

Fibromyalgia, Thyroid Dysfunction and Treatment Modalities

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ABSTRACT

Fibromyalgia is a debilitating condition presenting with symptoms of chronic muscular pain, fatigue, insomnia and cognitive dysfunction among other symptoms, which lead to a diminished quality of life. Although the exact pathogenesis and underlying mechanisms which lead to clinical manifestation are unknown, there is a growing line of evidence suggesting an association between fibromyalgia and thyroid dysfunction. Numerous studies have reported that patients with fibromyalgia have a high incidence of hypothyroidism. Further, thyroid autoimmunity has also been associated with fibromyalgia symptom severity. Circulating thyroid hormones do not provide an accurate status of thyroid function in patients with fibromyalgia, rather intracellular thyroid hormone levels are more relevant. Low levels of intracellular hormones may result from mitochondrial dysfunction as active transport of hormones across cellular membranes is required. It is well known that mitochondrial dysfunction is associated with fibromyalgia. In order to correct thyroid dysfunction and manage symptoms presenting in fibromyalgia patients, a multi-disciplinary approach should be taken incorporating dietary supplements, nutraceuticals, dietary changes and complementary alternative therapies.

Keywords: Fibromyalgia; Thyroid antibodies; Thyroid dysfunction; Thyroid hormones

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INTRODUCTION

Fibromyalgia syndrome is a condition characterized by chronic pain at multiple tender points affecting the musculoskeletal system, fatigue, joint stiffness, insomnia and cognitive dysfunction. Fibromyalgia leads to losses in job productivity among working adults and an impaired quality of life.¹ It affects an estimated 2–3% of the US population and has a world prevalence of approximately 5–6%. Although fibromyalgia can affect children and men of any ethnicity, it is most prevalent in women, with incidence rising with age. The prevalence in women exceeds men nearly 7:1.^{2,3} Direct annual medical costs are reported to average US\$3400 to \$3600/patient with total annual costs (indirect and direct costs) of \$5945.^{4,5}

The majority of associated medical costs are due to visits to the physician's office, emergency room visits, hospitalizations, procedures and tests.⁴ Patients with fibromyalgia have approximately one hospitalization every 3 years and account for 5.5 million ambulatory care visits annually. Much of the use of the healthcare system is due to medical and psychiatric co-morbidity.^{6,7}

Fibromyalgia syndrome is poorly understood and is difficult to diagnose, as symptoms do not align with a standardized set of diagnostic criteria. Diagnosis should not rely solely on an assumption or exclusion from other conditions. Instead, symptoms should be evaluated and consideration should be given to differential diagnoses. Common differentials to investigate include mental health disorders, rheumatoid arthritis, adrenal dysfunction and hypothyroidism.⁸ In 2010, the American College of Rheumatology (ACR) published criteria for diagnosis and severity classification. The ACR recommends that diagnosis be based on multiple tender points scored with a Widespread Pain Index (WPI) >7 and a symptom severity scale (SS) >5 or WPI 3–6 and SS >9; symptoms must be present at similar levels for at least 3 months; and there are no other disorders that would otherwise explain the pain.⁹

HYPOTHYROIDISM, AUTOIMMUNITY AND FIBROMYALGIA

Although the underlying mechanisms for fibromyalgia are not clearly understood it is often considered a stress related disorder involving interactions between the autonomic central nervous system, hypothalamic-pituitary-adrenal (HPA) axis and immune system.^{10–14} Thyroid autoantibodies among patients with fibromyalgia are reported to occur at twice the rate of healthy controls.^{15–17} Furthermore, approximately 25% of patients with fibromyalgia present with Tg Ab (thyroglobulin antibody) and/or TPO Ab (thyroid peroxidase antibody).^{15,16} Although these differences appear to exist between populations, the exact mechanism is not clearly understood. Interrelations between fibromyalgia, thyroid and an increased incidence of primary and central hypothyroidism have been reported. Compared to a 1–5% incidence of primary hypothyroidism in the general population, the incidence among fibromyalgia patients is 10–44% and secondary hypothyroidism is prevalent in 44%.¹⁸

A recent study identified that euthyroid patients with fibromyalgia had an increased prevalence of positive TPO Ab compared to age- and sex-matched controls (19% in fibromyalgia patients vs. 7% in control patients). In spite of this finding, TPO Ab positivity was not associated with clinical manifestations, which the authors suggested may support a hypothesis that thyroid autoimmunity may influence development of fibromyalgia; however, severity of fibromyalgia may not relate to the presence of TPO Ab.¹⁹ While associations between thyroid autoimmunity, fibromyalgia^{16,20} and symptom severity^{15,21} have been reported, the relationship between thyroid dysfunction and fibromyalgia has not yet been fully elucidated.

It has also been suggested that the characteristic pain experienced by fibromyalgia patients may relate to increased antibodies to muscle proteins, which are present in thyroid autoimmune disease.^{21,22} Additionally, pain distribution and pressure-pain threshold in patients with fibromyalgia have been positively associated with hypothyroidism and inversely associated with intracellular free T₃,

respectively.²³ Substance P, a neuropeptide signaling pain, is increased through the disinhibition of substance P synthesis and secretion by nociceptive afferent neurons with low T3 concentrations.^{24–26}

Most patients with fibromyalgia also have difficulties with both thyroid production^{27,28} and utilization.^{29,30} There is a line of collective evidence which indicates that inadequate thyroid hormone regulation, due to hypothyroidism (thyroid hormone deficiency) or peripheral resistance to thyroid hormone, may both be underlying mechanisms causing cellular thyroid deficiency.¹⁸ Both abnormalities cause symptoms mainly through the same subsequent common mechanism—inadequate thyroid hormone regulation of gene transcription in the cells of affected tissues.

THYROID HORMONE TRANSPORT AND FIBROMYALGIA

In patients with fibromyalgia, serum thyroid hormone levels often appear normal, even in patients with symptoms of hypothyroidism. The pituitary gland has unique thyroid transporters, different deiodinases and also differs with respect to high affinity thyroid receptors from all other cells and glands in the body.^{31,32} The pituitary thyroid hormone transporters are not energy-dependent and maintain or increase the uptake of T4 and T3 in low energy states. In contrast, transporters in other areas of the body are energy-dependent and in states of low energy have significantly impaired uptake of T4 and T3. Further, pituitary thyroid hormone transporters are not inhibited by environmental toxins and substances produced by the body during physiologic stress and calorie reduction, which typically inhibit thyroid transport into other cells in the body.

Thus, reduced uptake of T3 and T4 and subsequent intracellular hypothyroidism that occurs throughout the body due to conditions such as fibromyalgia, is not reflected by thyroid stimulating hormone (TSH) testing because thyroid uptake in the pituitary cells is not affected, making the TSH a poor marker for cellular thyroid in any tissue other than the pituitary.

Serum thyroid levels are routinely used as an indication of cellular thyroid activity. TSH and T3 may be indicators of primary hypothyroidism, but are poor indicators of cellular thyroid deficiency and subsequent hypometabolism. In order to have biological activity, T4 and T3 must cross the cellular

membrane from the serum into the target cells. It is the activity of these transport processes that may have an important influence on the regulation of biological activity of the thyroid hormones.

Although the association between depression, anxiety and thyroid autoimmunity are not fully understood,^{15,16,22} chronic emotional or physiologic stress associated with fibromyalgia can cause significant increases (or decreases) in cortisol, reductions of T4 transport into cells and reductions in peripheral conversion of T4 to T3. Interestingly, transport into the pituitary is unaffected, leading to a lack of recognition that T4 has reduced in other areas of the body and as a result, TSH levels are not affected.³³ It has been reported that serum from individuals with significant physiologic stress inhibits the uptake (transport) of T4 into the cell while the serum from non-physiological stress has no such effect.³⁴ Changes in response to acute and chronic stress can result in reduced T4 to T3 conversion and increased production of rT3.^{35–37} Though it has been hypothesized that rT3 is biologically active and blocks T4 to T3 conversion, this theory remains controversial.^{38,39} However, it can be concluded that serum T4 and TSH levels are poor markers for tissue thyroid levels in stressed individuals, and although not typically monitored, reverse T3 (rT3) and rT3/T3 ratio may be more relevant indicators of stress as well as tissue hypothyroidism.^{38,40}

FMA AND MITOCHONDRIAL DYSFUNCTION

The rate limiting step in the determination of thyroid activity is the rate of thyroid hormone transport into the cell as this process is energy dependent.^{41–43} Conditions associated with reduced production of cellular energy (i.e. mitochondrial dysfunction), are associated with reduced transport of thyroid hormones into the cell, resulting in cellular hypothyroidism. Again, this occurs despite having normal circulating thyroid hormone levels in the blood, thus standard blood tests may be unreliable, especially in the presence of conditions associated with reduced mitochondrial function. Reduced mitochondrial function prevents both T4 and T3 from crossing the membrane to the nuclear receptor site, as both require active transport.

Fibromyalgia is among several conditions associated with reduced mitochondrial function and impaired thyroid transport including metabolic

disorders (including insulin resistance and diabetes),^{44, 45} cardiovascular disorders,^{46, 47} obesity and dieting,^{45, 48} migraines,⁴⁹ psychological and neurological disorders including depression and anxiety,⁵⁰⁻⁵² chronic fatigue syndrome^{53, 54} and inflammation and chronic illness.⁵⁵ It is also common for patients with mitochondrial dysfunction to have decreased body temperature, which is evident in patients with fibromyalgia as they present with a basal body temperature 0.5°C lower than matched controls, and lower metabolic rates.^{23, 56}

THYROID HORMONE RESISTANCE

Specific mutations in the thyroid hormone receptor are associated with thyroid hormone resistance. General resistance to thyroid is a form of thyroid hormone resistance due to receptor site damage caused by a rare genetic disorder. In general resistance, both the peripheral tissues and pituitary gland are partially resistant to thyroid hormones. In patients with this disorder, TSH is usually normal or mildly elevated with elevated T3 and T4. Genetic anomalies of thyroid hormone receptors can result in lower heart rate (20% lower), lower body temperature (0.5°C lower) and mild hypothyroidism.⁵⁷ Peripheral resistance is a condition in which the peripheral tissues are

hyporesponsive to thyroid hormones.⁵⁸ Patients with peripheral resistance present with normal serum T3, T4 and TSH but a clinical profile suggesting thyroid hormone deficiency. Metabolism accelerates to normal in patients with peripheral resistance when thyroid hormone concentrations within the cell are high enough to override the resistance. Another form of resistance is a resistance to endogenous and exogenous hormones, where hormones are incompletely synthesized or cleaved. Several factors may be involved in this form of thyroid hormone resistance, including physiological antagonism; antibodies to hormones or hormone receptors; or absence of target cells (Figures 1 and 2).

THYROID HORMONE RECEPTOR DAMAGE

Thyroid dysfunction may arise from thyroid hormone receptor damage resulting from multiple factors including genetic anomalies of thyroid hormone receptors, autoimmune, oxidative or toxic damage to thyroid hormone receptors or competitive binding to thyroid-hormone receptors by environmental factors (e.g. pollutants, food additives, etc.). Some toxins reported to affect thyroid function include bisphenol A (BPA), polychlorinated biphenols (PCBs), polybrominated diphenyl ethers (PBDEs), Triclosan and organochlorine pesticides.

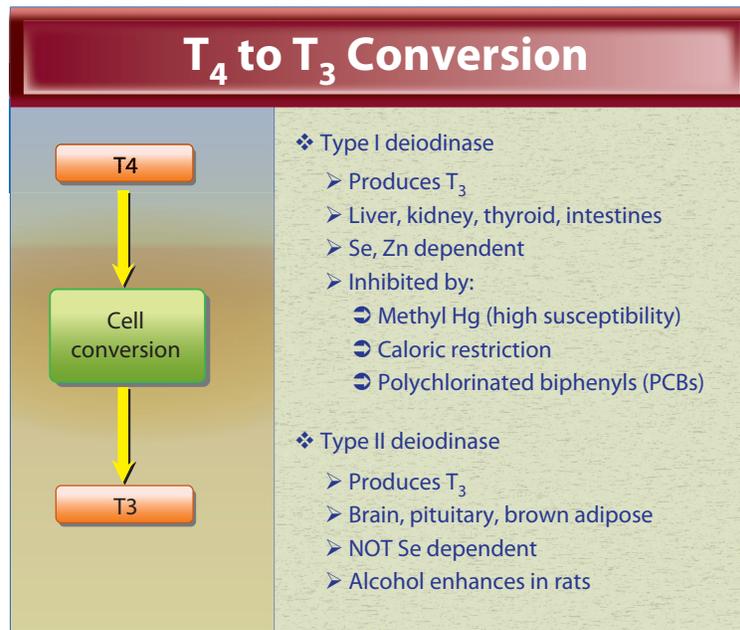


Figure 1: Type 1 and Type 2 deiodinase enzyme conversion of T4 to T3.

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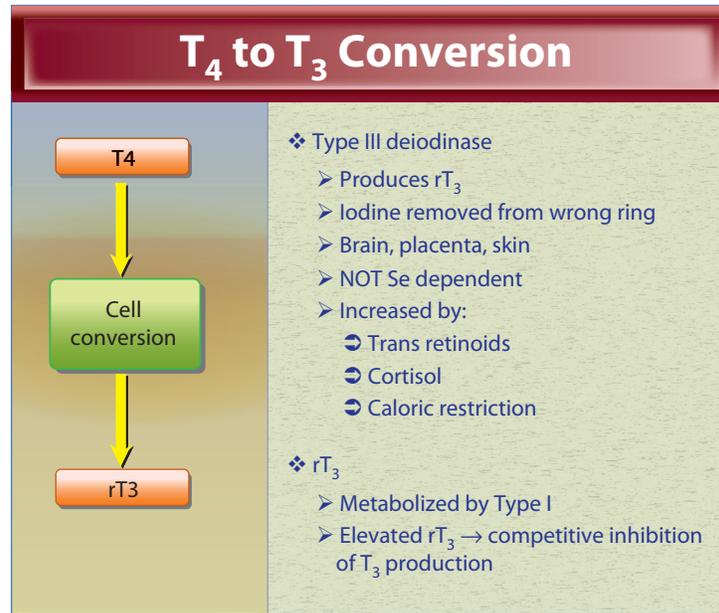


Figure 2: Type 3 deiodinase enzyme conversion of T4 to T3.

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BPA binds to thyroid hormone receptors and estrogen receptors, antagonizing thyroid hormone receptor activation.⁵⁹⁻⁶¹ BPA has also been shown to inhibit the regulation of most T₃-dependent responsive genes and affect T₃ signaling pathways.⁶² In an animal model, BPA exposure produced an endocrine profile similar to that observed in patients with T₃ resistance syndrome.⁶³

PCBs are persistent organic pollutants that have paired phenol rings with different degrees of chlorination. Their structure is similar to thyroid hormone and can bind to interact with the thyroid hormone receptor acting as an agonist or antagonist to the thyroid hormone receptor. PCBs were widely used from 1930 to 1979, at which time they were banned in the US. They are lipophilic compounds that have a half-life of 7 years and have been found in high amounts in breast milk. Prenatal exposure to PCBs has been shown to be associated with decreased cognitive function in children, impairing executive function, verbal abilities, visual recognition and memory.⁶⁴⁻⁶⁶

PBDEs have a structure similar to thyroid hormone and can displace T₄ from serum thyroid-binding protein transthyretin (TTR). PBDEs are widely used as flame retardants and in plastics, foams and building materials, and have also been detected in foods (meat, fish, vegetables and dairy). PBDEs

are detectable in 97% of US residents at levels 20 times higher than those seen in European residents. Increased PBDEs have also been associated with lower free T₃; TSH declines 16% for every ten-fold increase in PBDEs, increasing the risk of subclinical hyperthyroidism two-fold.^{67, 68}

Triclosan is an antibacterial/anti-fungal agent containing chlorinated organic molecules similar to PCBs, PBDEs and BPA. Triclosan suppresses serum thyroid hormone concentrations.⁶⁹ According to NHANES 2003–2004, Triclosan has been found in 75% of urine samples and has also been found at detectable levels in breast milk.⁷⁰

Other environmental toxins which affect thyroid function and hormone homeostasis include organochlorine pesticides, which activate hepatic uridine diphosphate glucuronyltransferases (UDPTGs) and increases T₄ metabolism, and perchlorate, which lowers both T₃ and T₄. Some degree of protection has been seen with iodine supplementation.⁷¹

TREATMENT MODALITIES

Pharmaceutical treatment of fibromyalgia includes tricyclic antidepressants, SSRIs, norepinephrine reuptake inhibitors, anticonvulsants, and analgesics, and is often directed only at management of pain

symptoms.⁷² As many as 98% of patients use some form of CAM therapy, to manage symptoms.⁷³ Multidisciplinary treatment of fibromyalgia is recommended including aerobic exercise, relaxation exercise, massage, meditation, acupuncture, hypnotherapy, cognitive behavior therapy, transcutaneous electrical nerve stimulation and dietary supplementation in addition to pharmacotherapy.

Addressing thyroid function may be key to effectively treating patients with fibromyalgia. Clinical protocols with T3 may include T3 (up to 150 µg per day) or T3/T4 combinations (4:1 combo 40 µg T3/10 µg T4 (1–2 times per day)). Treatment with T3 should continue until the patient achieves a body temperature of approximately 98.6°F for 3 weeks. As a general guideline temperature should be based on acrophase temperature taken between 16:00–21:00, when body temperature is highest. Taking first morning temperature before rising, between 03:00–06:00, temperature values would be expected to be approximately 1.8°F lower. It is also important to consider the patient's age, gender, and if female and ovulatory, the phase of her menstrual cycle.⁷⁴ Once this is achieved, T3 should be cycled down in a manner which maintains body temperature, usually every 2–5 days; however, this is dependent on the individual. In any case, body temperature must be monitored to ensure temperature is stabilized. T3 therapy has been reported to provide relief of symptoms associated with fibromyalgia, including fatigue, muscle pain, depression, headache and insomnia^{75–78} and has also been reported to increase metabolism rates and mitochondrial function.⁷⁹ In one study, follow up was continued after cessation of treatment, and improvements persisted for 1–5 years.⁸⁰ T3 can increase cardiac oxygen requirements, cardiac output and cardiac rate; therefore, although T3 normally reduces blood pressure, monitoring pulse for tachycardia is advised.

Despite wide-spread use of T4 to treat thyroid-related disorders and other non-thyroidal conditions, the effects of T4 are less clear with respect to mitochondrial function. It has been shown that treatment with T4 alone is not sufficient to elevate T3 in all affected tissues.⁸¹

In cases of long term hypothyroidism which can lead to hypoadrenalism and decreased cortisol levels, hydrocortisone (5 mg twice a day) or licorice (240 mg glycyrrhizin twice a day) may be efficacious.⁸²

Both hydrocortisone and licorice should be given upon rising and around noon to mimic the natural circadian rhythm. As licorice can lead to blood pressure elevation in some users, blood pressure monitoring is recommended while following this protocol. Should it become elevated, dosage should be reduced to 120 mg per day. Other treatments indicated to increase metabolism and reduce symptoms associated with fibromyalgia include the use of botanicals and nutraceuticals such as iodine, diiodotyrosine, blue iris and guggul, which stimulate and support normal thyroid function, promoting an increase in T3 levels,^{83–85} and black cohosh for pain relief,^{86–88} a debilitating symptom associated with fibromyalgia. Each of these natural ingredients provide activities that may aid in reducing inflammatory processes and/or symptoms associated with fibromyalgia, which may in turn increase quality of life in this demographic of patients.

CONCLUSION

The well-documented associations between fibromyalgia and thyroid dysfunction warrant further investigation to clarify the pathogenesis of this disease. The presence of thyroid dysfunction in fibromyalgia patients often goes undetected. Due to the complexity in detecting intracellular hypothyroidism, hypothyroidism may go undiagnosed and symptoms of fibromyalgia may worsen. Testing of freeT3/reverse T3 ratio may aid in diagnosing patients with intracellular hypothyroidism in patients with fibromyalgia.

In all cases, a combination of therapies is recommended combining dietary supplements, nutraceuticals and other therapies to address underlying mechanisms in addition to managing symptoms. T3 is widely reported for treatment of hypometabolism and fibromyalgia. Consideration should also be given to hydrocortisone and licorice for restoring cortisol levels in prolonged cases of hypothyroidism, and natural products such as iodine, guggul and blue flag to support thyroid function and thyroid hormone homeostasis, and black cohosh for pain management. These therapies should be combined with an organic diet (reducing exposure to organochlorine pesticides), avoidance

of food allergens, avoidance of Triclosan containing products which includes many antimicrobial hand sanitizers and even commercial toothpastes, use of BPA-free food storage containers and water bottles, and getting adequate exercise.

A multidisciplinary approach to managing the symptoms of fibromyalgia and addressing thyroid

dysfunction may be key to reducing symptom severity and improving quality of life for patients suffering from this debilitating disease.

DISCLOSURE OF INTERESTS

Dr. Friedman reports receipt of salary from WTSMED, outside the submitted work.

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