging (73,74,88-100); chronic fatigue syndrome (73,101,102); fibromyalgia (73,103,104); migraines (73); chronic infections (73); physiologic stress and anxiety (73,79); cardiovascular disease (73,99,104,105,108) and inflammation and chronic illness (73,109,110,111); Likewise, high cholesterol, fatty acids or triglyceride levels also selectively inhibit T4 transport into the cell as opposed to T3 (57,58,60,72,106,107,114), making T4-only preparations physiologically inappropriate for individuals with high cholesterol or triglycerides or who are chronic dieters, which dramatically increases serum free fatty acids (72). 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 study 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 thyroxine 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." (121)

The positive predictive value of the TSH, which is the likelihood that as suppressed TSH indicates over replacement or hyperthyroidism, was 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 and inappropriate marker to determine appropriate replacement dosing. Additionally, the TSH becomes an even worse indicator the optimal replacement dose in the following situations: if a person has insulin resistance or obesity (68,69,70,71,106); is a chronic dieter (4,51,66,72,112,113,114,115,116,117,118); has diabetes (69,73,74,75,76); has depression (73,77,78,79); has bipolar depression (73,77,81,82); has a neurodegenerative diseases (73,83,84,85,86,87); is of older age (73,74,88-100); has chronic fatigue syndrome (73,101,102); has fibromyalgia (73,103,104); migraines (73); has a chronic infections (73,103,104); is stressed or anxious (73,79,80); has heart failure or cardiovascular disease (73,99,104,105,108); suffers from migraines (73); has inflammation or a chronic illness (73,109,110,111); or has high cholesterol or triglyceride levels (57,58,60,72,106,107,114).

In a study published in the British Medical Journal, Meir et al also investigated the correlation of TSH and tissue thyroid effect. It was shown that the TSH level had no correlation with tissue thyroid levels and could not be used to determine a proper or optimal thyroid replacement dose. 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 (122).

Alevizaki et al also studied the accuracy of using the TSH to determine the proper thyroid replacement dose in T4 treated individuals. The study found that such a practice of using the TSH, although common, results in the majority of tissues being hypothyroid, 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 (123)."

In a study published in the Journal of Clinical Endocrinology and Metabolism, Zulewski et al also investigated the accuracy of TSH to determine proper thyroid replacement. The study found that the TSH was not a useful measure of optimal or proper thyroid replacement, as there was no correlation between the TSH and tissue thyroid levels. Serum T4 and T3 levels had some correlation, with T3 being a better indicator than T4. In contrast, a clinical score that involved a thorough assessment of signs and symptoms of hypothyroidism was shown to be the most accurate method to determine proper replacement dosing. The authors also agreed that it is improper to use the TSH as the major determinant of the proper or optimal doses of thyroid replacement, stating "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] (124)."

Conclusion

The most important determinant of thyroid activity is the intra-cellular level of T3, and the most important determinant of the intracellular T3 level is the activity of the cellular thyroid transporters (1-67). 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 (1-43,46,49,51,52,53,58,60,66,68,69,72-118).

This high incidence of reduced cellular thyroid transport seen with these conditions makes standard thyroid tests a poor indicator of cellular thyroid levels in the presence of such conditions. The pituitary has different transporters than every other tissue in the body; the thyroid transporters in the body are very energy dependent and affected by numerous conditions while the pituitary is minimally affected. Because the pituitary remains unaffected, there is no elevation in TSH despite wide-spread tissue hypothyroidism, making the TSH an inaccurate marker for tissue T3 levels under the numerous conditions listed above (1,3,4,17,22,43,50,52,55,59,60,61).

The reduced thyroid transport seen with these conditions results in an artificial elevation in serum thyroid levels (especially T4), making this a poor marker for tissue thyroid levels as well (5,40,41,49,52,53,62,66,67). An elevated or high-normal reverse T3 is shown to currently be the best marker for reduced transport of thyroid hormones and an indication that a person has low cellular thyroid levels despite the fact that standard thyroid tests such as TSH, free T4, and free T3 are normal (6,32,41,45,62,66,67,125-172) ([see Diagnosis of low thyroid due to stress & illness Graph](#) ^[2]).

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 (71,74,75,76,80,81,82,86,97,98,99,100,101,102,103,104,105,173-198). In the presence of such conditions, it should be understood that significant intracellular hypothyroidism may exist that remains undiagnosed by standard blood tests (the

freeT3/reverse T3 ratio may aid in the diagnosis). Thus, more appropriated testing beyond standard thyroid function tests should be considered and supplementation with T3 should be considered with such patients.

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