Thyroid Disease - A White Paper Monograph

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An important part of the BioTE® method of hormone optimization is reestablishing thyroid hormones to levels that maximize metabolism in our cells. As we meander through the "seasons" of our life, after our teenage years, many of our hormones begin a never-ending decline. One of the most important of these deteriorations in that which occurs with thyroid hormones.

Hypothyroidism is pervasive throughout our patient population and reportedly affects 50% of our population (Starr, 2011). Dr. Hertoghe, a Belgian endocrinologist, estimated the incidence to be as high as 80% in his country. Most often, it is not primary hypothyroidism with the traditional high TSH and low T4 and T3 that is seen. More commonly, patients exhibit type 2 hypothyroidism which results in normal TSH and low T3 levels. Thyroid symptoms may also present with completely normal lab values.

At BioTE ®, we have treated tens of thousands of patients incorporating thyroid optimization, testosterone and estradiol pellets, and nutraceuticals for additional cellular support.

For decades most prescribers, including endocrinologists, have assumed that normalization of TSH can be done with T4 alone, and that normalization of TSH indicates a euthyroid state. In the 1990s, studies disputed this commonly held thought. Authors concluded that T4 could maintain decent levels of T3 in the pituitary resulting in normal TSH, but virtually all other tissues throughout the body had low T3 concentrations (Escobar-Morreale, et al. 1996). Moreover, suppressed TSH did not indicate hyperthyroid state, in fact, the likelihood that a suppressed TSH indicated over replacement was approximately only 16% of the time (Fraser, W. et al., 1986). Over time, the Endocrine society has transitioned what is considered the normal parameters for TSH however they have never found what serum levels of TSH are optimal. Furthermore, ethnicity, iodine intake, gender, age, and body mass index can influence the reference range of serum TSH which is not reflected on lab reference ranges (Biondi, 2013).

Similar to what has been reported with testosterone, there are over 200 symptoms related to thyroid deficiency. These include, but are not limited to, cold hands and feet, thinning hair, weight gain, increase body fat, decreased energy, loss of cognition, depression, menstrual irregularities, and a compromised gut motility (Harrison's Principles of Internal Medicine, 20th edition). The long-term benefits of thyroid optimization have been reported to include an improvement in cardiovascular disease, brain function, weight loss, and improved lipid profile (Barnes, 1976). Optimization of T3 in obese patients, with normal thyroid labs, results in a statistically significant reduction in CV risk factors including lipid levels and insulin sensitization (Krotkiewski, 2000).

Thyroid deficiency is unfortunately often attributed to a decrease in hormone production by the thyroid gland. While this is one cause, two other significant causes should be considered. Thyroid deficiency can also be caused by decreased conversion of T4 to T3 as well as resistance at the receptor site causing low thyroid symptoms despite "normal" blood levels. These causes are similar to what is seen with testosterone deficiency and insulin resistance. (Larsen, 1982; Maia, 1995; Ortiga-Cavalho, 2014; Persani, 2012). Low T3 concentrations at the cellular level is a significant contributor to the symptoms of hypothyroidism. It is not the TSH nor the T4 levels that are erroneously purported. (Escobar-Morreale, 1995).

Understanding that symptoms that do not necessarily correlate with laboratory levels of TSH is critical as the American Thyroid Association and AACE Guidelines in 2012 indicate no treatment is needed with a normal TSH level despite symptoms being present. Unfortunately, these guidelines result in the persistence of symptoms due to undertreated hypothyroidism and the utilization of other types of drug therapy to treat weight gain, cognitive decline, and other low thyroid symptoms that result in poor quality of life for our patients.

When we are euthyroid and our body's homeostasis is present, thyroid hormone in the periphery and the pituitary are aligned. However, there is a disconnect between pituitary thyroid hormone levels and levels seen in the peripheral cells when stress, chronic inflammation, illness, obesity, insulin resistance, low testosterone and other disruptors of our generalized well-being occur. Unfortunately, TSH is poorly correlated to these reduced levels of thyroid hormone in peripheral tissue. It is serum free T3 levels that are the better barometer of peripheral thyroid dysfunction. (Lim et al., 1984).

Larsen eloquently stated that "Changes in pituitary conversion of T4 to T3 are often opposite of those that occur in the liver and kidney under similar circumstances. Given these results, it is not surprising that a complete definition of thyroid status requires more than the measurement of serum concentrations of thyroid hormones. For some tissues, the intracellular T3 concentration may only partially reflect those in the serum." This phenomenon manifests itself because the enzymes in the thyroid responsible for the deiodinase reaction converting T4 to T3 are different than the enzymes in the cells everywhere else in the body. (Larsen,1982)

Two studies clarify the point that as patients age, treating with T4 alone (e.g. Synthroid, levothyroxine) will never deliver optimal cellular active T3 levels and thereby mitochondrial function will be hampered. The first study indicates that, the majority of patients, at one time or another, suffer from stress, chronic inflammation, illness, obesity, insulin resistance, low testosterone or dyslipidemia, resulting in disrupted transport of T4 into the cells of our body. Thus, the substrate (prohormone) needed to make T3 is reduced resulting in an intracellular depletion of the active thyroid hormone T3 (Hennemann et al., 2001). The second study (Strich et al., 2016), clearly demonstrates that as we age we are less capable of converting T4 to T3 and therefore treatment with T4 alone will not deliver optimal T3 levels in our vital organs.

A final point regarding the variation in the deiodinase enzymes throughout our body is that in the heart muscle there is no deiodinase enzyme and therefore the heart cannot make T3 at the cellular level. (Danzi & Klein, 2005). We know from Dr. Broda Barnes' study that thyroid optimization is critical to reducing coronary heart disease and therefore adequate supplementation with T3 is critical. (Barnes, 1976)

In men and women, the leading cause of mortality is cardiovascular disease (CVD). It is generally accepted that the euthyroid state is preferred for the cardiovascular system because both hyperthyroidism and hypothyroidism cause or accelerate disease processes. Hypothyroidism is known to be associated with atherosclerosis and ischemic heart diseases. In order to reduce the incidence of CVD, we must reduce inflammation and improve blood flow to the heart. Thyroid Replacement Therapy (TRT) and more specifically thyroid optimization reduces C-Reactive Protein, reduces homocysteine, dilates the coronary arteries, promotes angiogenesis and neo-vascularization. In fact, it appears the lack of thyroid hormone leads to vaso-constriction of the arterioles. The reality is that survival post-acute myocardial infarction is greater if one's Free T3 is optimal. (Christ-Crain M Atherosclerosis 2003) (Nedrebo, 1998; Yingheng ,2010; Luldens, 2010; Pavlou, 2002).

A common alleged fear of TRT, not supported by the evidence, is that thyroid replacement and optimization causes arrythmias. The reality is treating thyroid to a euthyroid state has anti-arrhythmic properties. In fact, low T3 increases one's propensity to ventricular tachycardia. Post-operatively, low Free T3 increases the incidence of atrial fibrillation. (Shimoyama, 1993; Cerillo, 2003)

Another fear of prescribing thyroid hormone is that patients will develop osteoporosis secondary to TSH suppression. This is a myth, far from reality, and is not supported by the evidence in the literature. Thyroid replacement therapy in pre-menopausal and post-menopausal women does not cause a reduction in BMD. (Gorres, 1996; Garin, 2014; Quan, 2002)

The litmus test for any interventional therapy, including hormone optimization of all hormones, must start with improvement in clinical symptoms and encompass patient satisfaction while dually being cognizant of the side effects of the therapy. In a randomized double-blind crossover study comparing desiccated thyroid extract (DTE) to levothyroxine (L-T4), the majority of patients preferred DTE over L-T4. In all symptom categories, the desiccated thyroid was subjectively better which will translate into better patient compliance and continuation rates (Hoang, 2013) Overwhelming patient preference for DTE over levothyroxine was also seen in the Pepper et al. study comparing Armour thyroid to levothyroxine. (Pepper, 2014) In a large study involving 12,000 patients, T4 replacement had the lowest patient satisfaction score. Participants reported better success with weight management, fatigue, memory and overall cognition, and mood swings using DTE. (Peterson, 2018) Two tenets to always remember in diagnosis and treatment of hypothyroidism, from the legendary pioneer Dr. Broda Barnes: TSH is a poor lab test and fails to diagnose a large percentage of patients with hypothyroidism and secondly, desiccated thyroid is more efficacious than Synthroid (levothyroxine). Synthetic T4 was first manufactured in 1950's and was grandfathered by the FDA. Synthetic T4 was marketed as being a new and better drug in comparison to DTE that had been around for longer and was made to look like an antiquated treatment. Studies comparing DTE to T4 seem to conclude that DTE is "not superior to T4", indicating that T4 therapy should be utilized; however; there has never been a long-term study on its use in treating hypothyroidism.

In addition to Type 2 Hypothyroidism, a very common autoimmune condition known as Hashimoto's Thyroiditis, affects one's thyroid homeostasis via the destruction of the thyroid gland. Hashimoto's affects 10% of the U.S. population and is 7x more prevalent in women. It is the most common cause of hypothyroidism (Wentz, 2013). More than 90% of patients with Hashimoto's have elevated thyroid peroxidase antibodies (Gartner, 2002). Hashimoto's comprises a vicious cycle of triggers (e.g. gluten, low iron, stress, leaky gut) and destruction, leading to depletion of nutrients and further thyroid compromise. Patients can fluctuate between being hypothyroid and hyperthyroid until eventually the thyroid gland is destroyed. Laboratory testing of Thyroid Peroxidase Antibodies (TPO) provides the best confirmation of the disease. A positive diagnosis is indicated if TPO antibodies are above 35 IU/ml, and thyroglobulin antibodies are above 110 IU/ml. Ninety percent of patients with Hashimoto's will have elevated TPO antibody levels and eighty percent will have anti-thyroglobulin antibodies

(Elhomsy, 2014; Wentz, 2013). The autoimmune nature of Hashimoto's thyroiditis makes its treatment more unique and individualization is required. Some patients can be adequately managed on desiccated thyroid extract, but others do better on Synthroid and Cytomel. This serves as a reminder to "treat the patient not the lab". Iodine is an important precursor in thyroid hormone production, and also stimulates the production of Thyroid peroxidase enzyme (TPO). In patients with Hashimoto's, iodine can be beneficial to some with halide (fluoride, bromide, and chloride) toxicity, however iodine can also increase the production of TPO antibodies leading to further destruction of the thyroid gland. This phenomenon has been seen in a number of countries after adding iodine to their salt (Abraham, 2008; Mazziotti, 2003; Kharrazian, 2010). The majority of patients with Hashimoto's have gluten intolerance and the main protein in gluten is "gliadin" which has a lot of similarity to proteins in the thyroid. Therefore, a diet with gluten often exacerbates the symptoms of Hashimoto's thyroiditis (Starr, 2011). In summary, patients with Hashimoto's need to have their triggers (gluten, stress, leaky gut) treated aggressively. They need their depletions (low Fe, selenium, zinc) replaced.

Individualize synthetics vs DTE based on how the patient's symptoms resolve. Beware of too much Iodine increasing auto-antibodies.

The most common cause of hyperthyroidism is Graves' disease, which is an autoimmune disorder that directs antibodies against thyroid stimulating hormone (TSH) receptors which, ultimately, destroys them. In Graves' disease, the TSH receptor is stimulated. In Hashimoto's disease the TSH receptor is blocked. Interestingly, Graves' and Hashimoto's antibodies can coexist in the same patient and one can transform into another (Ohye , 2006; Lu et al., 2005). Thyroid stimulating immunoglobulins (TSIs) are considered diagnostic for Graves' disease even though only about 80% of Graves' patients have them. TSIs are elevated in 5-10% of patients with Hashimoto's thyroiditis (one reason Hashimoto's patients can become hyperthyroid sometimes). TPO antibodies are a sign of thyroid tissue destruction and are found in about 90% of Hashimoto's patients and 75% of Graves' patients. (Chardes, 2002; Saravanan, 2001). A hyperthyroid state (Graves') tends to suppress TSH levels and leads to excessive endogenous production of thyroid hormone which is linked to bone loss (El Hadidy, 2011). However as noted previously, when TSH levels are suppressed through exogenous replacement of thyroid hormone there is very little evidence that bone loss occurs. These studies show no increased bone loss in TSH suppressive therapy (Bauer, 1997; Reverter, 2005; Rosen, 1998; Heijckmann, 2005; Van Den Eeden, 2003, Quan, 2002, Sheppard, 2002).

In conclusion, thyroid management is imperative to optimization of hormone status and quality of life in patients. Low thyroid symptoms are widespread and not always accurately reflected in lab results, therefore, if the patient appears to be hypothyroid, treat them for their symptoms rather than focusing only on the lab tests. The incidence of secondary hypothyroidism is significant, and identification and treatment of this disease state is extremely important to actively managing patients' health status. The treatment of choice for most hypothyroid patients is DTE (T4 and T3) rather than T4 alone as several patients have issues converting T4 in the peripheral tissue. Identification of Graves' Disease and Hashimoto's Thyroiditis is extremely important as it greatly influences the treatment plan. Untreated thyroid disease causes patients to remain in a substandard state of health and increases their risk factors. Practitioners should take this into consideration when developing individualized treatment plans for their patients.

References

Abraham, G.E., (2008). Facts about iodine and autoimmune thyroiditis. The Original Internist, 15(2), 75-76.

Barnes, B. & Galton, L. (1976). Hypothyroidism: The unsuspected illness. Canada: Fitzhenry & Whiteside Limited.

Bauer, D.C. (1997). Low thyrotropin levels are not associated with bone loss in older women: a prospective study. J Clin Endocrinol Metab.,82(9), 2931-6.

Biondi, B. (2013). The normal TSH reference range: What has changed in the last decade? The Journal of Clinical Endocrinology & Metabolism, 98(9), 3584–3587.

Cerillo, A., Bevilacqua, S., Storti, S., Mariani, M., Kallushi, E., Ripoli, A., et al. (2003). Free triiodothyronine: a novel predictor of postoperative atrial fibrillation. Eur J Cardiothoracic Surgery, 24(4), 487-92.

Chardes, T., Chapal, N., Bresson, D., Bes, C., Giudicelli, V., Lefranc, M.P., et al. (2002). The human anti-thyroidperoxidase autoantibody repertoire in Graves' and Hashimoto's autoimmine thyroid diseases. Immunogenetics, 54, 141–57.

Christ-Crain, M., Meier, C., Guglielmetti, M., Huber, P.R, Riesen, W., Staubb, J., & Muller, B. (2003). Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. Atherosclerosi , 166(2), 379-86.

Danzi, S. & Klein, I. (2005). Potential uses of T3 in the treatment of human disease. Clin Cornerstone, 7 (suppl 2), S9-15.

El Hadidy, E.M., et.al. (2011). Impact of severity, duration and etiology of hyperthryroidism on bone turnover markers and bone mineral density in men. BMC Endocrine Disorders, 11, 2–7.

Elhomsy G.& Staros, E. (ed) (2014). Antithyroid Antibody. Laboratory Medicine.

Escobar-Morreale, H.F., et al. (1995). Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats. J Clin Invest, 96(6), 2828-2838.

Escobar-Morreale, H.F, del Rey, F.E., Obregon, M.J., de Escobar, G.M. (1996). Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. Endocrinology, 137(6), 2490-2502.

Fraser, W.D., Biggart, D., O'Reilly, St. J., Gray, H.W., McKillop, J.H., & Thompson, J.A. (1986). Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine therapy? British Medical Journal, 293, 1373.

Garin, M.C. (2014). Subclinical thyroid dysfunction and hip fracture and bone mineral density in older adults: The cardiovascular health study. J Clin Endocrinol Metab., 99(8), 2657-64.

Gartner, R. (2002). Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. JCEM, 87(4), 1687-91.

Gorres, G et al. (1996). Bone mineral density in patients receiving suppressive doses of thyroxine for differentiated thyroid carcinoma. Eur J Nucl Med, 23(6), 690-2.

Heijckmann, A.C. (2005). Hip bone mineral density, bone turnover and risk of fracture in patients on long-term suppressive L-thyroxine therapy for differentiated thyroid carcinoma. Eur J Endocrinol. 153(1), 23-29.

Hennemann, R.D., Friesema E, et al. (2001). Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. Endocrine Reviews, 22 (4), 451–476.

Hoang, T.D., Olsen, C.H., Mai, V.Q., Clyde, P.W., & Shakir, M.K. (2013). Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: A randomized, double-blind, crossover Study, J Clin Endocrin Metabolism, 98(5), 1982-1990.

Jameson, J., Fauci, A., Kasper, D., Hauser, S., Longo, D., & Loscalzo, J.(Eds.)(2018). Harrison's Principles of Internal Medicine, 20th edition. New York: McGraw Hill.

Kharrazian, D. (2010). Why do I still have thyroid symptoms when my lab tests are normal: A revolutionary breakthrough in understanding Hashimoto's disease and hypothyroidism. Morgan James Publishing.

Krotkiewski, M. (2000). Thyroid hormones and treatment of obesity. International Journal of Obesity, 24, S116-S119.

Larsen, P.R. (1982). Thyroid-pituitary interaction: feedback regulation of thyrotropin secretion by thyroid hormones. NEJM, 306(1), 23-32.

Lim,V.S., Passo, C., Murata, Y., Ferrari, E., et al. (1984). Reduced triiodthyronine content in liver but not pituitary of the uremic rat model: demonstration of changes compatible with thyroid hormone deficiency in liver only. Endocrinology, 114(1), 280-286.

Lu, R., Burman, K., & Jonklaas, J. (2005). Transient Graves' hyperthyroidism during pregnancy in a patient with Hashimoto's hypothyroidism. Thyroid, 15(7), 725-9.

Luidens, M., Mousa, S., Davis, F., Lin, H., & Davis, P. (2010). Thyroid hormone and angiogenesis. Vascular Pharmacology, 52 (3-4), 142-5.

Maia, A.L., et al. (1995). Pituitary cells respond to thyroid hormone by discrete, gene-specific pathways. Endocrinology, 136, 1488-1494.

Mazziotti, G., Premawardhana, L.D., Parkes, A., Adams, H., Smyth, P., Smith, D., Kaluarachi, W., et al. (2003). Evolution of thyroid autoimmunity during iodine prophylaxis--the Sri Lankan experience. European Journal of Endocrinology, 149, 103-110.

Nedrebo, B., Ericsson, U., Nygard, H., et al. (1998). Plasma total homocysteine levels in hyperthyroid and hypothyroid patients. Metabolism, 47(1), 89-93.

Ohye, H., Nishihara, E., Sasaki, I., et al. (2006). Four cases of Graves' disease which developed after painful Hashimoto's thyroiditis. Intern Med., 45, 385–9.

Ortiga-Carvalho, T.M., et al. (2014). Thyroid hormone receptors and resistance to thyroid hormone disorders. Nat Rev Endocrinology, 10(10), 582-591.

Pavlou, H., Kliridis, P., Panagiotopoulos, A., Goritsas, C., & Vassilakos, P. (2002). Euthyroid sick syndrome in acute ischemic syndromes. Angiology, 53(6), 699-707.

Pepper, G.M. & Casanova-Romero, P.Y. (2014). Conversion to Armour Thyroid from Levothyroxine improved patient satisfaction in the treatment of hypothyroidism. Journal of Endocrinology, Diabetes, and Obesity, 2(3), 1055.

Persani, L. (2012). Central Hypothyroidism: Pathogenic, diagnostic, and therapeutic challenges. Journal of Clinical Endocrinology & Metabolism, 9(7): 3068-3078.

Peterson, S.J., Cappola, A., Castro, R., Dayan, C., Farwell, A., Hennessey, J. et al. (2018). An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction, Thyroid. Epub ahead of print]; DOI: 10.1089/thy.2017.0681.

Quan, M.L. (2002). Bone mineral density in well-differentiated thyroid cancer patients treated with suppressive thyroxine: A systematic overview of the literature. J Surg Oncol., 79(1):62-70.

Reverter, J.L. (2005). Lack of deleterious effect on bone mineral density of long-term thyroxine suppressive therapy for differentiated thyroid carcinoma. Endocr Relat Cancer., 12(4), 973-81.

Rosen, H.N. (1998). Randomized trial of pamidronate in patients with thyroid cancer: bone density is not reduced by suppressive doses of thyroxine but is increased by cyclic intravenous pamidronate. J Clin Endocrinol Metab., 83(7), 2324-30

Saravanan, P. & Dayan, C.M. (2001). Thyroid autoantibodies. Endocrin Metab Clin North Amer., 30, 315–337.

Sheppard, M.C. (2002). Levothyroxine treatment and occurrence of fracture of the hip. Arch Intern Med., 162(3), 338-43.

Shimoyama (1993). Cardiology.

Starr, M. (2011). Hypothyroidism type 2: The epidemic. New Voice Publication.

Strich, D., Karavani, G., Edri, S., & Gillis, D. (2016). TSH enhancement of FT4 to FT3 conversion is age dependent. Eur J Endocrinology, 175, 49-54.

Van Den Eeden, S.K. (2003). Thyroid hormone use and the risk of hip fracture in women >/=65 years: A case-control study. J Womens Health (Larchmt).,12(1), 27-31.

Wentz, I. & Nowosadzka, M. (2013). Hashimoto's thyroiditis: Lifestyle interventions for finding and treating the root cause. Wentz, LLC.

Yingheng, L., Sherer, B., Redetzke, A., & Gerdes, M. (2010). Regulation of arteriolar density in adult myocardium during low thyroid conditions. Vascular Pharmacology, 52(3-4), 146-150.