A Review of Fibromyalgia

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Characterized by chronic widespread joint and muscle pain, fibromyalgia is a syndrome of unknown etiology. The American College of Rheumatology's classification criteria for fibromyalgia include diffuse soft tissue pain of at least 3 months' duration and pain on palpation in at least 11 of 18 paired tender points. Symptoms are often exacerbated by exertion, stress, lack of sleep, and weather changes. Fibromyalgia is primarily a diagnosis of exclusion, established only after other causes of joint or muscle pain are ruled out. The initial workup for patients who present with widespread musculoskeletal pain should include a complete blood count, erythrocyte sedimentation rate, liver function tests, hepatitis C antibody, calcium, and thyrotropin. The musculoskeletal system, the neuroendocrine system, and the central nervous system, particularly the limbic system, appear to play major roles in the pathogenesis of fibromyalgia. The goal in treating fibromyalgia is to decrease pain and to increase function without promoting polypharmacy. Brief interdisciplinary programs have been shown to improve subjective pain. Fibromyalgia is a complex syndrome associated with significant impairment on quality of life and function and substantial financial costs. Once the diagnosis is made, providers should aim to increase patients' function and minimize pain. This can be accomplished through nonpharmacological and pharmacological interventions. With proper management, the rate of disability appears to be significantly reduced.

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Fibromyalgia is a syndrome of unknown etiology characterized by chronic widespread joint and muscle pain. Fibromyalgia was previously referred to as *fibrositis*, a term coined by Sir William Gowers[1] in Europe referring to regional pain syndromes associated with profound fatigue and sleep disturbance. Fibromyalgia affects approximately 6 million people in the United States,[2] or up to 6% of the patients seen in general medical practices.[3] Patients are usually diagnosed between the ages of 20 and 50 years, but the incidence rises with age so that, by age 80, approximately 8% of adults meet the classification criteria established by the American College of Rheumatology.[4] The ratio of women to men with fibromyalgia varies between 9:1[5] and 20:1.[6] One prospective study[7] showed that patients with fibromyalgia have approximately 10 outpatient clinic visits per year, 1 hospitalization per 3 years, and more than $2000 per year in medical costs. Another prospective study[8] showed that total annual costs for fibromyalgia patients were close to $6000, compared with $2500 for typical patients. Six percent of these costs were attributable to fibromyalgia-specific claims. However, there may have been other hidden costs related to disability from fibromyalgia. This study also showed that, for every dollar spent on fibromyalgia-specific claims, the employer spent $57 to $143 on additional direct and indirect costs.

The American College of Rheumatology's criteria for fibromyalgia include diffuse soft tissue pain of at least 3 months' duration and pain on palpation in at least 11 of 18 paired tender points.[4] These criteria are approximately 88% sensitive and 81% specific for the diagnosis of fibromyalgia. Symptoms are often exacerbated by exertion, stress, lack of sleep, and weather changes. In half of all patients, symptoms appear after a flulike illness or after physical or emotional trauma.[9] Approximately 30% of patients with fibromyalgia are diagnosed as having concurrent depression or anxiety disorders (**Figure**).[10]

DIAGNOSIS

The main challenge in evaluating patients with suspected fibromyalgia is that there is no gold standard test for diagnosis. It is primarily a diagnosis of exclusion, established only after other causes of joint or muscle pain are ruled out. The initial workup for patients who present with widespread musculoskeletal pain should include a complete blood count, erythrocyte sedimentation rate, liver function tests, hepatitis C antibody, calcium, and thyrotropin. Some experts recommend that patients with suspected fibromyalgia have a limited amount of testing before assigning the diagnosis. The clinician should keep in mind that an antinuclear antibody is often of low yield when other features of systemic lupus erythematosus or other antinuclear antibody–associated diseases are absent. In addition, false-positive results are common. In one series, 10% of patients with fibromyalgia had a positive antinuclear antibody.[11] Up to 30% of healthy women may test positive as well.[12] Similarly, imaging tests and

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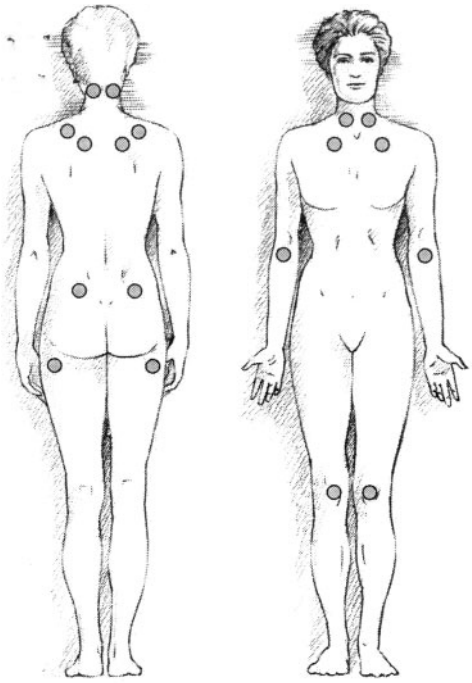
neurophysiological studies are not recommended as initial screening tests.[13]

In most cases, the patient's history can distinguish fibromyalgia from other systemic illnesses. However, fibromyalgia often coexists with and has a tendency to mimic other illnesses. Estimates of its concomitance with systemic lupus erythematosus range as high as 45%. In one study[14] of patients with lupus, 22% of the patients also met criteria for fibromyalgia. These patients had no difference in the measures of their lupus activity. However, they experienced greater disability associated with their illnesses. Twelve percent of patients with rheumatoid arthritis and 7% of patients with osteoarthritis meet the criteria for fibromyalgia.[15] Twenty-five to 50% of patients with fibromyalgia have Raynaud phenomenon or have symptoms consistent with sicca syndrome.[12] Patients with fibromyalgia may initially be misdiagnosed as having seronegative spondyloarthropathies, such as ankylosing spondylitis, because they share the common complaints of neck, spine, and back pain. However, in the absence of other inflammatory disease, patients with fibromyalgia have normal erythrocyte sedimentation rates and normal findings on radiographic studies. In older adults, the syndrome is most commonly confused with polymyalgia rheumatica, which typically presents with persistent severe morning stiffness in the shoulders, pelvis, and torso. The erythrocyte sedimentation rate will be elevated in 80% to 90% of patients with polymyalgia rheumatica, and its symptoms respond to low-dose systemic corticosteroids. Fibromyalgia symptoms do not respond to corticosteroids,[16] consistent with the noninflammatory nature of this disorder. However, patients with polymyalgia rheumatica who are tapered off corticosteroids too rapidly can occasionally develop symptoms similar to those of fibromyalgia. Most patients with chronic fatigue syndrome meet the criteria for fibromyalgia, and 70% of fibromyalgia patients meet criteria for chronic fatigue syndrome.[17]

In nonrheumatic illnesses, patients may present with symptoms similar to fibromyalgia. Hypothyroidism can present with muscle pain similar to fibromyalgia.[12] Patients with hepatitis C have a higher prevalence of fibromyalgia.[18] Research suggests that Lyme disease can also trigger fibromyalgia.[19] In one study,[20] patients with fibromyalgia had a greater number of desaturations per hour of sleep compared with healthy control subjects. Those patients complaining of daytime hypersomnolence had a higher number of tender points, about twice as many arousals per hour, and lower sleep efficiency compared with the other patients.

In terms of psychiatric morbidity, an estimated 30% of patients with fibromyalgia will have depression or anxiety at some point during their lifetime. One study[21] found that 40% of patients with fibromyalgia had depression, compared with 29% of patients with rheumatoid arthritis. The likelihood of depression in patients with musculoskeletal complaints was highest in patients with nonarticular diseases such as fibromyalgia or myofascial pain syndrome.[22] Fibromyalgia patients demonstrate higher levels of anxiety and depression than healthy control groups.[23] This may exacerbate or trigger their somatic complaints. However, according to some investigations, measures of depression, anxiety, and stress are comparable in patients with fibromyalgia and patients with other chronic medical conditions.[24] Therefore, patients with fibromyalgia may exhibit signs and symptoms of anxiety and depression, and their complaints should not be attributed to psychological illness alone.

Figure. Tender Points in Fibromyalgia Patients



*Used with permission from the Arthritis Foundation.[11]

PATHOGENESIS

The musculoskeletal system, the neuroendocrine system, and the central nervous system, particularly the limbic system, appear to play major roles in the pathogenesis of fibromyalgia.

Musculoskeletal

Many soft tissue injuries are thought to follow chronic muscle-tendon overload and muscle fiber "microtrauma." Continual vibration or muscle twisting along with repetitive muscle movements over time can lead to muscle spasm and nerve irritation. In fibromyalgia patients, it has been postulated that there is an inability to relax the shoulder flexor muscles between isokinetic muscle contractions.[25] This, over time, could lead to muscular pain.

Some studies[26,27] suggest that patients with fibromyalgia have abnormalities in muscle energy metabolism and muscle tissue oxygenation. For example, in fibromyalgia patients, biopsy specimens of tender areas of the trapezius muscle contain more ragged red fibers and fewer high-energy phosphate compounds than specimens of nontender muscles in these patients.[28] Some muscle biopsies of the tissue surrounding tender points have shown structural changes described as "moth-eaten fibers," mitochondrial changes, and type II atrophy, indicating dysfunction in the muscle microcirculation.[29] Together, these data may support the hypothesis that local tissue hypoxia contributes to the pain associated with fibromyalgia. However, it is not clear whether these muscle changes are a cause or an effect of fibromyalgia. The fact that local treatment of tender points is generally ineffective suggests 1 of 2 possibilities: either fibromyalgia is a systemic disease rather than an aggregate of localized muscle disturbances, or we simply do not have effective local therapies.[30]

Other more recent investigations show that there are no differences between fibromyalgia patients and sedentary controls in terms of adenosine triphosphate levels, lactate levels, muscle tension, hypoxia, or intracellular pH.[31] Results demonstrate that measures of muscle function such as force generation and lactate production during exercise, and muscle pain after exertion, are similar between women with fibromyalgia and healthy sedentary female control patients.[31] This suggests that the cause of fibromyalgia symptoms is unlikely to be a pathologic abnormality of the muscle itself.

Neuroendocrine

The neuroendocrine dysfunction in fibromyalgia involves the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-thyroid axis, the growth hormone axis, and the locus caeruleus–norepinephrine sympathetic nervous system. With respect to the hypothalamic-pituitary-adrenal axis, some findings suggest that fibromyalgia patients may have low adrenal responsiveness.[32] Griep et al[33] showed that in these patients, when corticotrophin-releasing hormone is released from the hypothalamus, there is a disproportionately high level of corticotropin released from the pituitary in response and an unexpectedly small amount of cortisol that are eventually released by the adrenal glands into the bloodstream. This suggests that these patients may have a blunting of the normal stress response and may not react appropriately to events such as infection or physical or emotional trauma.[34]

However, these same patients, when injected with synthetic corticotropin, showed a similar increase in their cortisol levels compared with healthy control subjects.[33] This shows that adrenal tissue in fibromyalgia patients may have a differing sensitivity to exogenous versus endogenous corticotropin. Therefore, perhaps these patients have a blunted response to endogenous corticotropin due to a downregulation of receptors, as might be found in settings of chronic stress, rather than true adrenal insufficiency.

Multiple studies have shown that fibromyalgia patients have elevated cortisol levels with a flattened diurnal pattern[35] and lack of suppression by dexamethasone.[36] Results have shown that patients with depression also have elevated levels of corticotropin and cortisol, with a flattening of the diurnal pattern.[37]

Investigations of the hypothalamic-pituitary-thyroid axis in fibromyalgia patients suggest that, when thyrotropin-releasing hormone is released, thyrotropin, triiodothyronine, and thyroxine are secreted, but to a lesser degree than expected.[38] These data imply that there is some pituitary dysfunction in these patients, perhaps related to a dampened stress response.

It is also thought that sleep disorders may induce neuroendocrine dysfunction, which, in turn, promotes disease development. During stage 4 sleep, the body produces most of its growth hormone. In patients with fibromyalgia, stage 4 sleep is often disrupted.[39] Although factors such as weight and age were not controlled for, the patients who were studied appeared to have a decreased level of somatomedin C, the precursor to growth hormone.[40] It has been suggested that this relative growth hormone deficiency may account for poor healing of muscle microtrauma, thereby contributing to nociceptive input.[40] It has been shown that patients with fibromyalgia have increased levels of corticotropin[33] and that corticotropin increases the secretion of somatostatin in the hypothalamus.[41] Somatostatin is one of the hormones that is able to inhibit growth hormone via the hypothalamic-pituitary portal system.[42] This may also contribute to the relative growth hormone deficiency in fibromyalgia patients. Approximately 30% of patients with fibromyalgia have growth factor deficiency if defined by low insulin-like growth factor 1 levels.[43] However, these low levels may be more common than clinically significant growth hor-

mone.[43] Another study[44] showed impaired reactivity of the hypothalamic-pituitary axis in one third of the patients with fibromyalgia, but did not show the presence of severe growth hormone deficiency. Some patients have experienced pain relief with injections of subcutaneous growth hormone versus placebo.[45]

Neurological

Fibromyalgia patients often exhibit allodynia, a phenomenon whereby formerly innocuous stimuli become painful. One showed that fibromyalgia patients have significantly higher scores than controls on an index of sensory discrimination for various mechanical stimuli at tender and control points. This is consistent with the theory that they receive increased neural input to stimuli relative to controls. Weigent et al[34] showed that the thresholds for detecting stimuli were similar between fibromyalgia patients and healthy controls. However, the points at which heat, electrical stimulation, and pressure became painful were different. Regional blood flow investigations using functional magnetic resonance imaging showed that, when the patients had similar subjective discomfort, they had the same level of blood flow to the corresponding regions of their brains.[46] For the same amount of pressure applied, however, the fibromyalgia patients experienced greater discomfort and increased regional blood flow and neurological activation than healthy controls.

Fibromyalgia patients generally have a greater sensitivity to stimuli diffusely, suggesting that there may be a central or a peripheral nervous system disturbance. This theory is supported by the fact that patients have 2 to 3 times normal levels of substance P, a pain modulator, in their cerebrospinal fluid.[47] Stress may potentiate the nociceptive effects of substance P in fibromyalgia by stimulating nerve growth factor. Fibromyalgia patients may have an increased amount of this factor in their cerebrospinal fluid.[48] This, in turn, may promote peripheral nerve growth and abnormal pain perception. These patients' cerebrospinal fluid also contains elevated levels of calcitonin gene–related peptide and dynorphin A, which normally increase after injury. Although there are multiple potential explanations for this change, one possibility is that there may have been an insult to the nervous system in fibromyalgia patients.

Serotonin is a neurotransmitter in the spinal cord that inhibits the transmission of pain. It is derived from λ-tryptophan, an amino acid that appears to be decreased in the cerebrospinal fluid of patients with fibromyalgia.[49]

Research by the National Cardiology Institute of Mexico has suggested that dysautonomia is frequent in patients with fibromyalgia.[50] They found that the sympathetic nervous system is persistently hyperactive at baseline, but hypoactive in response to stress.

MANAGEMENT

The goal in treating fibromyalgia is to decrease pain and to increase function without promoting polypharmacy. Brief interdisciplinary programs have been shown to improve subjective pain. A high pretreatment level of impairment was significantly associated with a better response to treatment.[51]

Critical elements in developing a self-management program for patients are improving self-efficacy, physical training, and cognitive-behavioral techniques.[51] In investigations of patients with rheumatoid arthritis, changes in self-efficacy were shown to significantly predict changes in pain, depression, and health status, regardless of changes in medical regimens.[52] Self-efficacy is promoted by mastery, modeling, social persuasion, and physiological feedback. To develop mastery, patients must have the chance to practice skills until they are able to succeed at them and use incremental successes as positive reinforcement for their continued efforts. Finally, physiological feedback such as pain scales may help patients visualize marginal improvements.[52]

Cognitive strategies that emphasize restructuring of negative thoughts and catastrophic generalizations about pain are powerful ways to cope with fibromyalgia pain and fatigue.[53]

Patients with fibromyalgia may be aerobically unfit[54] because of inactivity due to pain. Unaccustomed exercise may exacerbate the pain and lead to delayed-onset muscle soreness in the short run. Despite this, controlled trials of exercise demonstrate that people with fibromyalgia can increase their levels of physical fitness, with associated decreases in pain.[55,56] Bicycling, walking, and water aerobics are among the best-tolerated exercises. Perhaps this is because aerobic exercise increases the body's production of endogenous opioids. These powerful endorphins act through the limbic system to decrease pain and to induce the euphoria commonly known as runner's high. It has not been shown, however, that endorphin levels are decreased in fibromyalgia patients. Also, exercise facilitates sleep. Because sleep dysfunction compounds the symptoms of fibromyalgia, restoring sleep could disrupt the cycle in which increased pain leads to decreased sleep, which then results in increasing pain and disability. In addition, aerobic exercise increases oxygenation and circulation to muscle tissue.[56] Exercise can also have psychologically beneficial effects, such as promoting a

sense of well-being and a sense of accomplishment. Randomized controlled trials have shown that exercise improves mood and decreases disability in patients with fibromyalgia.[57] Therefore, patients should be encouraged to perform aerobic exercise at least 3 times a week. Flexibility training alone can improve symptoms, but to a lesser extent.[58] A systematic review of randomized controlled trials of nonpharmacological interventions in fibromyalgia between 1980 and 2000 did not provide strong evidence for any single treatment.[59] However, it showed moderate support for aerobic exercise as a therapeutic intervention.

Almost all patients with fibromyalgia have sleep dysfunction characterized by light unrefreshing sleep.[60] Tricyclic antidepressants may be helpful as a form of treatment, perhaps because they improve sleep and may reduce morning stiffness.[61] They may also act by inhibiting serotonin and norepinephrine reuptake, thereby suppressing polysynaptic neuronal discharge.[62] A randomized controlled trial of low-dose amitriptyline hydrochloride and naproxen sodium showed that patients improve with tricyclic antidepressants in terms of pain, sleep difficulties, fatigue on awakening, and tender point score.[63] Nonsteroidal anti-inflammatory drugs may have an additive effect,[64] although their effect may be analgesic rather than anti-inflammatory. Fluoxetine hydrochloride may improve symptoms of depression and fatigue, but has not been shown to decrease the number of tender points.[65] Amitriptyline and fluoxetine may work better in combination than either one alone.[66] Trazodone hydrochloride has also been shown to be effective, perhaps because it increases the duration of stage 3 and stage 4 sleep and decreases the alpha-delta sleep abnormality common in fibromyalgia.[67] Zolpidem tartrate does not appear to improve the pain of fibromyalgia, but may improve sleep and daytime energy.[68] Cyclobenzaprine hydrochloride may decrease the severity of pain and improve the quality of sleep in fibromyalgia patients, but it does not appear to alleviate the fatigue or morning stiffness.[69] Opioids may be helpful in treating fibromyalgia pain, but may be habit-forming, tolerageneic, and associated with adverse effects such as constipation, sedation, and nausea.

Transcutaneous electrical nerve stimulation, laser treatment, and acupuncture appear to have limited pain efficacy. Although there are no controlled trials demonstrating benefit, 1% lidocaine hydrochloride injections, botulinum toxin injections, and dry needling are sometimes offered to patients with fibromyalgia.[70] Despite a suggestion of relative growth hormone deficiency in persons with fibromyalgia and reports of improvement after receiving injections of growth hormone, adverse effects, frequent injections, and cost have dampened enthusiasm for this approach.

Relaxation strategies for the relief of muscle tension and anxiety are also effective.[70] Electromyograms with feedback exercises and hypnosis are therapeutic modalities that are being investigated.

Treatment of concomitant conditions may improve symptoms of fibromyalgia. For example, fibromyalgia may be particularly difficult to treat when untreated depression, anxiety, or sleep apnea is also present.

PROGNOSIS

Follow-up of patients with fibromyalgia after 14 years shows that patients may have minor change in their symptoms, but do not develop progressive disability from the disease.[71] Remissions are rare after many years of disease, but may occur in the first year or 2, especially in milder community-based settings. One study[72] of ambulatory patients showed that 47% no longer fulfilled the American College of Rheumatology's criteria for fibromyalgia syndrome. Remissions were identified in 24.2% of patients. Therefore, patients who are based in the community may have a good outcome. Thirty-five percent of patients who are able to be managed by their primary care physicians experience resolution of symptoms after 2 years.[73] One longitudinal prospective study[74] suggested that most fibromyalgia patients show improvement in terms of overall status, pain, fatigue, and function at 40 months. The only predictors for favorable outcome in this study were younger age and less sleep disturbance. However, it appears that patients sent to referral centers generally have no change in their pain, fatigue, sleep disturbance, anxiety, or depression symptoms after 8 years.[75]

Problems that may interfere with the employment of patients with fibromyalgia include difficulty in performing repetitive motor tasks, prolonged sitting or standing, loss of mental acuity, anxiety about poor performance, and workplace stressors.[76] One study[77] used computerized workstations in simulated work environments to physically stress the shoulders, spines, wrists, and elbows of fibromyalgia patients, patients with rheumatoid arthritis, and healthy controls. Patients with fibromyalgia could only perform 59% of the work performed by their healthy counterparts, compared with patients with rheumatoid arthritis, who could perform 62% of that workload.

Disability secondary to chronic pain appears to result from a combination of patients' past experiences, self-esteem, motivation, psychological distress, fatigue, ethnocultural background, education, income, and

potential financial compensation.[53] Disability in chronic pain does not appear to be related to the severity of the pain.[78] Thirty percent of patients with fibromyalgia are disabled, compared with 2% of the general population.[78] Patients with other forms of chronic pain have a disability rate of approximately 10%.[79]

CONCLUSION

Fibromyalgia is a complex syndrome associated with significant impairment on quality of life and function and substantial financial costs. Although its cause is not well understood, it is clear that interdisciplinary approaches to its management are probably the most beneficial. Therefore, once the diagnosis is made, providers should aim to increase patients' function and minimize their pain complaints. This can be accomplished through different nonpharmacological and pharmacological interventions. With proper management, the rate of disability appears to be significantly reduced.

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