- National Academy of Hypothyroidism - https://www.nahypothyroidism.org -

Deiodinases

Posted By *Kent Holtorf M.D.* On January 27, 2012 @ 6:09 pm In | Comments Disabled

---

Understanding Local Control of Thyroid Hormones:

(Deiodinases Function and Activity)

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 deiodinase figure).

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 systemic illness (11,100,102-115); chronic fatigue syndrome and fibromyalgia (121-125); chronic pain (116-120); and exposure to toxins and plastics (126-134). 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 (135-142).

In addition, D1 activity is also lower in females (143,144), making women more prone to tissue hypothyroidism, with resultant depression, fatigue, fibromyalgia, chronic fatigue

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 (91,100,92,94,147,184-193,235). 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 (91-99,233).

Pittman CS 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 S 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 decrease 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 J, 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 mcg 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 levels 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 (236,237). 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 (238-242). 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 (238,239,241,242).

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 (105-113). Any person with an inflammatory condition — including physical or emotional stress (243-248), obesity (248-252), diabetes (248,249,253), depression (254-257), menopause (surgical or natural) (258), heart disease (248,259,260), autoimmune disease (lupus, Hashimoto's, multiple sclerosis, arthritis, etc) (114,115,164,265), injury (266), chronic infection (261,262) or cancer (267-269) — 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 (105-113)

There is a direct inverse correlation between CRP and reduced tissue T3 (112,270), 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" (112,270). 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 (271).

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 (126-134,283). In addition to being 1000 times more efficient at converting T4 to T3 (1,145), D2 is 100 to 1000-fold less sensitive to suppression by toxins or by mineral or hormonal deficiencies (1,2-5,145,224,273,274). Thus, the D1 in the body is suppressed by