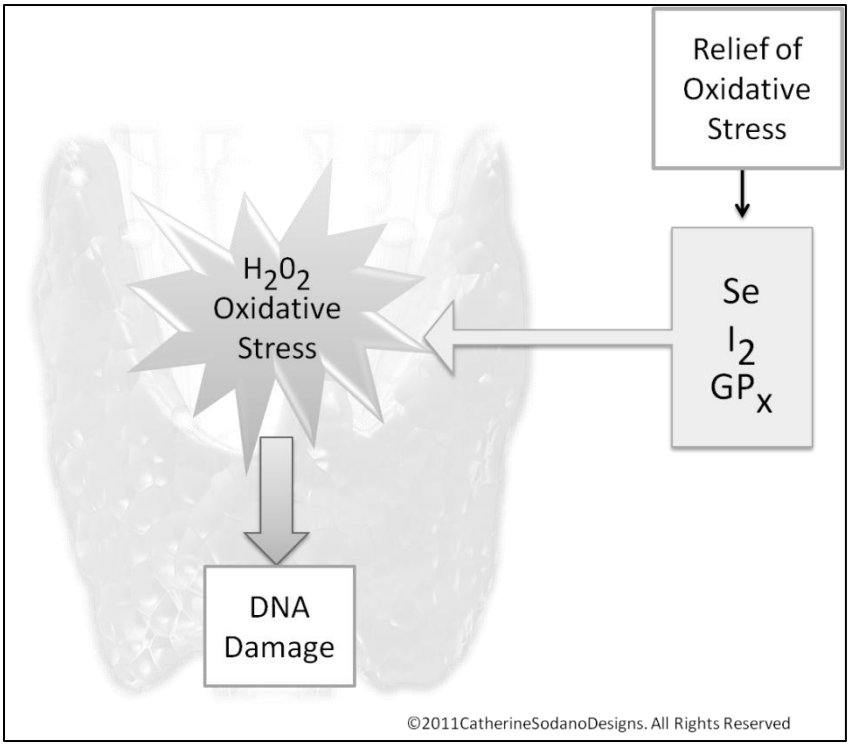
The Thyroid Gland and Oxidative Stress

'Thyroid Diabetes'



Organification (oxidation) of iodide is accomplished by H_2O_2 (hydrogen peroxide) catalyzed by the enzyme thyroid peroxidase, and leads to the formation of T3 and T4.[1] Thyroid hormone synthesis requires an adequate supply of iodide and the continuous production of hydrogen peroxide.[1] Hydrogen peroxide is toxic to the cells , can be the precursor of highly reactive peroxides, and if not properly reduced to water (H_2O) by intracellular defense mechanisms, can expose the thyroid to free radical damage.[1] The thyroid gland has several mechanisms to resist oxidative stress. The thyroid cells (thyrocytes) are protected by the enzymes, catalase (CAT) , glutathione peroxidase (GPx)and superoxide dismutase (SOD), both of which are selenium containing enzymes. Therefore, a selenium deficiency not only contributes to a decrease in peripheral conversion of T4 to T3, it also contributes to thyroid damage via oxidative stress. Iodine deficiency also contributes to oxidative damage to the thyroid gland. An iodine deficiency causes a compensatory increase in hydrogen peroxide in an effort to compensate for impaired thyroid hormone synthesis.[1]

Selenium /Iodine/Zinc

Selenium

The effect of selenium on autoimmune thyroiditis, as well as many other autoimmune diseases, such as rheumatoid arthritis and lupus, is well documented.[2] Selenium as an essential trace element is capable of exerting complex effects on the endocrine and immune system by its antioxidant capacity. [3] The role of selenium is important because the level of free oxygen radicals is elevated in the physiological thyroid hormone synthesis. [2] It seems that the immunomodulatory effect of this element may be more prominent than the other effects. [2] With severe selenium deficiency there is a higher incidence of thyroiditis due to a decreased activity of selenium-dependent glutathione peroxidase activity within the thyroid cells. [4] Selenium-dependent enzymes also have modifying effects on the immune system.[4] Therefore, even mild selenium deficiency may contribute to the development and maintenance of autoimmune thyroid diseases.[4] Selenium has been shown to decease thyroid antibody titer, in particular TPO Ab. [2] It is worth noting that selenium may be ineffective in the later stages of thyroiditis due to the atrophic phase of the pathology.[2]

Iodine

Around 90% of dietary iodine is excreted in the urine, and variable urine volumes cause variable dilution of the iodine excreted in the urine, and thus in the concentration of iodine in the urine. [1] In order to establish iodine status in an individual with thyroid disease or suspected thyroid disease, I suggest using a 24 hour iodine urine test and a serum thyroglobulin test. A 24 hour iodine test will significantly reduce the variability of iodine test results often observed with other urinary iodine tests. Thyroid volume, thyroid nodularity, or iodine excretion have close associations to serum thyroglobulin (Tg), which only originates in the thyroid.[1] Serum Tg was found to be a suitable marker for iodine nutrition status. [5] It is important to correlate serum Tg tests result with the condition of the thyroid gland. In general, inflammation/proliferation of the thyroid gland will cause an increase in serum Tg and suppressed activity of the thyroid gland will cause a decrease in serum Tg.

Influence of thyroid status and iodine intake on serum TG[1]

	Iodine Intake	Serum Tg Concentration
Normal Thyroid Function	Deficiency Adequate Excess	Increased Normal Normal or increased
Hypothyroidism	Deficiency Adequate Excess	Deceased Decreased Decreased
Hyperthyroidism	Deficiency Adequate Excess	Increased Increased Increased

The Paradox of Iodine Intake and Thyroid Autoimmunity[1]

In spite of the difficulties in interpreting and comparing results from epidemiological studies on thyroid autoimmunity, there are certain tendencies in the relationship between thyroid autoimmunity and iodine intake.[1] A sudden increase in iodine intake in an iodine –deficient population may induce enhanced thyroid autoimmunity. [1] A number of mechanisms have been suggested to explain the association between thyroid autoimmunity and the level of iodine intake. A sudden shift from very low to high iodine intake may induce damage to the thyroid tissue by free radicals and the enhancement of the autoimmunogenic properties of thyroglobulin by increased iodination.[1] Excessive iodine intake reduces organic binding of iodine, resulting in hypothyroidism and goiter, thyroiditis, and autonomous thyroid nodules. [53] Chronic intake of large amounts of iodine can limit thyroid hormone synthesis and release. [1] I recommend slow titration of iodine repletion in an iodine-deficient individual. We also recommend monitoring iodine status at frequent intervals (every 4-8 weeks) early in iodine supplementation.

Zinc

Zinc is essential for many biochemical processes and also for cell proliferation.[6] Thyroid hormones influence zinc metabolism by affecting zinc absorption and excretion. Significant relationships between thyroid volume and serum zinc levels in nodular goiter patients, between thyroid autoantibodies and zinc in autoimmune thyroid disease patients and between free T3 and zinc in subjects with normal thyroid were detected. [6] It appears that assessing zinc status is an integral part of assessing thyroid dysfunction and is certainly part of the functional medicine spectrum of considerations.

Thyroid Hormones and Oxidative Stress

Thyroid hormones influence several mitochondrial functions including oxygen consumption and oxidative phosphorylation, and to increase the metabolic activity of almost all tissues of the body. [1] T3 exerts significant action on energy metabolism, with the mitochondria being the major target for its calorigenic (increasing production of energy/heat and oxygen consumption) effects.[1] Acceleration of oxygen consumption by T3 leads to an enhanced generation of reactive oxygen and nitrogen species in target tissues, with higher consumption of cellular antioxidants and inactivation of antioxidant enzymes, and thus oxidative stress. [1] It was shown that T3 administration to rats induces a calorigenic response and liver glutathione depletion as an indication of oxidative stress, with higher levels of interleukin-6 (IL-6). [1] You may recall that IL-6 causes the liver to produce CRP. T3 induced oxidative stress can also enhance the DNA binding of NF-kB, which is involved if the inflammatory process.[7] Thyroid hormone has a pro-oxidant effect and increases the oxygen free radical production and hence the resultant decrease in antioxidant state in the case of hyperthyroidism when compared to the normal and hypothyroidism. [8]

Oxidative Stress, Thyroid Hormone Status and Diabetes

Oxidative stress is currently suggested as the mechanism underlying diabetes and diabetic complications.[9] The level of TSH has been shown to be decreased and the levels of T4 and FT4 have been shown to be increased in diabetics patients.[9] T3 and T4 are insulin antagonist that also potentiate the action of insulin indirectly. [9] While thyroid hormones oppose the action of insulin and stimulate hepatic gluconeogenesis and glycogenolysis, they up-regulate the expression of genes such as GLUT-4 and phosphoglycerate kinase, involved in glucose transport and glycolysis respectively, thus acting synergistically with insulin in facilitating glucose disposal and utilization in the peripheral tissues.[10] Failure to recognize the presence of thyroid dysfunction in diabetics may be a primary cause of poor management often encountered in the treatment of diabetes.[9]

'Thyroid Diabetes'

Hyperthyroidism and Glucose Regulation [10]

- Highly increased intestinal glucose absorption
- Increased hepatic gluconeogenesis and glycogenolysis (This explains why glucose control deteriorates when diabetic patients develop hyperthyroidism
- The increased hepatic glucose and post-absorptive glycemia cause an elevated fasting and/or postprandial insulin level. And apoptosis of the insulin producing cells. There is also increased peripheral tissue glucose utilization with insulin resistance.

Hypothyroidism and Glucose Regulation[10]

- Decreased intestinal glucose absorption
- Decreased hepatic gluconeogenesis and glycogenolysis
- Reduced hepatic glucose output and post-absorptive glycemia.
- The net effect of hypothyroidism on glucose regulation is: a decrease in peripheral tissue glucose disposal and a reduced baseline plasma insulin level with increased post glucose insulin secretion.

[Glucose disposal refers to the fate of glucose taken up by the tissues. About two thirds of the glucose taken up by the tissues undergoes glycolysis, with the remainder being stored]

The impact of thyroid dysfunction on glucose metabolism has been known for a long time. [10] Thyrotoxic patients usually lose their glucose control when thyroid decompensation is not properly solved. In other words, hyperthyroidism can lead to glucose dysregulation. Most recently, new pathways of thyroid hormone action at the tissue level have been unveiled and may be of relevance to understanding of insulin resistance present in both hypothyroid and hyperthyroid states.[10]

It is recommended that patients with glucose dysregulation and diabetes be assess for thyroid dysfunction (as well as for oxidative stress) due to the high prevalence of both endocrinopathies.[9,10,11]

From a functional medicine perspective, it is especially important to assess antioxidant status and oxidative stress in patients who are in a hypermetabolic state, as in hyperthyroidism, in patients who are on thyroid replacement hormone(s) and in patients with glucose dysregulation (insulin resistance/diabetes). The following functional medicine tests will assist in assessing antioxidant status and oxidative stress:

- Organic acid test
- Nutrient element test
- Antioxidant Vitamin test (vitamins A, beta-carotene, Coenzyme Q10)

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