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# Fibromyalgia

## *Symptom Constellation and Potential Therapeutic Options*

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**Fibromyalgia (FM) is a disease entity consisting of a heterogeneous cluster of symptoms that has thus far eluded identification of a causative etiology. The disease onset appears to follow physiological and/or psychological stressors and involves a subset of symptoms that are consistent with varied disorders found in multiple medical specialties to include rheumatology, immunology, endocrinology, neurology, and psychiatry. Owing to the heterogeneity of the symptom complex and the heretofore absence of serum markers that might serve as concrete diagnostic criteria, this disease has baffled clinicians and basic scientists alike. Recent findings regarding sleep architecture, immunology, and endocrinology have provided clues that may help in the understanding and resultant treatment of this entity. Women with fibromyalgia tend to present with an alpha–delta sleep anomaly, which when treated with a growth hormone secretagogue (GHS), reduces the rheumatological pain and restores slow-wave sleep architecture. These findings suggest the somatotrophic axis may be involved in the etiology and the treatment of this disorder. Those diagnosed with FM respond to various stressors with increased disruption of their physiological homeostasis. When compared to healthy age-matched cohorts, there are quantitative differences in various neuroactive steroid levels, immunological markers, and feedback mechanisms. The varied physiological alterations in patients diagnosed with fibromyalgia when compared to controls will be discussed along with the potential treatment options for this population.**

***The soul sympathizes with the diseased and traumatized body and the body suffers when the soul is ailing.***

***Aristotle, 4th century BCE***

**Key Words:** Fibromyalgia; alpha–delta anomaly; growth hormone secretagogues; IGF-1.

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## Introduction

Fibromyalgia (FM) remains a diagnostic and treatment dilemma for the clinician and patient owing to the lack of concrete disease "markers." This condition is a debilitating illness that severely compromises physical as well as cognitive abilities and psychological sense of well being. Patients experience intermittent and migrating joint discomfort, difficulty with sleep/wake cycles, constant fatigue, depression, and impaired concentration. The joint pain, discomfort, and nonrestorative sleep discourage exercise, thus contributing to a sedentary lifestyle that results in an elevated body mass index (BMI). This increased BMI has serious health as well as endocrinological ramifications due to the impact of obesity on the somatotrophic axis *(1)*. The related factors of a compromised quality of life together with the inability to work, results in many FM patients becoming "disabled." Not only does this have societal implications, but the patient is further stigmatized.

### *Etiological Perspectives and Diagnostic Criteria*

Theoretically, fibromyalgia appears to be multifactorial in etiology *(2)*. Underlying vulnerabilities to various stressors, perhaps a combination of biological, physiological, or psychological factors, result in the dysregulation of the various axes. The feedback mechanisms comprising endocrinological, immunological, and neurological systems and the resultant communication between these homeostatic systems are also possibly compromised. The American College of Rheumatology (ACR) criteria (Table 1) for this illness includes only musculoskeletal pain *(3)*. But patients diagnosed with fibromyalgia experience symptoms far in excess of the current diagnostic criteria. When compared to healthy controls, significant increases in muscle aches, widespread pain, nonrestorative sleep, joint aches, fatigue, and cognitive dysfunction have been documented in women diagnosed with FM. Post-exertional exhaustion, numbness and tingling, tension headaches, edema, comorbid chronic fatigue syndrome (CFS), temporal mandibular joint syndrome (TMJ), irritable bowel syndrome (IBS), reflex sympathetic dystrophy (RSD), and increased psychopathology have been described in the symptom complex *(4)*. Not only does this cohort respond differently when challenged by a biological agent (lipopolysaccaride or interleukin-6) or psychological stressor, but women with FM also exhibit baseline

**Table 1**
American College of Rheumatology
1990 Criteria for Fibromyalgia

1. History of widespread pain, defined as pain present in all of the following sites: left and right sides of the body, above and below the waist. Additionally, axial pain, must be present.
2. The presence of pain in 11 of the following 18 bilateral tender points sites upon digital palpation (approximate force of 4 kg; must elicit the subjective sensation of pain from the subject):
   - Occiput, at the suboccipital muscle insertions
   - Low cervical, at the anterior aspects of the intertranverse spaces at C5–C7
   - Trapezius, at the midpoint of the upper border
   - Supraspinatus, at origins, above the scapula spine near the medial borders
   - Second rib, at the second costrochrondral junctions, just lateral to the junctions on upper surfaces
   - Lateral epicondyle 2 cm distal to the epicondyles
   - Gluteal, in upper outer quadrants of buttocks in anterior fold of muscle
   - Greater trochanter, posterior to the trochacteric prominence
   - Knee, at the medial fat pad proximal to the joint line

variations in gonadal/adrenal hormones levels, proinflammatory cytokines activity, thyroid axis, HPA axis, somatotrophic axis, and sleep architecture *(5)*. This syndromic constellation far exceeds that of the musculoskeletal pain in the official criteria and implies a dysregulation of various physiological and homeostatic systems and feedback mechanisms. While a detailed examination of the HPA axis and sympathetic system in patients diagnosed with this condition is beyond the scope of this article, the somatotrophic axis dysregulation, the endocrine disparities, cognitive distinctions, and the immunological profile of women with FM will be discussed.

## Somatotrophic Axis and Fibromyalgia

Normal aging is accompanied by a progressive decline in growth hormone (GH) secretion at a rate of 14% per decade *(6)*. This etiology of the gradual somatotrophic axis senescence is not well understood but appears to coincide with a reduction of nonrapid eye movement (NREM) or slow-wave sleep (SWS) that occurs during aging *(7)*. The predominant GH secretory pulse occurs during the first period of SWS each night and occurs in a gender-related pattern *(8)*. A blunted somatotrophic axis or decrease in secretion of growth hormone has been posited as one of the deficiencies or contributors to the etiology and progression of FM *(9,10)*. More than 30% of women with FM are thought to have subnormal IGF-1 levels *(11)*. But this theory has come under heavy scrutiny due to numerous variables in the populations studied. In a placebo-controlled, double-blind study, recombinant growth hormone was given to 25 women who met the American College of Rheumatology diagnostic criteria for FM. Results demonstrated a significant improvement in symptoms and functional ability concurrent with an increase in IGF-1 levels. The entry criteria of an IGF-1 level < 160 ng/mL was titrated to 250 ng/mL by individualized dosing throughout the study. While recombinant GH was well tolerated, there was a 6-mo delay until symptom improvement occurred. This was validated by significance on the Fibromyalgia Impact Questionnaire (FIQ), which occurred with a reduction in tender point evaluation *(11)*. Other work has demonstrated a significant decrease of pain after 6 and 12 mo of treatment with GH in women with baseline IGF-1 levels < 125 ng/mL implicating the gradual senescence or a blunted somatotrophic axis may potentate the symptomatology experienced in women with fibromyalgia *(12)*.

## Sleep Architecture and GH Secretagogues

Sleep research suggests abnormal sleep architecture may contribute to the pain and the non-refreshing sleep experienced in FM. During aging, the decline in SWS also termed stage III and stage IV, coincides with GH secretion. When SWS is interrupted by noise, pain, or frequent awakenings, less GH is produced, and when SWS is interrupted in controls, joint pain and other symptoms consistent with FM occur *(13)*. In fibromyalgia, as well as certain other autoimmune rheumatological diseases, the frequent awakenings, possibly due to pain, were found to coincide with an abnormality in sleep architecture characterized by alpha waves or waking waves interrupting the delta waves characteristic of SWS *(14)*. A decreased amount of GH secretion has also been associated with the decrease of stage III and IV sleep in women diagnosed with FM *(10)*. Sleep studies or polysomnography recordings from women diagnosed with FM when compared to healthy cohorts illustrated three different patterns of alpha wave incursion affecting SWS *(15)*. The phasic alpha–delta anomaly presented in 50% of subjects with FM while only 7% of controls exhibited this pattern. Twenty percent of the patients had a tonic alpha pattern that was found in 9% of controls. The remaining 30% of subjects demonstrated a low alpha activity pattern, the predominant pattern found in 84% of controls. The subjects with the phasic alpha–delta pattern appeared to experience increased somatic symptomatology as well as a significant reduction in total sleep time, sleep efficiency, and SWS *(15,16)*. This innovative work clarified the different alpha–delta patterns (phasic versus tonic) and resultant gradation of symptomatology, but regrettably contained no treatment arm. Other work has examined the results of growth hormone secretagogues (GHS) on sleep architecture in this population *(17)*. GHS are administered orally, once daily, while recombinent GH must be injected on a daily basis. Although GHSs are able to restore the amplitude of pituitary GH secretion to that of a younger group, injectable GH supplemen-

tation cannot simulate the restoration of the physiological secretory pattern *(18)*. It has been theorized that increased somatostatin tone is the rationale for decreased GH secretion with aging complicated by the well-known effects of obesity resulting in hyposomatotrophism *(19,20)*. It has been suggested that women diagnosed with FM have increased somatostatic tone due to their lack of a sufficient GH response to exercise. This increased tone was reversed by the addition of pyridostigmine with resulted in GH levels reaching eight times that of FM baseline, ultimately comparable to controls *(21)*.

Because GHS have the ability to mimic the physiological pulsatility and amplitude of GH secretion, the effects of gamma-hydroxybutyrate (GHB), a potent growth hormone secretagogue, on alpha-wave incursion during SWS would clarify the importance of this sleep anomaly in FM. When patients were given GHB for 4 wk, alpha incursion percentage decreased significantly from a baseline measurement of 32.30 ± 19.83% to 10.20 ± 9.42%. The percentage of time spent in SWS increased from 12.59 ± 17.38% to 19.65 ± 9.43%, and the subjects related a significant reduction in pain and fatigue as well as an increase in morning alertness. The major "side effect" of GHB along with therapeutic sedation was a short half-life of 35–60 min, but this seemingly negative characteristic served to benefit women with FM. Many who had experienced difficulty initiating daily activities, found this "rebound alertness" welcomed *(17)*. IGF-1 levels, regrettably, were not measured during GHB treatment and may have provided data relating to an association of increased time spent in SWS, a change in IGF-1 levels and pain scales.

Others have not found the same relationship with alpha–delta anomaly and FM *(22)*. This could be due to syndromal heterogeneity of the "fibromyalgia" presentation or differences in the quality of polysomnographic equipment, including interpretation and scoring methodology and whether scoring was performed by machine or technician *(14,16)*. But despite the disagreement with regard to the alpha–delta anomaly being a "marker," sleep research has confirmed women with FM experience less consolidated sleep during the first half of the night with increased sleep fragmentation when compared to asymptomatic women *(23)*.

Although the impact of GHB on the somatotrophic axis has not been explored in healthy women, GHB ingestion in lean young men produced a doubling of GH secretion during the initial period of SWS *(24)*. The polysomnogram recordings did not demonstrate a significant increase in SWS associated with the GHB-induced stimulation of stage IV sleep, but it should be noted that these healthy young men were not deficient in SWS at baseline and did not exhibit an alpha–delta anomaly. There was no evidence of decreased levels of GH and IGF-1 or rheumatological pain. Also, the endogenous pattern of growth hormone secretion in healthy men versus healthy females exhibits a gender-related pattern that differs during sleep and wakefulness *(25)*. These

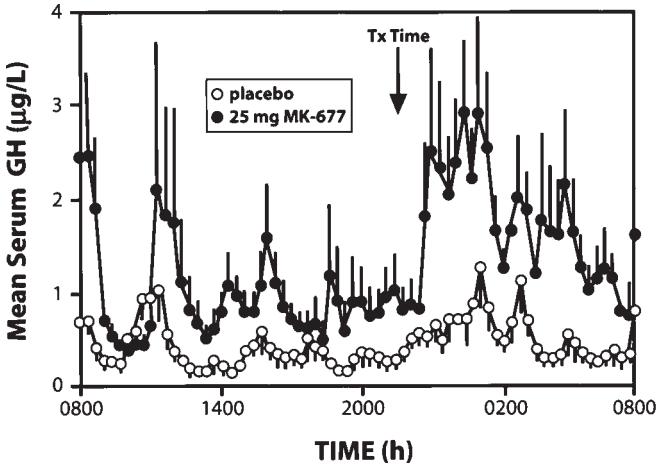


**Fig. 1.** Mean (± SE) serum GH concentrations (µg/mL) in older subjects after 2 wk of treatment with placebo (O; $n$ = 10) and 25 mg/d MK-677 (●; $n$ = 10). Evening treatment time (between 2200–2300 h) is indicated by an arrow. Adapted from Chapman et al. *(18)*.

gender-based differences make it difficult to extrapolate results from young men to perimenopausal and postmenopausal women. The mechanism for GHB elevating IGF-1 levels has not been elucidated.

The growth hormone releasing peptide (GHRP) mimetic, MK-677, has demonstrated a restoration of GH pulsatility in an aged population 61–84 to that of a young population in their early 20s (Fig. 1) *(18)*. MK-677 has excellent bioavailability after oral dosing and is able to sustain a physiological GH secretion along with resulting elevations of IGF-1 levels *(26)*. This GH mimetic has also demonstrated improved sleep quality in both healthy young and elderly populations. There was a significant increase in stage IV sleep in the 18–21-yr-old subjects accompanied by a dose-dependent increase in IGF-1. In the healthy older patients, given a lower dose of MK-677, REM duration increased, but SWS was not significantly altered *(27)*. Thus, while GH secretion is increased in the elderly, with MK-677, it does not appear to translate into increased time in SWS. Although this investigational substance has been tested in healthy populations, no research to date has been performed on patients diagnosed with FM.

## Endocrinological Characteristics

### *Current Endocrine Findings*

Sleep architecture and the somatotrophic axis are not the only systems affected in women with FM as the endocrine system appears to be markedly impacted. Women diagnosed with FM have significantly depressed DHEA-sulfate (DHEA-S) levels compared to healthy women of similar endocrinological and chronological profile. Depressed levels of androgens are present in the perimenopausal transition and the menopause *(28)*. When the FIQ was used to assess corre-

lations of androgen serum assays and IGF-1 levels with pain and physical functioning, pain was found to correlate negatively with DHEA-S levels. Free testosterone demonstrated a similar negative correlation with physical functioning. Free testosterone was also significantly decreased in the premenopausal group, but this finding lost significance during the postmenopausal period, which may be due to the low levels of free testosterone in women of this age group as well as the inaccuracy of current assays with regards to the lower limits of sensitivity for testosterone. When insulin-like growth factor I (IGF-1) levels were examined, values were significantly lower ($p < 0.03$) in women who were obese compared to those who were normal or overweight. This finding held true in both cohorts, patients diagnosed with FM as well as the normal controls. The relationship of obesity to decreased levels of IGF-1 appears to be a confound with regard to the possible etiological contribution of a blunted somatotrophic axis. Of the 57 patients studied, only 14% demonstrated a normal BMI (≤24 kg/m$^2$). Forty-two percent were classified as overweight (25–30 kg/m$^2$), while 44% were classified as obese (BMI > 30 kg/m$^2$). When the BMI was taken into consideration to adjust for pain, the correlations between increased pain, low DHEA-S, free testosterone, and low physical functioning were lost. These results would call for a stringent research paradigm where BMI was controlled and investigated subjects exhibited a BMI of ≤24kg/m$^2$ which is considered to be in the normal range.

The majority FM patients tend to be "middle-aged" or in the perimenopause or menopause, which implicates reproductive endocrinology or the aging process *(29)*. This further complicates the search for concrete serum markers as the endocrinological picture of "normal" women in their 40s and early 50s is an extremely complicated presentation. Besides fluctuating hormone levels over the course of the menstrual cycle, increased irregularity of cycles vary from month to month. In spite of these variables, there remain quantifiable aspects of hormone levels in this group. By age 40, a woman's testosterone level has declined to 50% from that measured in her 20s *(30)*. DHEA also suffers a continuous downward tend each decade in women, more so than in men, so that by age 35 women experience a 50% decrease from levels in their 20s *(31)*. This reduction in DHEA and DHEA-S occurs with no concurrent lowering of cortisol secretion *(32)*. While the ovary continues to secrete androgens during the menopause, the adrenal gland remains the major contributor of DHEA and DHEA-S. The female adrenal gland appears to be affected earlier by the adrenopause than that of the male. Besides the decrease in serum levels of DHEA and DHEA-S, with aging there are changes in size and zone margination of the zona reticularis, zona glomerularis, and zona faciculatis. The zona reticularis undergoes a significant atrophy of 30% in men from ages 30 to 55 *(33)*. In women this atrophy occurs earlier between the third and fourth decades. There is a further significant decrease in volume in the zona reticularis by the sixth decade, which parallels the steep decrease in serum levels of DHEA and DHEA-S (C.R. Parker, personal correspondence).

Declining androgen levels are not the only hormones implicated during the perimenopausal transition as progesterone decreases as well. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) increase and estradiol secretion becomes increasing irregular *(34)*. When the perimenopause transitions into the menopause, women demonstrate significantly lower levels of estradiol, progesterone, DHEA-S, IGF-1, and GH, while cortisol remains unchanged *(35)*. Although these decreasing levels of gonadal and neurosteroids have not been precisely implicated in the etiological and ongoing symptomatology of FM, they may contribute to the perpetuation and chronicity of this disease.

## Cognition

Women with FM complain of numerous cognitive symptoms that are similar to those experienced by growth-hormone-deficient adults including difficulty with cognition and impaired concentration *(9,10,36)*. Working memory, episodic memory, and verbal fluency has been found to be compromised in patients diagnosed with FM. Working memory is the ability to simultaneously retain recent information while processing new material. It is inherently necessary for multitasking, as well as the storage of new memory. Episodic memory is the ability to recall specific events. Under laboratory conditions, it is measured by the ability to retrieve newly presented data. Verbal memory involves accessing stored knowledge about words and is tested by examining the patient's ability to list as many words as they can in a defined period of time from a particular subject grouping. Neuropsychiatric test results of women diagnosed with FM demonstrate deficits in working memory (Table 2) *(37)*. When these same test results were compared to a cohort of healthy women 20 yr older than the FM population, the patients only significantly outperformed the older women in processing speed. There was no significant difference in working memory or episodic memory, but, interestingly, they performed significantly worse in verbal knowledge (Table 3). Their similarity with age-matched controls on processing speed demonstrated sufficient effort was extended during the testing procedure and ruled out poor performance due to depression or lack of motivation (37).

Other investigators have also demonstrated that patients with FM performed worse on tests of immediate and delayed recall as well as sustained auditory concentration. Anxiety and depression were felt to be a partial confound, but overall as a group, although patients with FM performed in the "normal" range, they performed significantly lower than the age-matched (by decade) controls. Notable were the results illustrating that 23% of the women with FM scored below two standard deviations on at least one test, while only 3.3% of the controls scored that far from the mean on these standardized tests. The authors concluded that these defi-

**Table 2**
Cognitive Task Performance:
Fibromyalgia vs 20-Yr-Older Women

| | Fibromyalgia ($n$ = 23) | Older controls ($n$ = 22) | |
|---|---|---|---|
| Information processing speed | 139.45 | 118.50 | $p = 0.013$ |
| Working memory | 22.2 | 22.09 | $p = 9.9$ |
| Free recall | 23.56 | 23.91 | $p = 0.588$ |
| Recognition memory | 2.53 | 2.80 | $p = 0.177$ |
| Verbal fluency | 49.78 | 49.43 | $p = 0.89$ |
| Verbal knowledge | 43.17 | 50.56 | $p = 0.009$ |

Adapted from Park *(37)*.

**Table 3**
Cognitive Task Performance:
Fibromyalgia vs Age Matched Controls

| | Fibromyalgia ($n$ = 23) | Age-matched controls ($n$ = 23) | |
|---|---|---|---|
| Information processing speed | 139.45 | 139.23 | $p = 0.975$ |
| Working memory | 22.2 | 26.30 | $p = 0.042$ |
| Free recall | 23.56 | 27.83 | $p = 0.005$ |
| Recognition memory | 2.53 | 2.95 | $p = 0.035$ |
| Verbal fluency | 49.78 | 56.08 | $p = 0.055$ |
| Verbal knowledge | 43.17 | 51.26 | $p < 0.0001$ |

Adapted from Park *(37)*.

cits involved attentional factors that relate to efficiency of memory and thus impact required daily cognitive skills *(38)*.

Although IGF-1 levels and cognition in a cohort of healthy aging women has not been studied, this work has been performed in older men, aged 65–87 *(39)*. There appears to be cognitive domains that change with aging, and those that remain stable. Information knowledge, vocabulary, reading speed, and basic perceptual processes appear to remain constant with aging in men, while perceptual motor processing speed, perceptual organization and construction, visual-motor tracking and processing speed, as well as long-term memory retention all decline with age. Healthy male subjects with higher endogenous IGF-1 levels significantly outperformed the groups with lower IGF-1 levels in cognitive and perceptual-motor processing speed, two age-related domains.

GH supplementation in GH deficient men has demonstrated significantly improved memory performance correlated with increased serum IGF-1 *(40)*. Study subjects given sufficient GH to induced supraphysiological levels of IGF-1 experienced subjective memory normalization within 6 mo of treatment, while those receiving lower doses of GH resulting in physiological levels of IGF-1 demonstrated a delayed time to memory normalization of 12 mo. While these findings should not be extrapolated to women with FM with their varied endocrinological picture, it is interesting to note that the time to symptomatic relief of improved cognition in growth-hormone-deficient men was similar to that experienced by the GH-supplemented women diagnosed with FM with regard to pain relief.

## Mood and Fibromyalgia

### *Depression/Chronic Disease*

Increased rates of depression accompany aging in both men and women, but, in adulthood, women are afflicted with depression at twice the rate of men *(41)*. Depression or other psychopathology is frequently diagnosed with FM. Attempting to discern cause versus effect with regards to depression is difficult when the chronic illness and disability coexist.

Growth hormone secretion measured over 24 h in depressed women is significantly decreased when compared to those without the affective disorder. When the area under the curve (AUC) of GH secretion was examined, depressed patients scored a value of $429.15 \pm 367.9$ vs controls who demonstrated $1281.07 \pm 379.33$ ($p < 0.008$). The difference was explained by the variation in nocturnal versus diurnal levels over the 24 h, as it appears there was a significant decrease in nocturnal secretion in the depressed patients *(42)*.

Adrenal androgens are decreased in depression. Women diagnosed with new onset depression in the perimenopause demonstrate significantly decreased DHEA-S levels, when compared to healthy endocrinologically matched women *(43)*. Depression has been associated with an increase or upregulation of inflammatory cytokines *(44)*. These cytokines along with other humoral mediators are able to direct and program inflammatory responses. Elevated interleukin-6, soluable receptor of IL-6, as well as soluable receptor of IL-2 were found to be possible "trait" markers of depression, since antidepressant treatment with full remission of depression resulted in no change in immunological status of these markers. Thus, it remains to be explored whether inflammatory cytokines such as IL-6 are an integral part of depression or if elevated levels of inflammatory cytokines results in a depressed state. The immune system and its intimate relationship with the endocrine system also requires further exploration with regard to the similarities found in patients diagnosed with depression and those diagnosed with FM.

### *Inflammatory Cytokines and Sickness Behavior*

Aging and the menopausal state appear to impact basal levels of cytokine production. This appears to be exacerbated in women with fibromyalgia. Healthy postmenopausal women ($54 \pm 8$ yr old) not on hormone replacement therapy

(HRT) when compared to their reproductive aged (32 ± 7 yr old) counterparts produced significantly more IL-6 and IL-18 *(35)*. Interleukin-6 not only increases with age, but, once mobilized, can direct the inflammatory response. An increased production of inflammatory cytokines is correlated with aging as well as decreased levels of DHEA-S *(45)*. Surprisingly no statistical relationship has been found between cytokines and a one-time measurement of GH or IGF-1 *(35)*.

A cytokine analysis was conducted with regard to IL-1β, IFN-γ, sIL-2r, IL-10, TNF-α, and IL-2 in the sera of 56 patients with FM, average age 50.4 yr, and matched controls. No statistical difference was found, but patients with FM demonstrated a 55% increase in interleukin 1 receptor antagonist (IL-1Ra). Plasma levels of IL-8 were significantly elevated, but IL-6 remained unchanged. During an in vitro analysis of peripheral blood mononuclear cells (PBMC), significantly increased levels of IL-6 and IL-1Ra were found in patients with FM along with, in vitro–induced IL-1Ra, IL-6, and IL-8. Although noted for their inflammatory potential, these cytokines tend to increase with the duration of the disease *(4)*.

The production or increase of inflammatory cytokines in the animal model has proved to be an interesting reference for the human condition. When laboratory animals are challenged with lipopolysaccaride (LPS) in order to produce increased levels of IL-1, they exhibit "sickness behavior." Sickness behavior is characterized by nonspecific infectious symptoms including weakness, malaise, listlessness, hypersomnia, depressed activity, and loss of interest in social activity. In the animal model, this sickness behavior is protective as the animal expends less energy in usual activities but instead remains inactive in an attempt to combat the infection *(46,47)*. The syndromic constellation of women diagnosed with FM appears similar to that of rodent "sickness behavior." But while animals recover from the transient challenge of LPS, women with FM appear unable to recover from the "sickness model" and perhaps are "stuck" in sickness behavior mode.

Interleukin-1 appears to be produced by phagocytic cells located in the choroid plexus and circumventricular organs. In this location at the junction of the blood–brain barrier transportation of cytokines from peripheral areas to the CNS may be facilitated. Substance P, another inflammatory marker, is known to stimulate the production of IL-8 and IL-6. It is elevated up to three times in the cerebral spinal fluid of women with FM. This increase in Substance P could contributes to the hyperalgia or increased pain experienced by this population. Substance P is also thought to increase pain perception and possibly amplify inflammatory cytokine production. Thus, increased Substance P may play a role together with increased inflammatory cytokines production in the etiology or the perpetuation of pain symptoms in FM *(48,49)*.

### *Study Design Critique and Clarification of Diverse Endocrine Populations*

The body of research on women diagnosed with this condition is difficult to interpret for a variety of reasons. The heterogeneous symptom cluster and the lack of criteria from disciplines other than rheumatology have resulted in difficulty with study design and numerous confounding variables. Many studies have included subjects with comorbid pathology of chronic fatigue syndrome (CFS) as well as major depression. The population examined in the multicenter group that proposed the original ACR Criteria for FM included women diagnosed with other rheumatological conditions to include 42% inflammatory arthritis, 30% axial skeletal syndrome, 10% osteoarthritis, 21% nonarticular disorders, and 4% arthralgia syndromes *(3)*. These comorbid conditions perpetuate the difficulty in diagnosing this entity. It would appear a population should not exhibit comorbid conditions when diagnostic criteria are to be defined. In other work, subjects have continued to take psychoactive medications as well as opioids while undergoing research protocol *(9,11,17,38)*. Besides disease comorbidity and the use of psychoactive medications, the subject's reproductive status is usually not accurately delineated. Often women from the premenopausal period and the perimenopausal transition are placed together with those in the menopause and "results" are often reported as if they applied to all women diagnosed with this condition without consideration of their reproductive or endocrinological status. The potential negative ramification of reporting results from diverse "cohorts" as if they applied to all women does not help further the scientific exploration of this entity. Other findings are confounded by the lack of differentiating the menopausal etiology (surgical versus physiological) and whether the patient is taking exogenous hormones. Furthermore, the exact type of hormone replacement therapy (HRT) is usually not defined nor are therapeutic levels of various hormones assessed. The route of estrogen administration, be it oral, transdermal, or subcutaneous, assumes an even greater importance in women with FM who have demonstrated adrenal hyposecretion. Oral estradiol whether it be conjugated equine estrogen (CEE) or 17β estradiol, increases liver production of sex hormone binding globulin (SHBG) by 160%, which further lowers androgen levels *(50)*. SHBG by binding testosterone further decreases bioactive or free androgen levels that are already depressed in the FM population. Exogenous estrogen can affect the somatotrophic axis as oral estrogens tend to increase GH and lower IGF-1, whereas the transdermal route appears to have a nonsignificant effect *(51,52)*. Some results have been equivocal and possibly a result of synthetic versus bio-identical estrogen use, with and without progestins as well as the possibility of estradiol increasing body weight leading to a down-regulation of somatotrophs *(53)*. Exogenous and endogenous estradiol and testosterone affect the GH–IGF-1 axis as well as sleep, thus further rationale for

study designs that combine populations with similar endocrine profiles for the purpose of scientific rigor *(54)*.

Obesity and BMI require strict criteria in study populations, as obesity is well known to impact IGF-1 levels and the somatotrophic axis and thus without classification along strict adiposity criteria, results are once again not conclusive.

Because viable treatment, aside from palliation, has proven elusive, many patients are prescribed antidepressants, muscle relaxants, opioids, and hydrocortisone in order to provide symptomatic relief. Although some find symptom reduction from various medication combinations, the literature does not report a standardized treatment regimen that provides total symptomatic relief. This state of incomplete treatment increases the investigational problem as these patients are extremely reluctant to discontinue their medications or participate in a "washout period" for clinical trials or research involving various treatment modalities.

Study design demands cohorts separated on the basis of their reproductive status, as well as their chronological age. The differing immunological and endocrinological profiles of reproductive age women versus women in the menopause would invalidate conclusions.

## Discussion

Current research raises numerous fascinating questions regarding this disease entity for which some doubt exists. It is certain that FM encompasses more than a rheumatological condition and perhaps, at present, owing to the classification criteria, a heterogeneous population. Besides a disruption in sleep architechture and a blunted GH–IGF-1 axis, the measurable cognitive consequence of fibromyalgia requires further investigation. Characteristic symptoms of afflicted patients suggest an involvement of neurological, endocrinology, or immunological processes that seriously impact cognitive abilities resembling an accelerated "aging" of the central nervous system (CNS). The etiology of this cognitive decline has not been elucidated. One could hypothesize that the gradual but perhaps accelerated senescence of the somatotrophic axis, together with decreased androgens and fluctuating estradiol levels may contribute. Thus, if estrogen, progesterone, testosterone, DHEA, DHEA-S, and other parent steroids and metabolic byproducts are important for ongoing CNS function as well as repair, deficiencies in neurosteroids as well as GH and growth-hormone receptors have the potential to greatly impact neural repair and cognitive processes.

But the question remains as to why women with FM suffer lower levels of various neurosteroids and increased levels of inflammatory cytokines when compared to healthy controls? Are the various inflammatory cytokines elevated due to depression, environmental stressors, or a possible autoimmune component that is yet to be identified? Does the disease entity of FM in some fashion cause the hyposecretion of adrenal androgens, or is the hyposecretion part of pathophysiology of the illness?

Testosterone levels in young male interns subjected to a stressful environment and sleep deprivation were compared to same-aged hospital employees. Their testosterone levels were found to be significantly lower (43%) than the controls *(55)*. Male military recruits undergoing intense physical training, sleep deprivation, and increased psychological stressors exhibited a significant decline in testosterone levels accompanied by a decrease in DHEA-S/cortisol ratio *(56)*. These results implicate both physiological and psychological stressors as well as sleep deprivation as a possible mechanism for lowered androgen levels, which have been described in fibromyalgia. It is known that testosterone and DHEA have direct anti-inflammatory effects on proinflammatory cytokine production *(57)*. Perhaps with further study these findings may shed light on these various aspects of fibromyalgia, which currently remain unanswered.

The GH–IGF-1 axis and its relationship to obesity raises numerous questions with regard to FM. Is a blunted GH–IGF-1 axis one of the etiological causes of FM, or does the obesity, found in numerous patients with FM result in lowered IGF-1?

The disrupted and fragmented sleep architechture found in this population with an accompanying phasic alpha–delta anomaly requires further exploration. Although this has been demonstrated in other painful rheumatologically or autoimmune conditions, women with FM tend to have a greater percentage of their SWS impacted by the phasic alpha–delta anomaly than control groups, or others with varied medical diagnosis *(16)*. Research with strict entry criteria with regard to a phasic alpha–delta sleep anomaly in women with fibromyalgia within normal BMI requires further investigation with the addition of a treatment arm to explore the use of GH mimetics such as MK-677 or GHB. This would result in clarification of the important relationships among the immune system, the GH–IGF-1 axis, and sleep.

## Conclusion

Although it would be comforting to summarize the current FM research and reach sound scientific conclusions, the lack of systematic study design with well-delineated, similar populations makes this extremely difficult. Various findings, though, provide the necessary theoretically guidelines for further research.

Although the causative factors of FM remain elusive, the differing endocrine, immune, sleep architechture, and neuropsychiatric profiles illustrated between normal women and those diagnosed with FM lead to interesting speculative conclusions and potential theories for therapy. Perhaps FM is a state of accelerated aging caused by a variety of insults. Various endocrine hormonal levels are decreased, predominately the androgens. This could cause a detrimental impact

on mood as well as cognition. It is well documented that androgens suppress various proinflammatory cytokines, namely, IL-6, which is felt to play a role in increased rheumatological pain. If the protective mechanism of adrenal androgen suppression of inflammatory cytokines is lost, increased rheumatological pain may result. If a type of "accelerated aging" is involved, does the menopausal condition or the experience of having been castrated in any way contribute to the disease progression or the speed of progression? Does ovarian and adrenal cross-talk exist, such that when one organ is compromised, the other ceases to work in the same manner as when both organs were fully functional?

If cognitive abilities in patients with FM resemble those of healthy women 20 yr older, could this be explained by the loss of various neurosteroids accompanying the decline in serum levels as well as the appearingly blunted somatotrophic axis? Perhaps, taken together with the concept of accelerated aging, FM is the result of a multisystem "breakdown" from continuous or repeated stressors: biological, environmental, or psychological. The fundamentally impaired sleep architecture, specifically the phasic alpha–delta sleep anomaly, may provide important insights into pain, sleep quality, and the production of growth hormone and IGF-1.

Treatment of FM currently consists of palliative care. Medical care of these patients should encompass a proactive model of care with replacement of hormones and peptides that are known to be deficient. This currently is not the case. The fact that most women diagnosed with FM are in their mid 40s to mid 50s highlights the involvement of the perimenopausal transition and the menopause as being important endocrinological events, which may precipitate the illness in a population that has an underlying vulnerability along with current stressor. This is also a time when women are androgen deficient, when compared to assays from their 20s and 30s. The evaluation of patients diagnosed with FM should include individualized endocrine evaluations where serum levels of various reproductive hormones are measured with special emphasis on the adrenal androgens. Perhaps, IGF-1 levels and GH challenge tests should be assessed in a strictly controlled cohort with phasic alpha–delta SWS anomaly while controlling for BMI. The resultant data would then address whether a correlation exists between sleep architecture and the somatotrophic axis and whether resultant correction of sleep architecture by use of a GH secretagogue also resulted in improved IGF-1 levels besides the noted reduction in pain. The data demonstrating a reduced alpha-wave incursion into SWS with reduced pain and improved quality of life with GHB appear to suggest that treatment with an oral GH secretagogue may indeed be indicated for this population that has a demonstrable objective disturbance of SWS.

Thus, the evaluation and treatment of women with FM calls for a clarification of the established diagnostic criteria that would encompass the endocrine, immune, psychiatric, and neurological components of the illness along with the established rheumatological criteria. The treatment demands a "team" approach with one physician assuming the leadership role, and coordinating treatment of various other medical specialties to provide an improved quality of life and most importantly the restoration of a productive and healthy life.

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