Inadequate Thyroid Hormone Regulation as the Main Mechanism of Fibromyalgia: A Review of the Evidence

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Abstract. All symptoms and most objectively verified abnormalities among fibromyalgia (FMS) patients are characteristic of subsets of patients with hypothyroidism or partial peripheral thyroid hormone resistance. Laboratory tests have shown a higher-than-normal incidence of thyroid disease among FMS patients. Among 40 objectively verified abnormalities that also occur in hypothyroidism and peripheral thyroid hormone resistance, FMS patients have abnormally low resting metabolic rates and basal body temperatures. In several open and blinded treatment trials, thyroid hormone therapy other than T_4-replacement has reduced or eliminated FMS symptoms and many study patients have ceased to meet the criteria for FMS. In addition, a 1-to-5-year follow-up study showed that patients treated with thyroid hormone remained improved and used fewer medications to control symptoms than did matched untreated controls. These study findings constitute rigorous testing of, yet failure to refute, the inadequate thyroid hormone regulation etiological hypothesis of FMS.

Competing etiological hypotheses of FMS account for only a fraction of the symptoms and objectively verified abnormalities among patients, and no treatment other than thyroid hormone therapy has been shown to relieve patients of FMS status. This review of the published research literature shows that inadequate thyroid hormone regulation is the most likely underlying mechanism of the symptoms and objective abnormalities of patients who meet the criteria for FMS.

Key Words. Basal body temperature, Fibromyalgia, Free T_3, Free T_4, Resting metabolic rate, Thyroid antibodies, TSH

Introduction

"Fibromyalgia syndrome" (FMS) is the diagnosis clinicians most often give patients who have chronic widespread pain and abnormal tenderness. Most FMS researchers state that the etiology of the disorder is unknown. In doing so, they fail to account for a substantial line of evidence showing that the main mechanism of FMS is inadequate thyroid hormone regulation.

In 2004, Wallace and Clauw published a book titled *Fibromyalgia & Other Central Pain Syndromes*.[30] Wallace and Clauw, chapter authors in—and editors of—the book, are central figures in the clique that continues life support for the decerebrated rheumatology paradigm of FMS.[1,pp.57-91] Their book can be fairly considered the latest update on the authors' knowledge of FMS, its mechanisms, and it treatments.

To say that these editors and chapter authors gave short shrift to inadequate thyroid hormone regulation of cell function as a putative etiological hypothesis of FMS would be a gross understatement. The terms "hypothyroidism" and "thyroid hormone" are not listed in the index of the book. In his chapter titled "Fibromyalgia in Inflammatory and Endocrine Disorders," Hallegua devotes two short paragraphs and one concluding sentence to hypothyroidism. In the concluding sentence he wrote, "Thus there is no conclusive evidence of specific thyroid dysfunction in FMS syndrome [sic], although it remains an important diagnosis to exclude when making the primary diagnosis."[31,p.190]

One purpose of this review is to counterbalance what I interpret as the 2004 book's editors' and authors' gross neglect of the published scientific literature on the relationship of thyroid hormone to FMS. Despite their neglect, I contend that the evidence I cite below indicates that the main underlying mechanism of most patients' FMS is inadequate thyroid hormone regulation of cell function.

Line of Evidence

The evidence that too little thyroid hormone regulation of cell function is the main underlying mechanism of FMS falls into four categories. These are: (1) symptoms, (2) studies of thyroid test results, (3) objectively verified abnormalities among patients, and (4) clinical trials with thyroid hormone therapy.

Symptoms

As many clinicians and researchers have reported,[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][209] FMS patients' symptoms are identical to those of a subset of patients who have either hypothyroidism or the "peripheral" form of thyroid hormone resistance. The patients' predominant symptoms are chronic widespread pain and abnormal tenderness. These two symptoms are considered essential to a diagnosis of FMS. But along with these symptoms, which are classic for a subset of patients with inadequate thyroid hormone regulation, most FMS patients also have other symptoms.

Table 1 lists the symptoms that rheumatology-paradigm FMS researchers term "associated symptoms" of FMS. Other clinicians use a different terminology: they state that when some hypothyroid patients first consult them, the patients do so with "presenting" symptoms of FMS.[209] To clinicians intimately familiar with the three relevant clinical categories (hypothyroidism, peripheral thyroid hormone resistance, and FMS), the symptoms of many patients in any one of the categories are indistinguishable from those of many patients in the other two categories.

Studies of Thyroid Test Results

In primary hypothyroidism, a thyroid hormone deficiency results from failure of the thyroid gland to produce adequate thyroid hormone. In central hypothyroidism, the patient's thyroid gland produces too little thyroid hormone for another reason: one or both of the two structures in the brain that regulate the thyroid gland (the hypothalamus or the pituitary gland) is malfunctioning. As a result, the thyroid gland does not produce an optimal amount of thyroid hormone. FMS patients as a group have a high incidence of thyroid function test results showing "primary" or "central" hypothyroidism.[20][21][22][23][24][25][26]

FMS patients also have a higher incidence of antithyroid antibodies than people at large.[18][19] High antithyroid antibodies means that a patient's thyroid gland is undergoing a destructive autoimmune process. In Hashimoto's thyroiditis (struma lymphomatosa),[214] suppressor T-lymphocytes are reduced. Helper T-lymphocytes increase in the interstitial spaces between the gland's follicles. This is followed by infiltration of the gland by B-lymphocytes and plasma cells. The gland's follicles then atrophy and fibrosis accumulates.[212][215,p.921] The B-lymphocytes and the plasma cells derived from them secrete antibodies against either or both the gland's thyroglobulin and thyroid peroxidase.[213] The gland itself is the major site of thyroid antibody production.[216]

Table 1. Most common symptoms associated with FMS.*λ

SYMPTOM	% OF PATIENTS WITH THE SYMPTOM
Widespread pain	97.6
Fatigue	81.4
Morning stiffness >15 min.	77.0
Sleep disturbance	74.6
Paresthesias	62.8
Headache	52.8
Anxiety	47.8
Sensation of swelling	47.0
Dysmenorrhea history	40.6
Sicca symptoms	35.8
Prior depression	31.5
Irritable bowel syndrome	29.6
Urinary urgency	26.3
Raynaud's symptoms	16.7
Female urethral syndrome †	12.0
Cognitive dysfunction ‡	—

*After: Wolfe, F.: Diagnosis of fibromyalgia. *J. Musculoskeletal Med*., 7:54, 1990.[136]

λ Originally published in Lowe, J.C.: *The Metabolic Treatment of Fibromyalgia*. Boulder, McDowell Publishing Co., 2000, p.785.[1]

†Yunus, M.B. and Masi, A.T.: Fibromyalgia, restless legs syndrome, periodic limb movement disorder, and psychogenic pain. In *Arthritis and Allied Conditions: A Textbook of Rheumatology*. Edited by D.J. McCarty, Jr. and W.J. Koopman, Philadelphia, Lea & Febiger, 1992, pp.1383-1405.[210]

‡Nielson, W.R., Grace, G.M., Hopkins, M., and Berg, M.: Concentration and memory deficits in patients with fibromyalgia syndrome. *J. Musculoskeletal Pain*, 3(Suppl.1):123, 1995.[211]

NOTE: The reported frequency of different symptoms varies according to source.

At some point in this destructive process, the gland ceases to produce enough thyroid hormone on average to maintain normal metabolism and

health. The patient can then develop symptoms of hypothyroidism without elevated blood thyroid antibodies.[185][186][187][188][189] Moreover, the patient with autoimmune thyroiditis (with or without symptoms) may have reference range TSH and thyroid hormone levels for years.[215,p.927] A significant percentage of FMS patients, especially females, with high antithyroid antibodies but "normal" TSH and thyroid hormone levels have chronic, widespread pain that is often diagnosed as "fibromyalgia."[15]

Before 2002 in the United States, researchers (based on a higher-than-current upper limit for the TSH) calculated that the incidence of primary hypothyroidism in the general population was 1%-to-5%.[27][28] Among FMS patients, based on studies of thyroid function test results, the reported incidence of primary hypothyroidism was 10%-to-24%.[20][23][24][29][32]

My research group studied the incidence of central hypothyroidism among FMS patients using thyroid function test results and the dynamic TRH-stimulation test. Results were consistent with central hypothyroidism in 44% of patients.[21] This percentage was 250,000 times that in the general population.

In 1990, Forslind published a study[32] that casts a dark shadow of doubt on the existence of *primary* FMS—that is, FMS as a distinct disorder not underlain by another medical disorder. He and his colleagues examined 21 of 25 consecutive patients 5 years after they had received the diagnosis of primary FMS at a tertiary-care day-ward for patients with pain syndromes. The researchers concluded that only 15 of the 21 patients still met the criteria for FMS. However, *all* patients had developed either psychiatric disturbances or thyroid dysfunction. Among the 4 patients the researchers did not examine, two had developed neurological diseases, one had developed rheumatoid arthritis, and one other was hypothyroid. "Thus," the researchers wrote, "after 5 years no patient fulfilled the criteria for primary fibromyalgia." Hypothyroidism was the disorder most common among the patients.

In 1988, Carette and Lefrançois examined 100 patients for FMS (then termed "fibrositis") who, according to thyroid function test results, had subclinical or primary hypothyroidism.[200] Only 19 of the patients reported having joint and/or muscle pain with stiffness. The researchers did not diagnose all 19 patients as having FMS, however, because an essential criterion for the diagnosis was abnormal tenderness.

When Carette and Lefrançois examined the patients for tender points, only 5 of the 19 patients had 7 or more abnormally tender points. Requiring that patients have pain, stiffness, and tenderness to qualify for a diagnosis of FMS, Carette and Lefrancois wrote that only 5% of the 100 patients met the criteria for FMS.

The researchers then treated the 19 patients with muscle and/or joint pain with "thyroid hormone replacement." The symptoms of 10 of the 19 patients improved, including 3 of the 5 patients the researchers had diagnosed as having FMS. However, the researchers reported "no significant changes in tender points." They concluded, "Our data indicate that fibrositis is uncommon in patients with primary hypothyroidism despite the frequent occurrence of symptoms suggestive of this syndrome."[200]

Some FMS researchers I have communicated with have unfortunately falsely concluded that the Carette and Lefrancois study shows that hypothyroidism cannot be the main underlying mechanism of FMS. This clear-cut illogical conclusion is important to the erroneous belief that FMS and inadequate thyroid hormone regulation are unrelated.

The appropriate interpretation of the Carette and Lefrancois study result is the following. As this review demonstrates, a substantial published research literature shows a relationship between FMS and too little thyroid hormone regulation of cell function. In view of this, the pain and tenderness that rheumatology-paradigm FMS researchers consider the hallmarks of FMS plausibly combine to be one of *many* clinical phenotypes of hypothyroidism.

Thus, if we are for the moment to accept the criteria Carette and Lefrançois' used to diagnose FMS, the researchers would have more properly concluded: "Among our sample of 100 hypothyroid patients, only 5% met the criteria for fibrositis; this raises the possibility that fibrositis is a rare clinical phenotypic expression of hypothyroidism."

Logically, it is perfectly clear that this study did not rule out hypothyroidism as the main underlying mechanism of the 5 patients they diagnosed as having FMS. Instead, that 3 of the 5 patients improved with thyroid hormone replacement points toward hypothyroidism as the underlying mechanism of their FMS.

More importantly, it is highly probable that the "thyroid hormone replacement" the authors referred to was T_4-replacement. I say this because I know that in their Canadian province, T_4-replacement is typically autocratically imposed on hypothyroid patients. The importance of the use of T_4-replacement with these patients is that several studies show that many hypothyroid patients continue to suffer from hypothyroid symptoms despite their use of T_4-replacement.[196][197][198][201][202][203][204][205]

In a large community study, for example, close to 50% of patients on T_4-replacement continued to suffer from hypothyroid symptoms.[201] (For a critique of these studies, see Lowe.[199]) Had Carette and Lefrançois used a more effective approach to thyroid hormone therapy, it is highly likely (in view of the clinical trials cited below) that all 5 of their patients would have fully recovered, and they would no longer have had tender points.

Soy et al.[206] found that among patients with autoimmune thyroid disease, 62% had what they termed "rheumatic" conditions. Among patients with these conditions, the highest percentage (31%) met the criteria for FMS, which the authors falsely presumed to be a rheumatic disorder.

As with the Carette and Lefrançois study,[200] a reasonable conclusion from the finding of Soy et al. would be: "The clinical phenotypic expression termed 'FMS' is clearly not the clinical outcome of *all* patients with autoimmune thyroid disease." This conclusion does *not* rule out autoimmune-induced hypothyroidism as the main underlying mechanism of many patients' FMS.

Reports of studies conducted to determine whether there is a relationship between FMS and thyroid disease must be read carefully; otherwise, one might easily miss the indications of the relationship. Consider, for example, a 1993 study by Shiroky et al.[24] The researchers tested for the incidence of thyroid dysfunction among rheumatoid arthritis patients compared to patients with osteoarthritis and others with FMS. Shiroky et al. reported that 30% of women with rheumatoid arthritis had thyroid dysfunction. They noted that this percentage was three times the incidence of thyroid dysfunction among FMS patients. As I wrote above, based on the upper limit of the TSH at that time, researchers considered 1%-to-5% of the population at large to be hypothyroid. Considering Shiroky's statement, compared to the 30% of rheumatoid arthritis patients who were hypothyroid, 10% of FMS patients were hypothyroid. At that time, this percentage was significantly higher than the incidence in the general population.[24]

Objectively Verified Abnormalities Among FMS Patients

According to a group of French medical authors, "Fibromyalgia is a syndrome characterized by chronic musculoskeletal pain and fatigue *without biological detectable disturbances*."[207] (Italics mine.) This italicized statement is blatantly false; it suggests to me that the authors did not comply with the scientific responsibility of reviewing the relevant research literature before publishing statements on a scientific issue. For a journal's reviewers to fail to identify and prevent publication of such patently false statements reflects poorly on the journal. What is more, in my view, publication of such false information is a disservice from both the authors and the journal to clinicians who depend on the journal for scientifically accurate information.

Contrary to the false statement by these authors, Table 2 shows the objective abnormalities identified among FMS patients. These abnormalities have been documented through more than thirty years of research.

Hypotheses abound concerning the mechanism of FMS symptoms and some of these objective abnormalities. However, only a few such hypotheses have any scientifically credible backing. Of the hypotheses supported by some plausible evidence, none (except the inadequate thyroid hormone regulation theory) account for more than a few of the objectively verified abnormalities.

In stark contrast, the inadequate thyroid hormone regulation hypothesis (specifically, that too little thyroid hormone regulation is the main underlying mechanism of most patients' FMS) credibly accounts for at least 40 objectively verified abnormalities of FMS. As I documented in *The Metabolic Treatment of Fibromyalgia*, studies show that these same abnormalities also occur in a subset of patients with hypothyroidism or peripheral thyroid hormone resistance.[1,p.71(Table1.1.1),pp.341-766]

In Table 2 (40 objectively verified abnormalities in FMS), the cited studies show that each abnormality identified in FMS patients has also been identified in patients with hypothyroidism, peripheral thyroid hormone resistance, or both.

Table 2. Same objectively verified abnormalities in fibromyalgia (FM) as compared to hypothyroidism (HO) or peripheral resistance to thyroid hormone (PRTH).

ABNORMALITIES	FM	HO or PRTH
Histological		
↑ Hyaluronic acid	34,35	36
↑ Ground substance proteoglycans	11,12,37-39	40-43
↓ Collagen	44,45	46,47
↓ Pyridinoline	48,49	50,51
↓ Procollagen III	52-54	36,55,56
↓ Hydroxyproline	44,45,48,49	47,50,57,58
↑ Mast cells	37,38,59	46,60-64
CSF		
↑ Substance P	65-68	69-72
↓ Dopamine (homovanillic acid)	73	74,75
↓ Tissue norepinephrine	73	76-78
↓ Urinary 5-hydroxyindole acetic acid	79	80
↓ Brain 5-hydroxytryptophan	73,81	82
↑ Nerve growth factor	83	84,85
Molecular		
↑ α-Adrenoceptors	86,87	88-95
Mitochondria		
Ragged red fibers	96,97	98,99
↓ Cytochrome-c-oxidase	100	98,99
Physiological		
↓ Basal body temperature	183,184	192-195
↓ Resting metabolic rate	183,184	57,183,184
Exercise intolerance	101-104	105-108
↓ Muscle relaxation time	109	110
Blunted cortisol response to ACTH	111,112	113
Orthostatic hypotension	114,115	116
Joint hypermobility	117,118	119
↓ Brain blood flow	120-122	123
↓ Peripheral blood flow	124-126	127
Blunted sympathetic and end-organ response to stress	101,115,128-131	132-135
Excess urination	136,137	138,139
↓ Delta-wave and nonrestorative sleep	140,141	138,142-144
High-energy phosphates		
↓ ATP	145	146-149
↑ Phosphodiesters	150-152	153
↑ Inorganic phosphate (Pi)	151	153,154
↓ Phosphocreatine (PCr)	145	146
↓ PCr/Pi ratio	145	154,155
Carbohydrate metabolism		
↑ Pyruvate	156-158	105,156,159
↓ LDH	150,156	150,156
↓ Intracellular pH	150	153,154
↓ Skeletal muscle glucose use	160	161-163
Endocrine		
↓ HPA axis function	131,164	165,166
↓ GH and IGF-1	167-169	170,171
↑ Hypothyroidism	20-26	NA
↑ Hypothyroidism	20-26	n/a

Could the 40 abnormalities occur in all three disorders if the disorders did not have the same underlying mechanism? That is definitely within the realm of possibility. On the other hand, the mechanism could be the same, and I argue that logical analysis dictates that this conclusion is true—in the sense of "scientific truth," which, of course, is never conclusive.[217][218]

In my research team's efforts to refute the inadequate thyroid hormone regulation hypothesis, we conducted and published two studies in 2006. In each of these studies we measured the resting metabolic rates and basal body temperatures of FMS patients and compared them to healthy matched controls.

These studies came close to being the most vigorous challenges possible to the inadequate thyroid hormone regulation etiological hypothesis. Had our conjecture that FMS is mainly underlain by too little thyroid hormone regulation been refuted by these studies, the hypothesis would have been conclusively refuted and essentially demolished. However, the studies failed to refute the inadequate thyroid hormone hypothesis. To use an inductivist term, the outcome of the studies "supports" the inadequate thyroid hormone regulation hypothesis.

Because the studies failed to disprove the inadequate thyroid hormone regulation hypothesis, I describe the study results in the two sections below. Statistical analyses show that the differences between patients and controls were highly significant, both for basal temperatures and resting metabolic rates. Compared to matched healthy controls, women with FMS had significantly lower resting metabolic rates and basal body temperatures—*objective findings most consistent with too little thyroid hormone regulation of cell function in these FMS patients*. In each of the studies we ruled out any likely cause of patients' low resting metabolic rates and low basal body temperatures other than inadequate thyroid hormone regulation. *It is especially important to emphasize that in both studies, patients and controls were matched for level of physical activity, which rules out low physical fitness as the cause of the patients' lower mean metabolic rates and temperatures.*

Low resting metabolic rates of FMS patients. In the first study, patients' mean resting metabolic rate was 29% below their predicted rate (that which is considered normal) based on sex, age, height, and weight. The mean of the healthy control subjects' metabolic rates was only 8% below their predicted rates. (The "reasonable reference range" for resting metabolic rate is generally accepted as 10% below or above the predicted rate.)

In the second study, the mean resting metabolic rate for patients was 30% below the predicted rate. The mean metabolic rate of healthy controls was, again, 8% below the predicted rate.

Low basal body temperatures of FMS patients. In the first study, patients' average basal temperature was 96.95˚F. The average for healthy women was 97.54˚F. In the second study, the average temperature of patients was 96.38˚F. The average for healthy controls was 97.54˚F. Statistically, the patients' temperatures in both studies were significantly lower than those of controls.

Clinical Trials with Thyroid Hormone Therapy

Most FMS patients and their cooperative doctors want to know mainly one thing: Do we have an effective treatment for FMS? The answer is yes, although rheumatology-paradigm FMS researchers have *totally* ignored what Garrison and Breeding explained in *Medical Hypotheses* as "experimentally proven treatments."[208]

Patients have recovered from their FMS symptoms in two types of studies conducted by my research team and several others: open[172][173][174][175][176][190][191] and blinded[177][178][179][180][181] clinical trials. In 2002, Peter Warmingham commented on some of these studies in an article titled "Fibromyalgia Has Been Solved."[33] These are the only studies (those involving the use of thyroid hormone) in which patients have largely or fully recovered from FMS symptoms.

All these trials have included the use of thyroid hormone therapies *other than T_4-replacement*. I italicize the last phrase for an important reason: as I explained above [see "Studies of Thyroid Test Results"], T_4-replacement is ineffective for possibly 50% of hypothyroid patients who use it. As Garrison and Breeding noted after helping hundreds of thyroid hormone resistant FMS patients to recover with thyroid hormone, treatment usually involves supraphysiologic doses of T_3.[208] As my research team and others have found through at least two decades of clinical experience, a small percentage of hypothyroid FMS patients recover with T_4 alone. But few of them recover with T_4-replacement;

most must use TSH-suppressive dosages of T_4. For most patients to fully recover, however, they must use either combined T_4/T_3 therapy (with a 4:1 ratio of T_4-to-T_3) or T_3 alone.

A follow-up study by my research team showed the long-term effectiveness of treatment with thyroid hormone therapy other than T_4-replacement. In that study, we evaluated patients 1-to-5 years after they had undergone treatment with thyroid hormone therapy (combined with synergistic lifestyle practices). *It is important to note that most patients used thyroid hormone dosages larger than those used in T_4-replacement, in which patients use T_4 dosages that keep their TSH levels within the reference range; instead, safe and effective dosages were typically ones that kept patients' TSH levels below the lower end of the reference range*. We compared these patients to matched controls—patients we had evaluated earlier but who did not undergo treatment. Compared to the matched controls, the treated patients had statistically significantly improved. Moreover, their improvement lasted through the 1-to-5 year span, depending on the time of follow-up since they began treatment.[182]

In 1993, pediatricians at the Pediatric Rheumatology Center in Philadelphia described 5 children who had what they considered varied "rheumatic" conditions, including FMS and joint pain. They wrote, "*All musculoskeletal symptoms improved after thyroid replacement therapy.* We conclude that rheumatic manifestations of hypothyroidism can be as varied in children as in adults."[191] (Italics mine.)

Summary

Is it likely that too little thyroid hormone regulation of cell function is the main cause of most patients' FMS? I believe the line of evidence I have presented here sufficiently answers that question.

I fully anticipate, however, that rheumatology-paradigm FMS researchers will—as they have in the past—(1) marginalize any possible role of too little thyroid hormone regulation in FMS, (2) ignore the factual existence of thyroid hormone resistance, and (3) state or imply that hypothyroidism merely mimics FMS and should be differentiated from it by measuring patients' TSH levels.

For rheumatology-paradigm FMS researchers to disagree with the inadequate thyroid hormone regulation hypothesis of the etiology of FMS is respectable scientific conduct. However, to ignore the evidence upon which we base this conclusion is (to be euphemistic) not respectable scientific conduct. On behalf of FMS patients, I hope that these researchers finally open-mindedly consider the evidence I have assembled here, and acknowledge through their future publications that they can no longer simply ignore the evidence as though it did not exist.

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