Peripheral Thyroid Hormone Conversion and Its Impact on TSH and Metabolic Activity

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ABSTRACT

There have been recent advances in understanding of the local control of thyroid activity and metabolism, including deiodinase activity and thyroid hormone membrane transport. The goal of this review is to increase the understanding of the clinical relevance of cellular deiodinase activity. The physiologic significance of types 1, 2 and 3 deiodinase (D1, D2 and D3, respectively) on the intracellular production of T3 are discussed along with the importance and significance of the production of reverse T3. The difference in the pituitary and peripheral activity of these deidoidinases under a wide range of common physiologic conditions results in different intracellular T3 levels in the pituitary and peripheral tissues, resulting in the inability to detect low tissue levels of thyroid hormone in peripheral tissues with TSH testing. This review demonstrates that extreme caution should be used in relying on TSH or serum thyroid levels to rule out hypothyroidism in the presence of a wide range of conditions, including physiologic and emotional stress, depression, dieting, obesity, leptin insulin resistance, diabetes, chronic fatigue syndrome, fibromyalgia, inflammation, autoimmune disease, or systemic illness, as TSH levels will often be normal despite the presence of significant hypothyroidism. The review discusses the significant clinical benefits of thyroid replacement in such conditions despite having normal TSH levels and the superiority of T3 replacement instead of standard T4 therapy.

Keywords: Deiodinase; T3; Reverse T3 (RT3); D1; D2; D3

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INTRODUCTION

To accurately assess thyroid function, it must be understood that deiodinase enzymes are essential control points of cellular thyroid activity that determine intracellular activation and deactivation of thyroid hormones. This local control of cellular thyroid levels is mediated through three different deiodinase enzymes present in different tissues in the body; type I deiodinase (D1) and type II deiodinase (D2) increase cellular thyroid activity by converting inactive thyroxine (T4) to the active triiodothyronine (T3) while type III deiodinase (D3) reduces cellular thyroid activity by converting T4 to the anti-thyroid reverse T3 (reverse T3)[1–9] (see Figure 1).

The activity of each type of deiodinase enzyme changes in response to differing physiologic conditions, and this local control of intracellular T4 and T3 levels results in different tissue levels of T4 and T3 under different conditions. Because it is the activity of these deiodinases and transport of T4 and T3 into the cell that determines tissue and cellular thyroid levels and not serum thyroid levels, serum thyroid hormone levels may not necessarily predict tissue thyroid levels under a variety of physiologic conditions.

DEIODINASE TYPE I (D1)

D1 converts inactive T4 to active T3 throughout the body, but D1 is not a significant determinant of pituitary T4 to T3 conversion, which is controlled by D2.[1, 7, 10] D1 but not D2 is suppressed and down-regulated (decreasing T4 to T3 conversion) in response to physiologic and emotional stress;[11–22] depression;[23–45] dieting;[46–51] weight gain and leptin resistance;[47–91] insulin resistance, obesity and diabetes;[91–99] inflammation from autoimmune disease or

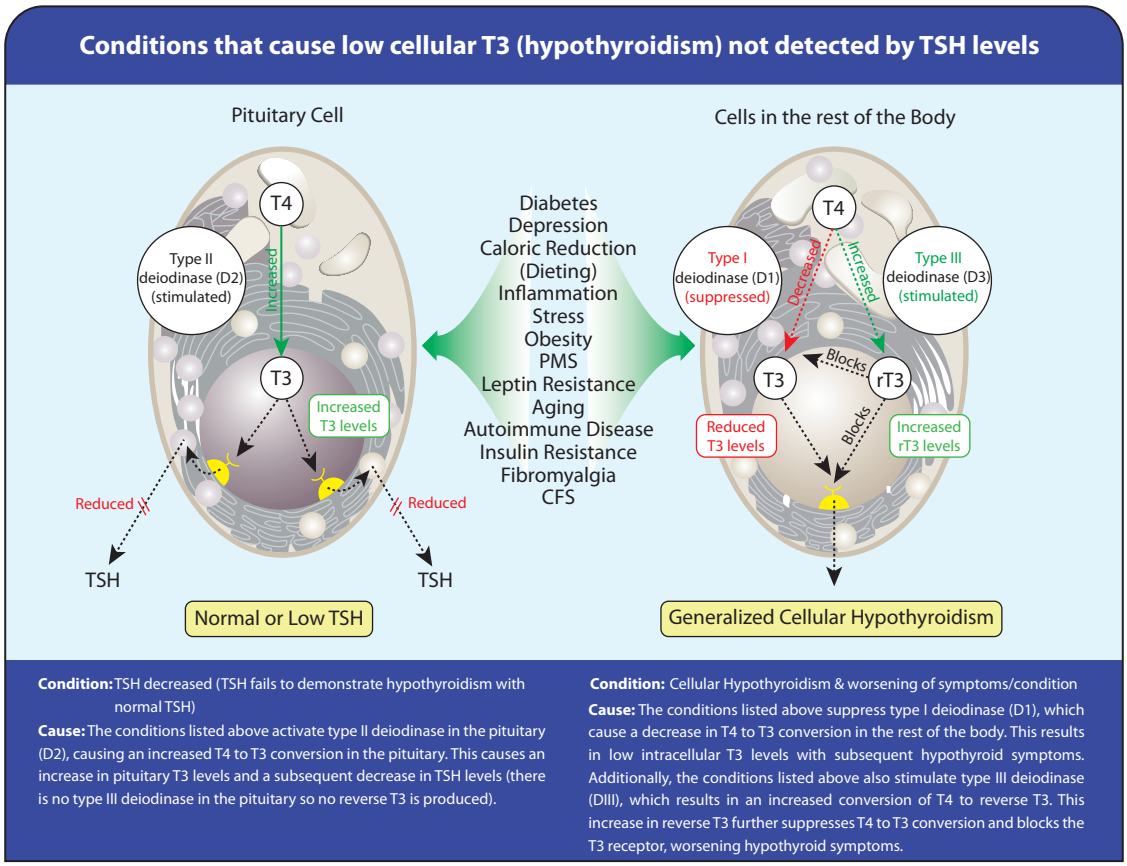

Figure 1:

systemic illness;[11, 100–113] chronic fatigue syndrome and fibromyalgia;[114–118] chronic pain;[119–123] and exposure to toxins and plastics.[124–132] In the presences of such conditions there are reduced tissue levels of active thyroid in all tissues except the pituitary. The reduced thyroid tissue levels with these conditions is often quoted as a beneficial response that lowers metabolism and thus does not require treatment, but there is no evidence to support such a stance, while there is significant evidence demonstrating it is a detrimental response.[133–140]

In addition, D1 activity is also lower in females,[141, 142] making women more prone to tissue hypothyroidism, with resultant depression, fatigue, fibromyalgia, chronic fatigue syndrome, and obesity despite having normal TSH levels.

DEIODINASE TYPE II (D2)

Thyroid stimulating hormone (TSH) is produced in the pituitary and is regulated by intra-pituitary T3 levels, which often do not correlate or provide an accurate indicator of T3 levels in the rest of the body. Using the TSH as a indicator for the body's overall thyroid status assumes that the T3 levels in the pituitary directly correlate with that of other tissues in the body and that changes directly correlate with that of T3 in other tissue of the body under a wide range of physiologic conditions. This, however, is shown not to be the case; the pituitary is different than every other tissue in the body.

Due to a unique make-up of deiodinases in the pituitary, it will respond differently and often opposite to that of every other tissue in the body. Numerous conditions result in an increase in pituitary T3 levels while simultaneously suppressing cellular T3 levels in the rest of the body, making the pituitary, and thus the TSH, a poor indicator for tissue thyroid levels in the rest of the body under numerous physiologic conditions.

In addition to having a unique make-up of deiodinases, the pituitary also contains unique membrane thyroid transporters and thyroid receptors. As opposed to the rest of the body that is regulated by both D1 and D3, the pituitary contains little D1 and no D3;[134] so pituitary T3 levels are determined by D2 activity,[1, 7, 10] which is 1000 times more efficient at converting T4 to T3 than the D1 enzyme present in the rest of the body[1, 10, 46, 143, 144] and is much less sensitive to suppression by toxins and medications.[145] Though D2 activity is present in human skeletal muscle (unexpected from studies in rats), there is less D1 and D3 present in the pituitary than in the other tissues of the body.[274] In the pituitary, 80–90% of T4 is converted to T3[2, 4, 146] while only about 30–50% of T4 in the peripheral tissue is converted to active T3.[2, 147] This is due to the inefficiency of D1 and the presence of D3 in all tissues of the body except the pituitary that competes with D1 and converts T4 to reverse T3.[7]

Additionally, D2 also has an opposite response from that of D1 to physiologic and emotional stress, depression, both dieting and weight gain, PMS, diabetes, leptin resistance, chronic fatigue syndrome, fibromyalgia, inflammation, autoimmune disease, and systemic illness. D2 is stimulated and up-regulated (increased activity) in response to such conditions, increasing intra-pituitary T4 to T3 conversion while the rest of body suffers from diminished levels of active T3. This causes the TSH to remain normal despite the fact that there is significant cellular hypothyroidism present in the rest of the body.

Thus, the pituitary levels are under completely different physiologic control and T3 levels will always be significantly higher than anywhere else in the body.[2, 4, 148–154] Consequently, if the TSH is elevated, even mildly, it is clear that many tissues of the body will be deficient in T3; but due to the different physiology, a normal TSH cannot be used as a reliable indicator for normal T3 levels in the rest of the body.

Different thyroid levels and conditions will have different effects on the T3 levels in the pituitary than in the rest of the body, resulting in different T3 levels in the pituitary and the rest of the body, making the TSH unreliable under numerous circumstances. For instance, as the levels of T4 decline, as in hypothyroidism, the activity of the D2 increases and is able to partially compensate for the reduction in serum T4.[3, 155–163] On the other hand, with reduced T4 levels, the activity and efficiency of D1 decreases[164–169] resulting in a reduction in cellular T3 levels while the TSH remains unchanged due to the ability of the pituitary D2 to compensate for the diminished T4.

As stated above, this lack of correlation of TSH and peripheral tissue levels of T3 is dramatically

worsened in numerous conditions. These include chronic emotional or physical stress, chronic illness, diabetes, insulin resistance, obesity, leptin resistance, depression, chronic fatigue syndrome, fibromyalgia, PMS, and both dieting and weight gain. In such conditions, tissue levels of T3 are shown to drop dramatically out of proportion with serum T3 levels.[8, 9, 100–102, 105, 106, 111, 170] While serum T3 levels may drop by 30%, which is significant but still may be in the so-called "normal range," tissue T3 may drop by 70–80%, resulting in profound cellular hypothyroidism with normal serum TSH, T4, and T3 levels.[8, 11, 100–102, 111, 144, 170] Consequently, in the presence of such conditions, the TSH is a poor indicator for peripheral thyroid levels and a normal TSH should not be considered a reliable indicator for an individual being euthyroid (normal thyroid), especially in the presence of symptoms consistent with thyroid deficiency.

Doctors in the thyroid division of the Department of Medicine at Brigham and Women's Hospital and Harvard Medical School investigated how the pituitary's unique deiodinase makeup responds differently than the tissues of the rest of body and how the pituitary is a poor indicator for thyroid levels in the rest of the body. In their review published in *Endocrine Reviews*, the authors state, "The approximately 1000-fold lower Km of D2 than D1 [D2 is 1000 times more efficient] may give this enzyme a major advantage in terms of extrathyroidal T3 production... The free T3 concentration in different tissues varies according to the amounts of hormone transported and the activity of the tissue deiodenases. As a result, the impact of the plasma thyroid hormones on target tissues is not the same in every tissue."[1]

In the journal *Endocrinology*, Lim *et al.* measured peripheral (liver) and pituitary levels of T3 in response to induced chronic illness.[208] They found that pituitary T3 and TSH levels remained unchanged while the peripheral tissues were significantly reduced. The authors summarize their findings by stating:

> "The reduction in hepatic nuclear T3 content and T3-Cmax in the Nx2 rats is consistent with the presence of selective tissue deficiency of thyroid hormones. The pituitary, however, had normal T3 content, suggesting a dissociation in thyroid hormone-dependent metabolic status between peripheral tissue (liver) and the pituitary. This explains the failure to observe an increase in serum TSH level, a manifestation of reduced intracellular rather than serum T3 concentration…Most interesting, we found that, in contrast to the liver, the pituitary of the Nx rats was not deprived of thyroid hormone. This finding offers a convincing explanation of the failure to observe an increase of serum TSH when illness or stress-induced reduction of hepatic T4 5′-monodeiodination causes a fall in serum t3 concentration."[208]

In the *New England Journal of Medicine*, Larsen *et al.* summarize the fact that the pituitary has a unique composition of deiodinases that is not present in any other tissue in the body, making the pituitary T3 levels, and thus the TSH, a poor indicator for tissue T3 in the rest of the body – stating that the TSH cannot be reliably used as a marker of thyroid status in the rest of the body.[146]

> "Changes in pituitary conversion of T4 to T3 are often opposite of those that occur in the liver and kidney under similar circumstances. The presence of this pathway of T3 production indicates that the pituitary can respond independently to changes in plasma levels of T4 and T3…Given these results, it is not surprising that a complete definition of thyroid status requires more than the measurement of the serum concentrations of thyroid hormones. For some tissues, the intracellular T3 concentration may only partially reflect those in the serum. Recognition that the intracellular T3 concentration in each tissue may be subject to local regulation and an understanding of the importance of this process to the regulation of TSH production should permit a better appreciation of the limitations of the measurements of serum thyroid hormone and TSH levels."[146]

DEIODINASE TYPE III (D3)

The pituitary is the only tissue that does not contain D3,[7] which converts T4 to reverse T3 and competes with D1 that converts T4 to T3.[8, 9, 11, 12, 23, 24, 92, 103, 171–175] Reverse T3 is a competitive inhibitor of T3, blocking T3 from binding to its receptor and blocking T3 effect,[176–181] reduces metabolism,[176, 179, 180] suppresses

D1 and T4 to T3 conversion,[145, 177, 179, 182–184] and blocks T4 and T3 uptake into the cell,[175, 185] all reducing intracellular T3 levels and thyroid activity. Because many tissues may have abundant D3 levels while the pituitary is uniquely void of D3,[7] the inhibitory effects on the peripheral tissues causing hypothyroidism are not reflected by TSH testing (see Figures 2 and 3).

Reverse T3 is present in varying concentrations in different tissues and with different individuals.[1, 9, 12, 61, 62, 148, 171–175, 186, 187] It is up-regulated with chronic physiologic stress and illness[1, 9, 187] and is an indicator for reduced T4 to T3 conversion and low intracellular T3 levels even if the TSH is normal.[9, 12, 103, 171, 174, 176, 185, 187, 188]

Because increased serum and tissue level of reverse T3 will result in a blocking of the thyroid receptors, even small increases in reverse T3 can result in a significant decrease in thyroid action and result in severe hypothyroidism not detected by standard blood tests.[176–181] Because any T4 given will contribute to more reverse T3, T4-only preparations should not be considered optimal thyroid replacement in the presence of high or high-normal reverse T3 levels[189–193] while T3 can be significantly beneficial.[52, 53, 114–117, 193–207]

STRESS

Chronic physiologic stress results in decreased D1 activity[11–17, 208] and an increase in D3 activity,[1, 9, 187] decreasing thyroid activity by converting T4 into reverse T3 instead of T3.[1, 9, 187, 208, 209] Conversely, D2 is stimulated, which results in increased T4 to T3 conversion in the pituitary and reduced production of TSH.[11, 16, 18–22, 208] The increased cortisol levels seen with stress also contribute to physiologic disconnect between the TSH and peripheral tissue T3 levels.[16, 18–20] This stress induced reduced tissue T3 level and increased reverse T3 results in tissue hypothyroidism and potential weight gain, fatigue, and depression.[12, 13, 186, 210–212] This vicious cycle of weight gain, fatigue, and depression that is associated with stress can be prevented with supplementation with timed-released T3[25, 26, 52, 114–117, 191, 193–207, 213, 214] but not T4.[52, 189–191, 193, 215, 216]

The reduced immunity from chronic stress has been thought to be due to excess cortisol production, but the associated reduction in tissue thyroid levels are shown to play a larger role in the decreased immunity seen with stress, and thyroid supplementation is shown to reverse the stress induced reduction in immunity.[210]

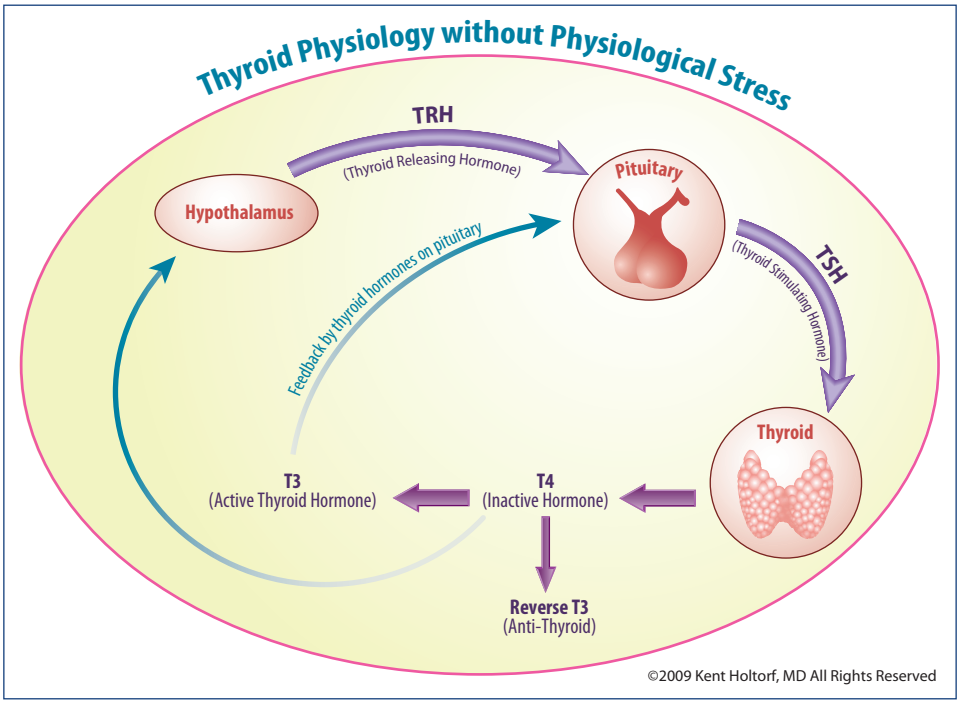

Figure 2:

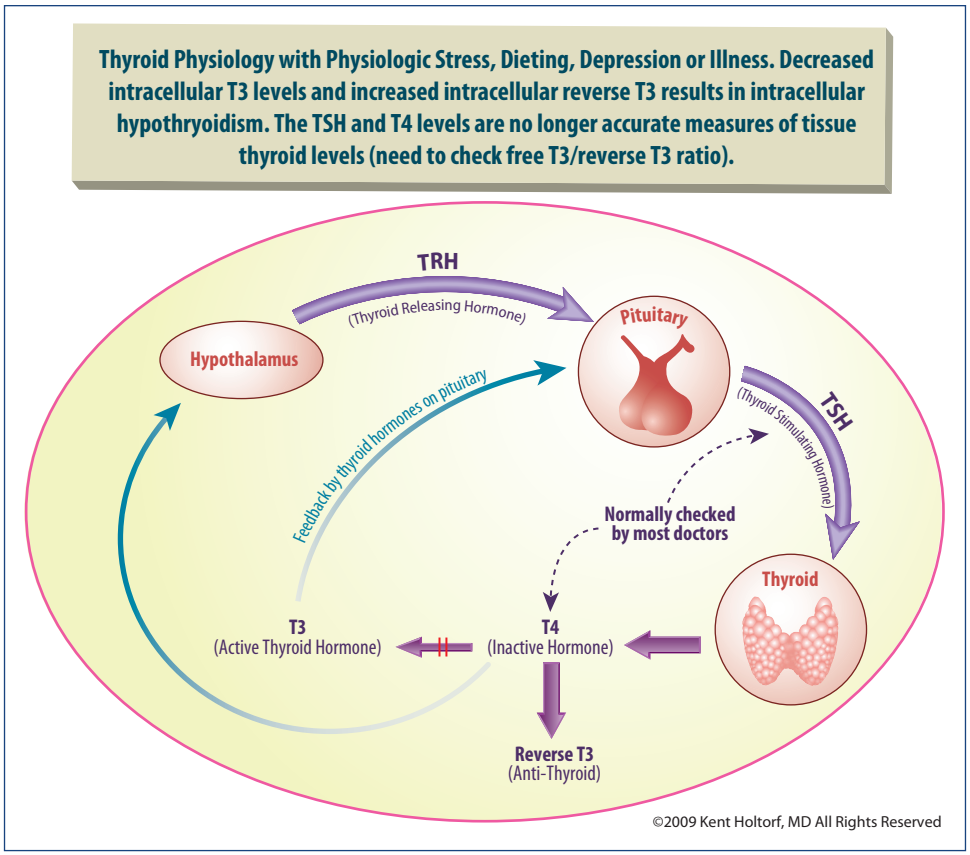

Figure 3:

As with stress, treatment with prednisone or other glucocorticoid will suppress D1 and stimulate D3, reducing T4 to T3 conversion and increasing T4 to reverse T3, causing a relative tissue hypothyroidism that is not detected by TSH testing.[12, 13, 18–21, 186, 211] This low cellular thyroid level certainly contributes to the weight gain and other associated side-effects with such treatment. Thus, in stressed patients or those treated with corticosteroids, there are reduced tissue T3 levels that are not reflected by the TSH level, making the TSH an inappropriate marker for tissue levels of T3.

DEPRESSION

Many depressed and bipolar patients have undiagnosed thyroid dysfunction as the underlying cause or major contributor to their depression.[23–38] The dysfunction present with these conditions includes down regulation of D1 (reduced T4 to T3 conversion) and reduced uptake of T4 into the cell, resulting in increased serum T4 levels with low intracellular T3 levels[24–26, 30, 31, 35, 39–45] and upregulated D3, resulting in elevated reverse T3,[23, 24, 30, 31] which blocks the thyroid effect[145, 176–186] and is an indicator of reduced transport of T4 into the cell.[175, 185] Additionally, studies show that depressed patients have reduced T4 transport across the blood brain barrier due to a defective transport protein, transthyretin, resulting in significantly reduced thyroid levels in the brains of depressed patients despite "normal" serum levels and standard thyroid tests[23, 39, 40] as well as a reduced TSH response to TRH.[28–31, 43–50]

It is not surprising that T4 and T4/T3 combinations may have some benefit in depression; but due to the suppressed T4 to T3 conversion from suppressed D1[24–26, 30] and reduced uptake of T4 into the cell and brain,[25, 31, 39, 40] timed-released T3 is significantly more beneficial than T4 or T4/T3 combination supplementation.[25, 41, 194, 213, 217–219]

In the *International Journal of Neruopsychopharmacology*, Posternak *et al.* published a double blind placebo control trial of 50 patients with normal thyroid function as defined by a normal TSH (1.5±0.8). The patients were randomized to receive 25 µg of T3 or placebo in addition to antidepressant therapy.[214] The study found almost a two-fold increase in response rate with T3 and a 4.5 times greater likelihood of experiencing a positive response at any point over a six-week period with the addition of T3. Side effects were higher in placebo group on 10/11 criteria including a significant increase in nervousness with the placebo group.

Kelly *et al.* investigated the effectiveness of T3 for the treatment of biopolar disorder in patients who had failed to adequately respond to an average of 14 medications used to treat their bipolar disorder. The average dose of T3 used was 90.4 µg (range 13–188 µg). The medication was found to be well tolerated and 84% experienced significant improvement and 33% had a full remission. Again, this is in patients who had not previously responded to numerous medications. One patient who was switched to T4 for cost reasons experienced a return of symptoms, which resolved with the reintroduction of T3. The authors concluded, "Augmentation with supraphysiologic doses of T3 should be considered in cases of treatment resistant bipolar depression…."[219] The authors thanked several doctors who encouraged them to go beyond the traditional 50 µg of T3 because it has helped so many of their patients.

With over 4000 patients, The Star*D Report is the largest trial comparing antidepressant effectiveness for depression. It found that 66% of patients fail to respond to antidepressants or have side-effects severe enough to discontinue use. Of those who do respond, over half will relapse within one year.[220] The trial found that T3 was effective even when other medications – such as citalopram (Celexa), bupropion (Wellbutrin), sertraline (Zolft), venlafaxine (Effexor), or cognitive therapy – were not. It was shown to be 50% more effective, even with the less than optimal dose of 50 µg, under direct comparison with significantly less side effects than commonly used therapeutic approaches with standard antidepressants. The authors included a case study to exemplify the effectiveness of T3, especially when other medications are not:

> "Ms. 'B,' a 44-year-old divorced white woman, became depressed after losing her job as a secretary in a law firm. She initially sought treatment from her primary care physician and then entered the STAR*D study. Ms. B met criteria for major depressive disorder and generalized anxiety disorder. Her baseline QIDS-SR score was 16. After 12 weeks on citalopram, her QIDS-SR score was 10 [minimal response]. She was then randomly assigned to augmentation with buspirone; she soon experienced gastrointestinal distress, and she stopped taking buspirone after 6 weeks. She elected to try one more augmentation agent and was randomly assigned to T3 augmentation. When she started T3 augmentation, her QIDS-SR score was 12. After 4 weeks, she felt that her mood and energy had lifted substantially. She felt better able to make decisions, organize, and prioritize and felt that she was able and ready to look for another job. 'I felt as if my brain suddenly had oxygen,' she said, 'and everything became clearer.' After 12 weeks, Ms. B felt back to normal, and her QIDS-SR score was 0 [complete resolution of symptoms]."[220]

With an understanding of thyroid physiology and associated dysfunction that is present in depressed patients, it is clear that timed-released T3 supplementation should be considered in all depressed and bipolar patients despite "normal" serum thyroid levels. Additionally, straight T4 should be considered inappropriate and suboptimal therapy for replacement in such patients.

PAIN

Chronic pain will significantly suppress D1 and upregulate D2, resulting in a reduction in tissue T3 without a change in TSH. Thus, the significant cellular hypothyroidism is not detected by serum TSH and T4 testing.[119–122] This cellular hypothyroidism, which again is undiagnosed by standard blood tests, increases the risk of the associated fatigue and depression seen with chronic pain.[119–221]

Narcotic pain medication can, of course, alleviate pain and thus potentially improve the diminished tissue T3 levels seen with chronic pain; but narcotics also suppress D1 but not D2, so such treatment

is ineffective at reversing the suppressed tissue T3 levels.[119–121, 221] Thus, for those with significant chronic pain or using significant amounts of narcotic pain medicine, it must be understood that such a condition is associated with low tissue thyroid levels not detected by standard blood tests. Tolerance to the inhibitory effect of narcotics on TSH secretion and T4 to T3 conversion does not occur.[119, 122] Expert pain specialists understand this and recommend T3 supplementation to patients with significant pain or on narcotic pain medications.[221]

DIETING

Acute or chronic dieting can result in a significant decrease in intracellular and circulating T3 levels by up to 50%,[46, 47, 51, 90] which significantly reduces basal metabolic rate (number of calories burned per day) by 15–40%.[48, 222, 223] With chronic dieting, the thyroid levels and metabolism often do not return to normal levels; the body stays in starvation mode for years with significantly reduced metabolism despite the resumption of normal food intake, making it very difficult to lose or maintain lost weight.[48]

A study by Araujo *et al.* published in *American Journal of Physiology, Endocrinology and Metabolism* found that 25 days of calorie restriction (dieting) significantly reduced D1, resulting in reduced T4 to T3 conversion with a 50% reduction in T3. This dramatic reduction in T3 was associated with an increase in D2, so there was no increase in TSH but rather a decrease from an average of 1.20 ng/mL to 0.7 ng/mL, demonstrating the fact that the TSH is a poor marker for tissue T3 levels, especially in a chronically dieting patient.[47]

Fontana *et al.* found that T3 levels were significantly decreased by 25% in chronically dieting individuals compared to non-dieting individuals with no difference in TSH and T4 (thus undetected by TSH and T4 testing). This clinically significant reduction in T3 levels, potentially causing inability to lose weight or regaining of lost weight, fatigue, and depression, remained in the normal range despite the significant decline, demonstrating the weakness and unreliability of the common use of population reference ranges that consider 95% of the population as "normal".[49]

A study by Leibel *et al.* published in the journal *Metabolism* found that individuals who had lost weight in the past had a significantly lower metabolism than those of same weight who had not gained or lost significant weight in the past.[48] The metabolism in the weight reduced patients was 25% less than an equal weight person who did not lose or gain significant weight in the past and equal to someone who weighed 60% less than they did. Additionally, the reduction was shown to be present years later.

This 25% percent reduction in metabolism equates to an approximate deficit of 500–600 cal per day. Thus, if the previously overweight persons are to maintain the reduced weight they lost, they must either eat 600 cal per day less compared to a person of the same weight who has not had a weight problem or must jog about 1 ½ hours per day to maintain the lost weight. This equates to approximately a pound per week of weight gain, explaining why weight is so quickly gained without continued very strict dieting. So many people who have difficulty keeping weight off don't eat excessively but are continually told they are eating too much or they need to exercise more by people who have never had a weight problem. They are made to feel it is a character issue and that nobody believes how little food they actually consume. Unless the physiologic thyroid dysfunction is corrected, any diet and exercise strategy is doomed.

Croxson *et al.* in *Journal of Endocrinology and Metabolism* found that individuals with a history of intense dieting had dramatic reductions in T4 to T3 conversion with an intracellular deficiency of T3. The inadequacy and inaccuracy of standard TSH and T4 testing was demonstrated, as such testing failed to detect the dramatic reduction in tissue levels of T3 in all of the patients.[50]

INSULIN RESISTANCE/DIABETES/ METABOLIC SYNDROME/OBESITY

As with leptin resistance, it has been shown in numerous studies that insulin resistance, diabetes, or metabolic syndrome have associated significant reduction in T4 to T3 conversion, an intracellular deficiency of T3, and an increased conversion of

T4 to reverse T3, further reducing intracellular T3 levels.[91, 92, 94, 100, 145, 176–185, 224] Additionally, the elevated insulin will increase D2 activity and suppress TSH levels, further decreasing thyroid levels and making it inappropriate to use the TSH as a reliable marker for tissue thyroid levels in the presence of elevated insulin levels as occurs with obesity, insulin resistance, or type II diabetes.[91–99, 225]

Pittman *et al.* found that normal individuals had a 77% conversion of T4 to T3, while diabetic individuals had a 45% conversion of T4 to T3 and increased T4 to reverse T3. Improvement in glucose levels only slightly increased T4 to T3 conversion to 46%.[93]

Islam *et al.* investigated the T4 to T3 conversion in 50 diabetic patients compared to 50 non-diabetic controls. There was no difference in TSH and free T4 levels, but the diabetic individuals had significantly decreased free T3 levels (P=0.0001) that averaged 46% less than controls. The FT3/FT4 ratio was 50% less in diabetic patients versus controls. The TSH failed to elevate despite the fact that serum T3 was approximately half of normal.[92] Saunders *et al.* also found that diabetics had approximately a 50% reduction in T3 levels and significantly increased reverse T3 levels and decreased T3/reverse T3 ratios.[94]

In the *International Journal of Obesity*, Krotkiewski *et al.* published the results of their investigation of the impact of supplemental T3 on cardiovascular risk in obese patients to partially reverse the reduced T4 to T3 conversion seen with obesity.[53] Seventy obese patients with "normal" standard thyroid function tests were treated with 20 µg of straight T3 for six weeks. While the dose was not high enough to completely reverse the reduced T4 to T3 conversion seen with obesity, there was a significant reduction in a number of cardiovascular risk factors, including cholesterol and markers for insulin resistance. There were no side-effects in any of the patients. The authors conclude, "T3 may be considered to ameliorate some of the risk factors associated with abdominal obesity, particularly in some subgroups of obese women with a relative resistance to thyroid hormones possibly dependent on decreased peripheral deiodination of thyroxine (T4)."[53]

Thus, replacement with timed-released T3 preparations to normalize the reduced intracellular T3 levels is appropriate in such patients despite so-called "normal" levels while, on the contrary, T4-only preparations do not address the physiologic abnormalities of such patients and should be considered inappropriate replacement for obese patients or those with insulin resistance, leptin resistance, or diabetes, as they do not address the physiologic abnormalities in this group.

LEPTIN

The hormone leptin has been found to be a major regulator of body weight and metabolism. The body secretes leptin as weight is gained to signal the brain (specifically the hypothalamus) that there are adequate energy (fat) stores. The hypothalamus should then stimulate metabolic processes that result in weight loss, including a reduction in hunger, an increased satiety with eating, an increase in resting metabolism, and an increase in lipolysis (fat breakdown). New research has found that this leptin signaling is dysfunctional in the majority of people who have difficultly losing weight or are unable to lose weight.[54–58]

The problem is not in the production of leptin; studies show that the majority of overweight individuals who are having difficulty losing weight have a leptin resistance, where the leptin is unable to produce its normal effects to stimulate weight loss.[54–58] This leptin resistance is sensed as starvation, so multiple mechanisms are activated to increase fat stores, rather than burn excess fat stores.[54–83] Leptin resistance is shown to suppress D1 and stimulate D2, resulting in reduced cellular T3 but a reduction in serum TSH.[47, 84–89] A study by Cettour-Rose *et al.* published in *American Journal of Physiology, Endocrinology and Metabolism* demonstrated that physiologic reversal of leptin resistance restored deiodinase activity except in the presence of elevated reverse T3.[86] Thus, in the presence of elevated leptin level (above 10) there is a reduction of cellular T3 and a suppression of TSH, making the TSH an unreliable indicator of thyroid status, especially when combined with an elevated reverse T3. Thus, for anyone who has difficulty losing weight, a leptin level above 10 demonstrates that low intracellular thyroid level is contributing to this difficulty, especially if

combined with a high normal or elevated reverse T3 (above 150).

EXERCISE

It has been shown that women or men who perform more than moderate exercise, especially when associated with dieting, have reduced T4 to T3 conversion and increase reverse T3, counteracting many of the positive effects of exercise in women including weight loss.[226, 227] Consequently, T3 and reverse T3 levels should be evaluated in individuals who exercise and/or diet to better determine cellular thyroid levels, as TSH and T4 would not necessarily reflect tissue levels in such patients.

IRON DEFICIENCY

Iron deficiency is shown to significantly reduce T4 to T3 conversion, increase reverse T3 levels, and block the thermogenic (metabolism boosting) properties of thyroid hormone.[228–232] Thus, iron deficiency, as indicated by an iron saturation below 25 or a ferritin below 70, will result in diminished intracellular T3 levels. Additionally, T4 should not be considered adequate thyroid replacement if iron deficiency is present.[228, 229, 231, 232]

INFLAMMATION ASSOCIATED WITH COMMON CONDITIONS

The inflammatory cytokines IL-1, Il-6, C-reactive protein (CRP), and TNF-alpha will significantly decrease D1 activity and reduce tissue T3 levels.[102, 104–111] Any person with an inflammatory condition – including physical or emotional stress,[233–238] obesity,[238–242] diabetes,[238, 239, 243] depression,[244–246] menopause (surgical or natural),[247] heart disease,[238, 248, 249] autoimmune disease (lupus, Hashimoto's, multiple sclerosis, arthritis, etc.),[112, 113, 160, 250] injury,[251] chronic infection[252, 253] or cancer[254–256] – will have a decreased T4 to T3 conversion in the body and a relative tissue hypothyroidism. The inflammatory cytokines will, however, increase the activity of D2 and suppress the TSH despite reduced peripheral T3 levels; again, making a normal TSH an unreliable indicator of normal tissue thyroid levels.[102, 104–111]

There is a direct inverse correlation between CRP and reduced tissue T3,[110, 257] so individuals with elevated CRP (greater than 3 mg/L) or other inflammatory cytokines will have a significant reduction in cellular T3 levels. The suppression of intracellular T3 levels correlates with the degree of elevation of CRP, despite serum thyroid tests being "normal".[110, 257] Thus, if any inflammation is present, which is found in numerous clinical and subclinical conditions (as above), the body will have lower cellular T3 levels that are often inadequate for optimal functioning; but the pituitary will have increased levels of T3, resulting in a lowering of the TSH that would potentially be inappropriately interpreted as an indication of "normal" thyroid levels.

Thus, any person with an inflammatory condition will have diminished tissue levels of T3 potentially severe enough to cause symptoms, but these symptoms will not be detected by standard thyroid testing. Additionally, due to the reduced T4 to T3 conversion induced by the inflammation in these conditions, effective treatment must include T3 (combination or, ideally, timed-released T3). Also, due to the inflammatory suppression of TSH, not only is a normal TSH necessarily an indication of euthyroidism (normal thyroid), but also a suppressed TSH is not necessarily an indication of excessive thyroid with treatment. Rather, free T3 and reverse T3 levels along with clinical parameters should be used to determine optimal replacement doses of thyroid.

Additionally, inflammation will stimulate D3, producing more reverse T3, further causing cellular hypothyroidism not detected by TSH testing by suppressing intracellular T4 to T3 conversion and blocking the T3 receptor inside the cell.[258]

ENVIRONMENTAL TOXINS

Numerous toxins, including plastics such as bisphenol-A, pesticides, mercury, and flame retardants such as PBDE, are shown to block tissue thyroid receptors and reduce T4 to T3 conversion with resultant low tissue levels of thyroid that are not detected by standard blood tests.[124–132, 259] In addition to being

1000 times more efficient at converting T4 to T3,[1, 143] D2 is 100- to 1000-fold less sensitive to suppression by toxins or by mineral or hormonal deficiencies.[1–5, 143, 215, 260, 261] Thus, the D1 in the body is suppressed by toxins, pesticides, and plastics at levels that are hundreds to thousands times lower than required to suppress the D2 in the pituitary. This is proving to be a major problem for the population in general; levels of plastics and other toxins commonly found in individuals (toxins that are considered "normal" exposure) result in reduced levels of T3 in all tissues with the exception of the pituitary, which is resistant to the effect of toxins. Because the pituitary is relatively unaffected, the reduced tissue thyroid levels are not detected by standard TSH testing.

For instance, bisphenol-A, which is ubiquitous in the environment and large amounts of which can leach into food and liquids from plastic water bottles and the lining of aluminum cans, is shown to significantly block thyroid activity in all tissues except the pituitary, potentially contributing to or causing weight gain, fatigue, and depression but not detected by TSH testing.[126, 127, 130, 131, 262] Levels of a number of thyroid blocking toxins, including bisphenol-A and PBDEs, are significantly higher in individuals in the United States (PBDEs being especially high in California),[262, 263] resulting in reduced T3 effect in all tissues in almost all individuals in the United States compared to the rest of the world that is not detected by standard thyroid testing. This is potentially a significant contributor to the epidemic of obesity and depression in the US.

TESTOSTERONE

Low testosterone in men will result in a lowering of D1 activity without changing pituitary D2.[141] Thus, a drop in testosterone will result in lower tissue levels of T3 without producing an elevation of TSH.[141, 142] Environmental factors, including pesticides, plastics,

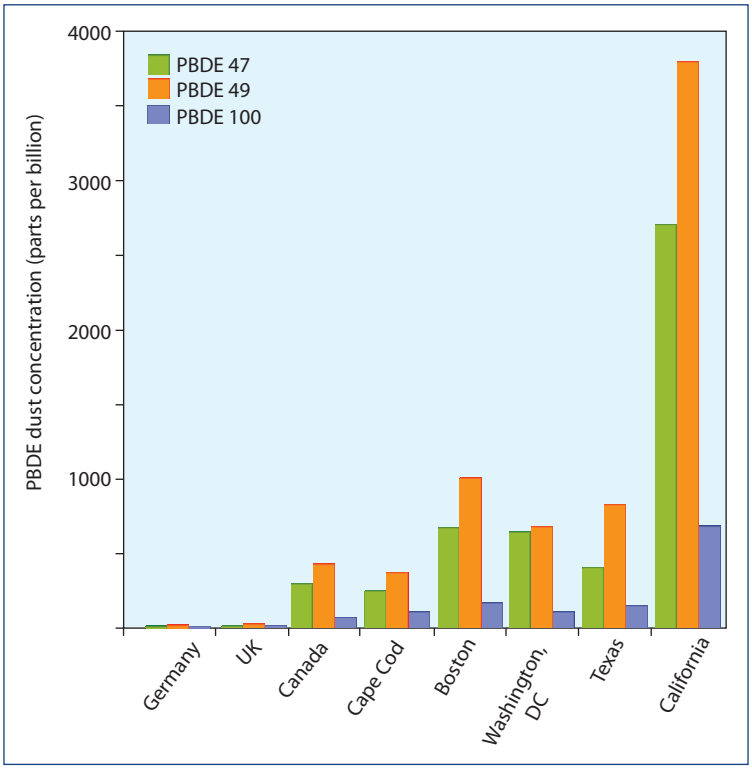

Figure 4:

Reprinted (adapted) with permission from Zota AR, Rudel RA, Morello-Frosch RA, Brody JG. Elevated house dust and serum concentrations of PBDEs in California: unintended consequences of furniture flammability standards? *Environ. Sci. Technol.* 2008;42:8158–64.

Age dependent variations in mean serum levels of Free T4 (A), Free T3 (B) and TSH (C) in healthy individuals – a combined analysis of the literature. Demonstrates that TSH is not a reliable marker of active thyroid (T3) levels (low T3 levels are associated with decreased, not increased, TSH levels).

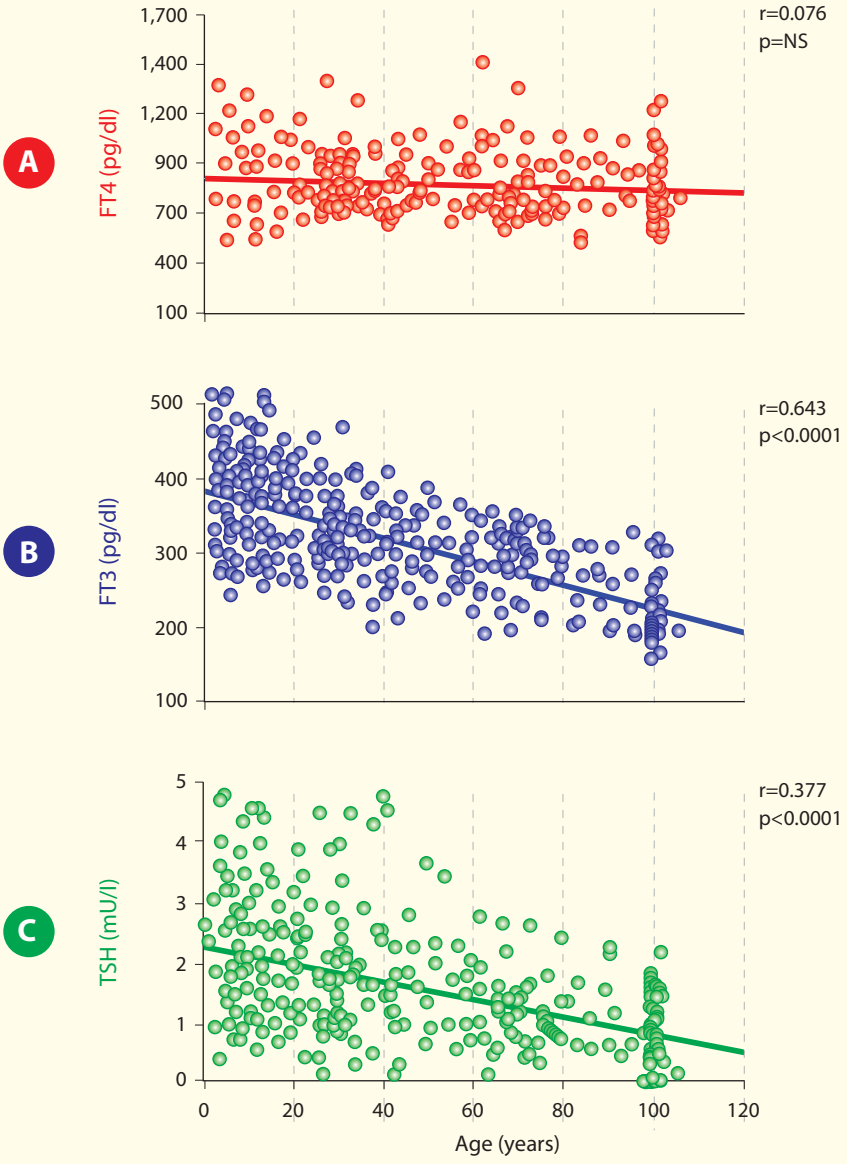

Figure 5:

1. Schwartz E, Holtorf, K. Hormones in Wellness and Disease Prevention: Common Practices, Current State of the Evidence, and Questions for the Future. *Prim Care Clin Office Pract*. 2008;35:669–705.
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5. Jankowska H. The effect of age on parameters of thyroid function. *Endokrynol Pol*. 1993;44(2):117–27.

and other pollutants, have resulted in a significant decrease in the average testosterone levels for men, so most men will have, at least, a relative deficiency of testosterone.[264] Major laboratories have, unfortunately, reduced the "normal" range of free testosterone to maintain the 95th percentile as normal, the result being that many abnormally low levels will now be considered normal.

In particular, the majority of male diabetics and those with insulin resistance will have suppressed testosterone level that is in the low or low-normal range, which further suppresses D1 and tissue T3 levels and perpetuates the weight gain or inability to lose weight – worsening these conditions.[265–267]

GROWTH HORMONE

Growth hormone deficiency reduces T4 to T3 conversion and increases reverse T3 while supplementation with growth hormone improves T4 to T3 conversion and reduces reverse T3.[186, 225, 268, 269] The age-associated decline in growth hormone certainly contributes to the reduced T3 levels with age not detected by TSH and T4 testing (see Figure 5).

INDIVIDUAL VARIATIONS IN DEIODINASE

The relative amounts of D1, D2, and D3 vary in different tissues among different individuals[270] and under varying conditions,[8, 11–21, 23–26, 28–45, 100–102, 105, 106, 111, 119–127, 144, 170, 209, 221] resulting in hundreds of possible symptoms with hypothyroidism; some people have one symptom, some have a few, and some people have many, depending on the relative level of T3 in each tissue. Unfortunately, serum thyroid levels often do not accurately reflect intracellular tissue levels or levels in a particular tissue.

SUMMARY

With an improved understanding of thyroid physiology that includes the local control of intracellular activation and deactivation of thyroid hormones by deiodinases, it becomes clear that standard thyroid tests often do not reflect the thyroid status in the tissues of the body, other than the pituitary. This is especially true with physiologic and emotional stress, depression, dieting, obesity, leptin insulin resistance, diabetes, chronic fatigue syndrome and fibromyalgia, inflammation, autoimmune disease, or systemic illness. Consequently, it is inappropriate to rely on a normal or low TSH as an adequate or sensitive indicator of normal or low tissue levels of T3 in the presence of any such conditions, making the TSH a poor marker for the body's overall thyroid level.

In order to be appropriately and thoroughly evaluated for thyroid dysfunction and obtain optimal treatment, it is important that patients find a thyroidologist who understands the limitations of standard thyroid testing and can clinically evaluate patients by taking an extensive inventory of potential signs and symptoms that may be due to low tissue thyroid levels despite normal standard thyroid tests.

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