

6 The scope of rheumatic disease

6.13 Soft-tissue rheumatism

6.13.1 Fibromyalgia and diffuse pain syndromes—adult onset

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Introduction, the development of the concept of fibromyalgia

Fibromyalgia is a clinical syndrome, characterized by chronic, generalized pain in joints, muscles, and the spine. Although pain is felt in joints, there is no arthritis; the pain originates from muscles and other so-called soft tissues. Therefore, fibromyalgia is commonly classified as soft tissue rheumatism. The pain is often accompanied by several non-specific symptoms, such as fatigue, depressive mood, and sleep disturbance, hence the term syndrome. The Mexican painter Frida Kahlo beautifully depicted her fibromyalgia in a self-portrait named 'The broken column', expressing generalized peripheral and axial pain, tender points, headache, depression, and social isolation. Most patients experience early morning stiffness, but there are no signs of inflammation. At physical examination tender points are found, that is, soft tissues are painful on pressure. Laboratory investigations give normal results. The old synonym fibrositis, suggesting inflammation, is misleading and obsolete. Damage to joints or other tissues does not occur.

Although the demanding modern Western society might be seen as a risk factor for development of musculoskeletal complaints, chronic musculoskeletal pain has been described frequently over the past centuries. All kinds of abnormalities in muscle tissue were thought to be the cause of pain. However, currently the hypothesis that muscle abnormalities play a primary or key role in the pathophysiology of fibromyalgia has been rejected (Simms 1998). Another hypothesis for the cause of chronic musculoskeletal pain was expressed by the label 'psychogenic rheumatism', as it was thought to be the musculoskeletal expression of psychoneurosis. From the 1970s onward, the multidimensional concept of the chronic generalized musculoskeletal pain state now termed 'fibromyalgia' really developed. Milestones were investigations into sleep disturbances (Moldofsky et al. 1975), extensive description of the clinical picture and development of diagnostic features (Yunus et al. 1981), development of classification criteria (Wolfe et al. 1990), and research into neurohormonal dysregulation (Griep et al. 1993) and aberrant central pain processing.

In this chapter, the focus will be on fibromyalgia. Other diffuse pain syndromes will be discussed in the context of fibromyalgia. Many of the mechanisms described in fibromyalgia also apply to other chronic pain disorders.

Epidemiology

Estimations of prevalence of fibromyalgia differ, because prevalence depends on the population that is investigated and the methods of case-finding. In the general population, prevalence was 2 per cent, 3.4 per cent for women, and 0.5 per cent for men (Wolfe et al. 1995), but lower prevalences of 0.7–1.3 per cent have also been reported. Fibromyalgia occurs in children and adolescents, but the prevalence increases with age, with highest values between 55 and 65 years (Wolfe et al. 1995). For chronic widespread pain in the general adult population, a prevalence as high as 11 per cent was found (Bergman et al. 2001).

Of consecutive new referrals to a general rheumatology clinic, 10 per cent had fibromyalgia in one (Reilly and Littlejohn 1992), and 4 per cent in another study (Wolfe and Cathey 1983).

Female sex, middle age, lower household income, being disabled, divorced or separated, and lower educational status are factors associated with fibromyalgia and chronic generalized pain in general (Wolfe et al. 1995).

No clear genetic predisposition exists, but in families with many fibromyalgia cases, a weak genetic predisposition might play a role (Yunus et al. 1999).

Clinical picture

Symptoms, pain-modulating factors

In addition to generalized pain, patients with fibromyalgia report manifold non-specific symptoms (see Table 1) (Yunus et al. 1981; Campbell et al. 1983; Quimby et al. 1988; Straus 1988; Wolfe et al. 1990; Jacobs et al. 1996). These, together with chronic generalized pain characterize fibromyalgia. Patients with fibromyalgia use more adjectives to describe their pain than patients with rheumatoid arthritis or osteoarthritis. Another characteristic of fibromyalgia is that pain, in contrast to articular rheumatic conditions, does not respond well to pain medication. Commonly, symptoms are reported to be increased by exposure to noise and light or stress, posture, pregnancy (especially the last trimester); the pre-menstrual period and weather may also exacerbate symptoms. However, in quantitative research no relation between the severity of complaints and meteorological factors was found (de Blecourt et al. 1993), nor did hormonal changes connected with abortion, breast feeding or the use of hormonal contraceptives modulate symptom severity (Ostensen et al. 1997).

Signs, tender points

On physical examination, multiple painful spots on pressure are evident, especially over bony prominences, localized in muscle, ligaments, bursae, fat pads, muscle–tendon junctions, and tendon–insertions: *tender points*. Test–retest stability and interobserver agreement of tender point scores at manual palpation or using a pressure algometer is moderate to high (Cott et al. 1992; Jacobs et al. 1995; Tunks et al. 1995), but manual palpation and pressure algometer scores are not equivalent (Cott et al. 1992). Tender points are not specific of fibromyalgia. Healthy adults often have some tender points, but it is the number and severity that is characteristic of

Table 1 Prevalences of symptoms (%) among patients with fibromyalgia in secondary referral centres, in comparison with prevalence of symptoms among patients with chronic fatigue syndrome (in *italic*)

	Yunus et al. (1981)	Campbell et al. (1983)	Quimby et al. (1988)	Wolfe et al. (1990)	Jacobs et al. (1996)	Straus (1988)
Pain in muscles	100	100	100	100	100	<i>80</i>
Morning stiffness	72	91	86	76	85	
Fatigue	92	100	91	78	83	<i>100</i>
Sleep disturbance	56	68	79	76	71	<i>70</i>
Paraesthesia	58			67	60	
Headache	44	55	63	54	56	<i>90</i>
Psychiatric symptoms	70		56	45	47	<i>65</i>
Irritable bowel	34	50	37	36	29	<i>40</i>

fibromyalgia (Wolfe 1997). Among patients with fibromyalgia, tender point scores show a lack of correlation with most of the typical symptoms of fibromyalgia (Jacobs et al. 1996; Wolfe 1997).

Some locations have been defined as non-tender or control points, for example, the forehead, forearm (ulna mid-shaft), the thumb, hyopthenar, and shin (mid-tibia, anteromedial surface) (Campbell et al. 1983). The utility of control points is low; control points are less tender than tender points in fibromyalgia patients (Campbell et al. 1983; Smythe et al. 1992), and not (Campbell et al. 1983) or somewhat (Smythe et al. 1992) more tender than in control patients. Possibly, control points are a reflection of the pain threshold and tender points of distress, pain behaviour, and coping (Wolfe 1997). Less frequently, *trigger points* are encountered: painful, sometimes palpable taut bands of muscle fibres that trigger pain in a referred area on pressure, but trigger points are more characteristic of myofascial pain syndrome (regional pain syndromes). Swelling of joints often reported by patients cannot be objectified. In the older literature subcutaneous 'fibrositic nodules' are mentioned, but this is an occasional and non-specific finding.

Classification criteria

In 1990, classification criteria for fibromyalgia were published (Wolfe et al. 1990). To develop the criteria, patients in whom the participating treating rheumatologist had made the clinical diagnosis fibromyalgia and control patients were studied. Widespread pain (axial plus upper and lower segment plus left- and right-sided pain) was found in 98 per cent of all patients with fibromyalgia and in 69 per cent of all control patients. The combination of widespread pain and pain at 11 or more of 18 specific tender point sites yielded a sensitivity of 88 per cent and a specificity of 81 per cent for fibromyalgia. On the basis of these results, criteria for the classification of fibromyalgia are (i) widespread pain (Table 2) in combination with (ii) pain at 11 or more of the 18 specific tender point sites (Fig. 1). As the criteria performed equally well in primary (no underlying disease, as is most frequently the case) and secondary or concomitant fibromyalgia (associated with a disease), no exclusions are made for the presence of concomitant radiographic or laboratory abnormalities or for underlying conditions (Wolfe et al. 1990). In the absence of a gold standard, the diagnosis fibromyalgia in the classification study was made on clinical grounds, including generalized pain and tender points. It is thus not surprising that generalized pain and tender points are included as classification criteria (Quinter and Cohen 1999). Fibromyalgia is clearly a descriptive diagnosis: fibromyalgia does not cause pain, it is pain.

Classification criteria are used for discrimination of groups of patients, for example, to include or exclude patients for studies. At the individual patient level, classification criteria for fibromyalgia are not intended for use as diagnostic criteria. Sometimes, the diagnosis is made in a patient who does not meet the classification criteria.

A source of confusion is that in the ACR-criteria 'tender points' that are only tender, do not fulfil the definition of tender point: tender points have

Table 2 The American College of Rheumatology 1990 criteria for classification of fibromyalgia^a

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|--|
| A. History of widespread pain for at least three months. Pain is considered widespread when it is present at all of the following sites: ^b
The left side of the body
The right side of the body
Above the waist
Below the waist
In the axial skeletal (cervical spine or anterior chest or thoracic spine or low back) |
| B. Pain on digital palpation in at least 11 of the following 18 tender point sites; all sites bilateral (see Fig. 2): ^c
Occiput: at the suboccipital muscle insertion
Low cervical: at the anterior aspect of the intertransverse spaces at C5–7
Trapezius: at the midpoint of the upper border
Supraspinatus: at the origin, above the scapular spine near the medial border
Second rib: at the second costochondral junction, just lateral to the junction on the upper surface
Lateral epicondyle: 2 cm distal to the epicondyle
Gluteal: in the upper outer quadrant of the buttock in the anterior fold of muscle
Greater trochanter: posterior to the trochanteric prominence
Knee: at the medial fat pad proximal to the joint line |

^a For purposes of classification, patients will be said to have fibromyalgia if both criteria A and B are satisfied. The presence of a second clinical disorder does not exclude the classification of fibromyalgia (Wolfe et al. 1990).

^b Pain in a patient in for instance the left shoulder, right buttock, and cervical spine is generalized, according to these criteria.

^c Digital palpation should be performed with an approximate force of 4 kg. For a tender point to be considered positive, the palpation has to be painful. 'Tender points' that are only tender are not tender points.

to be painful. In this sense, pain points would have been a more appropriate term. Patients with fibromyalgia can have many more than 18 tender points; the ones selected in the ACR criteria performed best.

Why classification as soft-tissue rheumatism?

Being a non-articular, non-inflammatory condition, fibromyalgia is a somewhat atypical entity in the field of rheumatology, a medical specialty dealing typically with articular, inflammatory diseases. Muscle abnormalities do not play a key role in the pathophysiology; at the level of joint pathology and impairment there are no serious problems, in contrast to the degree of problems on the level of handicap. In this respect, fibromyalgia differs from an inflammatory joint disease such as rheumatoid arthritis (see Table 3). So why do we still classify fibromyalgia as soft-tissue rheumatism or as a rheumatic condition? Our answer is that rheumatologists are the



Fig. 1 Localization of tender points (a) 2, 3, 5, 6, 8, and 9; (b) 1, 3, 4, 7, and 8; (c) 2, 3, and 5; (d) 1, 3, and 4; (e) 6; (f) 7–9; and (g) 9 (see Table 2).

specialists best able to discriminate this condition from other causes of pain in and around joints and spine, and to look for an underlying condition.

Diagnosis and differential diagnosis

Diagnosis is based on pattern recognition of the above mentioned, characteristic set of symptoms and presence of tender points. Fibromyalgia does not seem to be a distinct disease entity in the sense that only patients have the symptoms and tender points and controls do not (Croft et al. 1994; Wolfe et al. 1995). For pain and tender points, fibromyalgia appears to be

the extreme of the normal population distribution. In that respect, it resembles conditions like osteoarthritis and osteoporosis.

Sometimes, a patient reports such a wide range of somatic symptoms that the diagnosis is not easy to make. Fibromyalgia is a descriptive diagnosis; the physician should always look for an underlying condition. However, when the diagnosis of primary fibromyalgia can be made, only rarely an underlying somatic disease is present (Ledingham et al. 1993). In general, a patient with long-standing (years) symptoms suggestive of fibromyalgia has much less risk of an underlying disorder if it is clinically not evident than a similar patient with complaints for only some months. In all patients,

Table 3 Differences between the biomedical disease rheumatoid arthritis and the dysfunctional syndrome fibromyalgia

Level	Signs, symptoms	Rheumatoid arthritis	Fibromyalgia
Synovial pathology	Effusion, warmth	+++	–
Impairment	Stiff, painful knee, with limited flexion	+++	+
Disability	Cannot walk	+++	++
Handicap	Cannot do shopping	+++	+++
Additional symptoms	Fatigue, headache, sleep disturbance	+++	++++

a full physical examination should be done. In patients with recent or atypical features for fibromyalgia, a careful diagnostic process particularly is warranted. 'Red flags' are a history of unexplained weight loss and fever. Signs, such as muscle atrophy, arthritis, or myxoedema must be looked for.

Laboratory and other tests should be guided by the clinical picture of each individual patient. Overinvestigation must be avoided because it can cause or consolidate illness behaviour. Routine testing with tests like rheumatoid and antinuclear factor and serology for viruses and Lyme disease is not adequate, because these tests lack specificity.

In Table 4, differential diagnoses for fibromyalgia and investigations, to discriminate each condition from fibromyalgia are listed. Often myofascial pain syndrome is mentioned in the list of differential diagnoses of fibromyalgia, but the former is a regional and the latter a generalized pain syndrome.

Some physicians worry about the diagnostic label 'fibromyalgia', and argue against using it. However, in case of long-standing severe unexplained symptoms, the diagnosis fibromyalgia can be a relief for the patient. A long hunt for a diagnosis can be harmful to a patient's health, because the next step cannot be taken, which is acceptance and dealing as best as possible with the situation. One has to avoid that a diagnostic label causes a patient to remain sick, though. The diagnosis should be presented with adequate patient information and education.

Secondary fibromyalgia; is it clinically relevant?

In the publication of the American College of Rheumatology 1990 classification criteria for fibromyalgia, it is stated that *on the diagnostic or classification level*, the distinction between primary and secondary fibromyalgia is abandoned (Wolfe et al. 1990). This does not mean that the clinical entity secondary fibromyalgia has been abandoned. Among new patients seen in an outpatient rheumatology clinic, secondary or concomitant fibromyalgia was diagnosed in 12 per cent of patients with rheumatoid arthritis and 7 per cent of patients with osteoarthritis (Wolfe and Cathey 1983). In a study of 100 patients with subclinical or biochemical primary hypothyroidism, in 5 per cent the diagnosis of fibromyalgia was made (Carette and Lefrancois 1988). Other underlying or concomitant conditions are for instance ankylosing spondylitis, and Sjögren's syndrome. Secondary fibromyalgia could respond beneficially to treatment of the underlying condition (Carette and Lefrancois 1988).

Overlapping dysfunctional syndromes

Fibromyalgia shares symptoms and neuroendocrine dysfunction with other common disorders without obvious organ pathology, called by many different names: functional, psychosomatic, somatization, stress-related, affective spectrum, central sensitivity, and dysfunctional syndromes or disorders. Symptoms of patients with fibromyalgia and those of patients with chronic fatigue syndrome show clear overlap (Table 1) (Yunus et al. 1981; Campbell et al. 1983; Quimby et al. 1988; Straus 1988; Wolfe et al. 1990; Jacobs et al. 1996). Dysfunctional syndromes, which have key overlapping symptoms with fibromyalgia, are shown in Table 5. Overlap can exist for symptoms only or for whole syndromes. The classification criteria for the chronic

Table 4 Differential diagnosis of fibromyalgia^a

Disease	Key investigation ^b
<i>Inflammatory rheumatic diseases</i>	
Sjögren's syndrome	Ophthalmologic, ESR, ENA
Polymyalgia rheumatica	ESR
Myopathy, myositis	Serum creatine kinase
Early rheumatoid arthritis	(ESR, rheumatoid factor)
Systemic lupus erythematosus	(ESR, full blood count, antinuclear factor)
Systemic vasculitis	ESR
<i>Non-inflammatory rheumatic diseases</i>	
Generalized osteoarthritis	(Joint X-rays)
Hypermobility	Beighton's clinical score
<i>Endocrine disorders</i>	
Hypothyroidism	Thyroid function
Hyperparathyroidism	Serum calcium and alkaline phosphatase
Hypovitaminosis D, osteomalacia	Serum 25-hydroxy-vitamin D
<i>Chronic Infections</i>	
Hepatitis C virus infection	Serology, liver enzyme tests
<i>Malignancy</i>	
Disseminated malignancy	Bone scintigraphy
Myeloma	Plasma and urine paraproteins
<i>Adverse-effect of medication</i>	
Glucocorticoid withdrawal	Medical history
Post-chemotherapy arthralgia	Medical history
Eosinophilia-myalgia syndrome	Check of medication (L-tryptophan?)
HMG-CoA reductases (statins)	Check of medication

^a If a patient with one of these conditions also fulfils the fibromyalgia classification criteria, secondary or concomitant fibromyalgia is diagnosed.

^b Key investigation: additional to full physical investigation. ESR, erythrocyte sedimentation rate; ENA, extractable nuclear antigens. Between brackets are investigations with low diagnostic value for the given situation, e.g. in case of early rheumatoid arthritis, the ESR is often normal and rheumatoid factor not present; for systemic lupus erythematosus, antinuclear factor is a sensitive, but not a specific test.

fatigue syndrome (Table 6) resemble those of fibromyalgia (Fukuda et al. 1994). In a study, among females, 58 per cent of fibromyalgia cases met the full criteria for chronic fatigue syndrome, compared to 26 and 13 per cent of controls with widespread and localized pain, respectively. Male percentages were 80, 22, and 0 per cent, respectively (White et al. 2000). Because of the overlap, one could hypothesize that fibromyalgia and related syndromes are not separate diagnostic entities, but overlapping manifestations of one single dysfunctional syndrome. The existence of separate diagnoses could be an artifact, because medical specialties focus on symptoms pertinent to their specialty. However, the reported overlap of fibromyalgia and related syndromes in research at secondary or tertiary care settings is probably an overestimate. In a community-based sample, patients showed less overlap (Jason et al. 2000). Moreover, there are differences in pathophysiological mechanisms and findings between fibromyalgia and related syndromes.

Table 5 Dysfunctional syndromes that overlap with fibromyalgia^a

Syndrome	Key overlapping symptoms
Chronic fatigue syndrome	Fatigue, generalized pain
Myalgic encephalomyelitis	Fatigue, cognitive dysfunction
Post-traumatic stress syndrome, Persian Gulf syndrome	Fatigue, depression, pain
Temporomandibular dysfunction	Facial pain
Irritable bowel syndrome	Abdominal cramps and pain
Tension headache	Headache, psychological stress
Restless legs syndrome	Muscle cramps, paraesthesia
Depression and anxiety disorders	Depression, anxiety, psychological stress
Primary dysmenorrhoea	Abdominal cramps and pain
Multiple chemical sensitivity	Autonomic dysfunction

^a This is not a complete list. Overlap can exist for symptoms only or for whole syndromes: e.g. if a patient meets both the classification criteria for fibromyalgia and chronic fatigue syndrome, both syndromes are supposed to be present.

Table 6 Revised Centers for Disease Control criteria for chronic fatigue syndrome^a

A case of chronic fatigue syndrome is defined by the presence of:

1. Clinically evaluated, **unexplained, persistent, or relapsing fatigue** that is of new or definite onset; is not the result of ongoing exertion; is not alleviated by rest; and results in substantial reduction of previous levels of occupational, educational, social, or personal activities; and
2. Four or more of the following symptoms that persist or recur during six or more consecutive months of illness and that do not predate the fatigue:

Muscle pain

Multijoint pain without redness or swelling

Unrefreshing sleep

Headaches of a new pattern or severity

Self-reported impairment in short-term memory or concentration

Sore throat

Tender cervical or axillary nodes

Post-exertional malaise lasting at least 24 h

^a Bold and italic symptoms overlap with those of fibromyalgia.

Patients with fibromyalgia are already a heterogeneous group with respect to psychosocial and behavioural characteristics as well as response to pharmacological treatment.

Discrimination of dysfunctional syndromes enables the specialist (e.g. the rheumatologist in case of pain in muscles and joints) to distinguish the alleged dysfunctional syndrome from other, somatic disorders, to find specific therapeutic modalities and to give adequate advice. These aims are not served by grouping all dysfunctional syndromes together.

Psychiatric disorders in fibromyalgia

Psychiatric disorders that have been most frequently reported in association with fibromyalgia are depression and anxiety or panic disorders. These problems clearly occur more often in fibromyalgia than in the general population (Epstein et al. 1999), although it can be argued that the psychological and psychiatric studies of patients with fibromyalgia have utilized instruments that do not control for pain and therefore may be falsely interpreted (Goldenberg 1989). Difficult questions are whether psychiatric disorders or symptoms occur more frequently in fibromyalgia than in

rheumatic diseases, for example, rheumatoid arthritis [no (Clark et al. 1985; Goldenberg 1989), yes (Walker et al. 1997a)], and whether psychiatric disorders are the cause of fibromyalgia, or vice versa. The finding of an increased rate of somatoform disorders in patients with fibromyalgia with psychological questionnaires is virtually identical to the clinical finding of manifold somatic symptom reporting in fibromyalgia and does not answer the question of cause or consequence. Other hypotheses are that there is a coexistence of fibromyalgia and psychiatric symptoms or disorders because of common pathophysiological mechanisms and that the finding of concomitant psychiatric disorders is related to health care-seeking behaviour associated with these disorders. In pain patients, concurrent psychological factors are predictive of persistence of the symptoms (McBeth et al. 2001). Similarly, in pain patients, concurrent manifold symptoms, including psychiatric problems, were associated with subsequent development of fibromyalgia in a longitudinal population study (Forseth et al. 1999). However, this temporal relationship between manifold symptoms and development of chronic pain may not be a causal one.

Pathophysiological mechanisms

Theories about the pathogenesis of fibromyalgia have shifted over time from peripheral pathology (muscles) to central pathology (pain processing) and from uncausal to multicausal hypotheses. Some hypotheses have been abandoned, for example, that the primary cause is localized in muscles. Associations of development of fibromyalgia with infections in the past seem coincidental, not causal. However, there may be a relationship between hepatitis C virus infection and fibromyalgia symptoms (Rivera et al. 1997). Other hypotheses, for instance about psychogenic factors and sleep disturbances still play a role, but only as one of many aspects of fibromyalgia. We will first discuss separate mechanisms in fibromyalgia and thereafter integrate these mechanisms in a model.

Chronic psychosocial stress

A current hypothesis is that fibromyalgia is a stress related, neuroendocrine disorder. In acute stress, pain is inhibited via central pain modulation called stress-induced analgesia, but chronic stress could have the opposite effect. Humans today have the same neuroendocrine and pain regulatory systems as our caveman forebears. The environment of humans however has changed: acute physical stress encountering predators has changed into chronic daily psychological stress of the modern society. Instead of running or fighting we try to cope with situations, which are for a major part beyond our direct control. This chronic stress could via its influence on central mechanisms lead to symptoms, like pain. Patients with fibromyalgia report more stressful life events in the past as well as more daily stressful 'hassles' than patients with rheumatoid arthritis or pain-free healthy controls. A higher frequency of sexual abuse in childhood has also been reported (Boisset-Pioro et al. 1995; Walker et al. 1997). It should be born in mind however that persons who currently experience psychological stress are likely to report more adverse events in the past (McBeth and Silman 2001). Probably also recall bias can play a role in the reporting of virus infections and traumata preceding fibromyalgia. Work related psychological factors, such as work demands, job control, and social support and psychological distress are associated with reporting of musculoskeletal pain, especially when pain is reported at multiple sites (Bergman et al. 2001).

Sleep disturbance

Studies on sleep in patients with fibromyalgia reported alpha–delta sleep anomaly in the electroencephalogram during non-rapid eye movement (non-REM) sleep, reflecting light, unrefreshing sleep. The hypothesis of sleep disturbance as the cause of fibromyalgia was attractive, because it would explain many of the problems of patients with fibromyalgia, such as unrefreshed awakening with pain and stiffness, fatigue, headache, and in addition to these somatic features of malaise also psychic malaise. However,

sleep disturbance proved to be not specific for fibromyalgia: it was also found in patients with rheumatoid arthritis, osteoarthritis, Sjögren's syndrome, chronic fatigue syndrome and in normal controls when deep pain was induced during sleep. Moreover, different sleep anomalies have been described in different studies and only some fibromyalgia patients have sleep disturbances. Thus, sleep disturbances are neither uniform nor specific for fibromyalgia. Sleep anomalies could cause disturbance in nocturnal metabolic and endocrine functions, such as growth hormone secretion in non-REM sleep (Spiegel et al. 1999). For the development and persistence of fibromyalgia, sleep disturbance seems to be a non-specific risk factor.

Neuroendocrine dysregulation

Neuroendocrine dysfunction found in fibromyalgia can be divided into alterations of the two major stress systems, the hypothalamic–pituitary–adrenal (HPA) axis and the autonomous nervous system.

HPA-related functioning

In fibromyalgia, almost all hormonal feedback mechanisms controlled by the hypothalamus are dysfunctional. After stimulation of the HPA axis with exogenous corticotropin-releasing hormone (CRH) or by insulin induced hypoglycaemia, exaggerated pituitary adrenocorticotropin hormone (ACTH) release has been observed, with (given this ACTH hyper-responsiveness) adrenal hypo-responsiveness (Griep et al. 1993; Crofford et al. 1994) (see Fig. 2). Moreover, indications for sub-normal basal levels of serum growth hormone have been found consistently (Dinser et al. 2000). Serum thyroid hormone levels are normal, but after intravenous injection of 400 µg thyrotropin-releasing hormone, patients with primary fibromyalgia responded with a significantly lower secretion of thyrotropin and thyroid hormones within a 2 h observation period (Neeck and Riedel 1992). How should these data be interpreted? HPA axis studies could be seen as being indicative of HPA hypofunction, but also

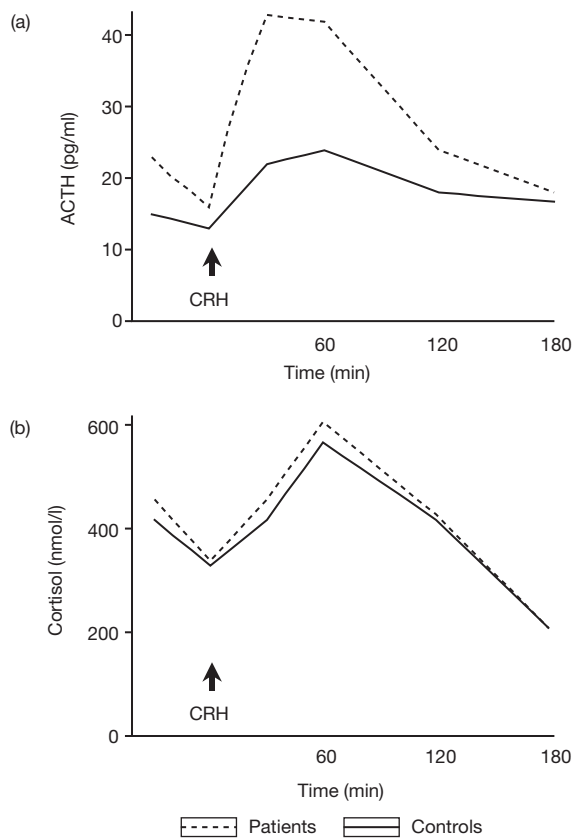


Fig. 2 Responses of (a) ACTH and (b) cortisol to injection with CRH in patients with fibromyalgia and controls (Griep et al. 1993).

has been attributed to hyperactivity of CRH neurons. The latter hypothesis seems compatible with the hypothesis that fibromyalgia is a stress-related, neuroendocrine disorder, but not with some hypotheses on serotonin metabolism in fibromyalgia.

Autonomic nervous system

In several studies, altered autonomic nervous system activity has been observed in fibromyalgia, but the results are difficult to interpret. Most studies did not control for physical activity levels of participants (Petzke and Clauw 2000), but if effects of physical activity are taken into account, results might be interpreted as being indicative of tonic sympathetic hyperactivity in a subset of patients. This observation is consistent with the hypothesis of hyperactivity of CRH neurons. With respect to autonomic nervous system reactivity, aggregate data suggest a somewhat blunted stress response (Petzke and Clauw 2000).

The finding of neuroendocrine dysregulations does not mean that they have a causal relation to the development and persistence of fibromyalgia. They could be secondary to pain mechanisms or merely be epiphenomena. Furthermore, at the group level, neuroendocrine functioning of fibromyalgia patients tends to deviate from norm reference groups, but apparently only sub-groups of patients suffer from clinically significant altered autonomic nervous system activity, HPA axis perturbations, or subnormal growth hormone secretion. It could well be that individual patients differ in the spectrum of dysregulations.

In other dysfunctional syndromes, dysregulation of the HPA axis and of the autonomous nervous system have also been described. However, there are differences, for instance between fibromyalgia and chronic fatigue syndrome, with respect to HPA axis dysregulation (Crofford and Demitrack 1996), autonomic nervous system dysfunctioning (Naschitz et al. 2001), and growth hormone metabolism (Buchwald et al. 1996).

Disturbed pain modulation

Pain has biophysiological and psychological aspects. Initially, the hypothesis was that psychological aspects dominated the pain in fibromyalgia, hence the label 'psychogenic rheumatism'. In recent years, the role of abnormal sensory processing in fibromyalgia has become clear. Patients with fibromyalgia often have *allodynia*, the perception of pain in response to stimuli that are normally not painful, such as touch, moderate heat or cold, electrical stimulation, and proprioceptive input. In addition, pain has exaggerated intensity and duration: *hyperalgesia*. Mechanisms of abnormal sensory processing in fibromyalgia can be divided into increased activity in pain-facilitating (pronociceptive) mechanisms and reduced pain-inhibiting (antinociceptive) mechanisms on the spinal and cerebral level.

Enhanced pain-facilitating mechanisms

Sensitization of nociceptive neurons in the spinal dorsal horn by hyperexcitable receptors, such as the glutamate receptor *N*-methyl-D-aspartate (NMDA), could be one of the mechanisms responsible for pain in fibromyalgia. In animal and human studies, NMDA antagonists like ketamine seem to inhibit pain-facilitating mechanisms, but whether this is specific for patients with fibromyalgia or a general phenomena in painful musculoskeletal disorders is not known. The NMDA hypothesis is compatible with correlation of intensity of pain in fibromyalgia and levels in the cerebrospinal fluid of amino acids, which appear to modulate NMDA receptors (Larson et al. 2000).

Pain regulation by supraspinal centres is poorly understood. Fibromyalgia shares increased reactivity to various stimuli (sensitization) with several other syndromes such as multiple chemical sensitivity and irritable bowel syndrome. This suggests that shared stimulus-facilitating pathways are involved in these syndromes. The limbic system has been hypothesised to play a role in sensory gating, and may contribute to the increased 'weight' that is given to various sensations. An abnormality that is consistent with the conception of fibromyalgia as a central pain amplification syndrome, is the repeated observation of elevated cerebrospinal fluid

concentrations of several chemical pain mediators including substance P (Russell 1998). Levels of substance P in cerebrospinal fluid in patients with chronic fatigue syndrome are normal (Evengard et al. 1998).

Decreased pain-inhibiting mechanisms

From the brain stem as well as from the thalamus, hypothalamus, limbic system, and cortex originate multiple descending, pain-inhibitory pathways, modulating the activity of spinal nociceptive neurons. Patients with fibromyalgia as well as other chronic pain patients have low levels of regional cerebral blood flow in the caudate nucleus and thalamus, possibly indicating decreased descending, pain-inhibitory activity. Serotonin is one of the neurochemical modulators of the descending inhibitory pathways; the finding of low concentrations of serotonin in serum and cerebrospinal fluid of patients with fibromyalgia in several studies might indicate decreased pain-inhibiting mechanisms. However, the role of serotonin in the pathophysiology of fibromyalgia is not clear.

Physical deconditioning

Neuroendocrine dysfunction, for example, via altered growth hormone metabolism, sleep disturbances, and avoidance of physical activities because of pain may all cause physical deconditioning in patients with fibromyalgia. Abnormalities found in muscle biopsies are a non-specific result of this deconditioning. Physical deconditioning will lead to more stiffness, fatigue, and pain at physical activities, causing a vicious circle or downward spiral.

Biopsychosocial model

Based on the increasing knowledge about pathophysiological mechanisms in fibromyalgia, a biopsychosocial model can be developed as a functional framework, integrating mechanisms of persistence of symptoms (Fig. 3). The model is functional, not anatomical. Some relations described in the model are more hypothetical than others; not all vicious circles described are equivalent in their (supposed) effect.

Recurrent psychological stress is associated with chronic sleep disturbance, which directly results in decreased physical fitness. The poorly rested muscles 'protest' by causing symptoms of pain, stiffness, and fatigue. Sleep anomalies also contribute to neuroendocrine dysregulation. An example is growth hormone, as about 80 per cent of this hormone is secreted (in pulses) during this phase of sleep. Susceptibility to muscle deconditioning could be increased as a result of dysregulation of growth hormone as it has an anabolic function. Compatible with this hypothesis is the finding that levels of the collagen precursor serum procollagen III—that is, growth hormone dependent—were related to the amount of symptoms and tender points in fibromyalgia patients (Jacobsen et al. 1990). Apart from these mechanisms via sleep disturbances, stress in general can lead to altered pituitary–adrenal and autonomic responses (Heim et al. 2000). So also indirectly, via neuroendocrine disturbances physical fitness may be lowered by chronic sleep disturbances and psychological stress. Chronic neuroendocrine disturbances could be sensitizing the central nervous system by neuropeptides and other regulatory mechanisms change the processing of sensory input and ultimately lead to pain. The model also shows the detrimental role of decreased physical activity and deconditioning. Physical inactivity might also facilitate pain perception by incomplete extinguishing of a neurophysiological 'pain memory' (Harvey 1990).

Using Fig. 3 as a hypothetical model, the clinical relevance of pathophysiological mechanisms, their interplay with symptoms and the mode of action of therapeutic interventions can be better placed into perspective.

Management

Patient information

The first step in management of diseases, illnesses, ailments, and afflictions is patient information and education. Patients should be informed that the

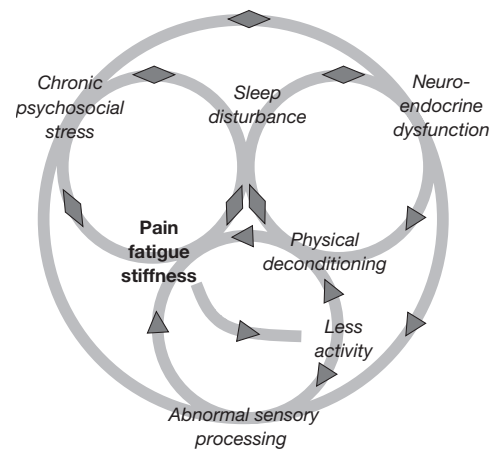


Fig. 3 Vicious circles with pathophysiological mechanisms (in italic) and ensuing symptoms (in bold), with uni- and bi-directional influences: shaded triangles and diamonds, respectively. Neuroendocrine dysfunction, due to psychosocial stress and sleep disturbances causes physical deconditioning and disturbed pain modulation. Disturbed pain modulation, together with physical deconditioning, psychosocial stress, and sleep disturbances causes the symptoms pain, fatigue, and stiffness.

symptoms they experience are real and severe and that the physician takes the patient seriously, but that fibromyalgia can be better described as an ailment or condition than as a disease. To convey this message properly, the physician should realize that the contradiction between the patients' perception of disease and the lack of objective findings is stressful: patients may feel rejected, misunderstood, and disbelieved, which prevents them from dealing with their situation constructively. The patient should be informed that the condition is neither crippling nor deforming, and does not have to be treated aggressively with drugs. This is the positive side of the coin. The other, negative side is that symptoms may wax and wane, but that they do not disappear for the majority of patients with long-standing fibromyalgia. It can be explained that it is not exactly known how fibromyalgia develops, but that some mechanisms of how symptoms persist, are known.

Patient education and principles of management

The message that fibromyalgia cannot be cured is an important aspect of patient education. It must be made clear that the primary aim in the management of fibromyalgia is enhancement of functional capacity and quality of life and that an active role of the patient is essential. The role of the physician is more supportive than therapeutic in character. From a clinical and behavioural point of view, it must be avoided that pain gets a central place in management. Pain is very hard to treat in fibromyalgia. A poor or at best a moderate response to analgesics and non-steroidal anti-inflammatory drugs is a characteristic of fibromyalgia, it is almost a diagnostic feature. The same holds true for other pain treating modalities. To enhance patient's self-management and to induce adherence to physical exercise, it is necessary to tackle possible wrong attributions the patient has about the origin of the complaints. A simple question that the physician could ask is: 'what do you think is the cause of the symptoms?' Often, patients think physical activities and exercise should be avoided to prevent damage to joints. A key principle of management is to tailor the therapy to the needs of the individual patient. Problems due to fibromyalgia and causes of stress should be identified and discussed with each patient, and help should be provided on how to cope with these problems. The intention should be to omit long-lasting drug-therapy; for instance sleep disturbances could be tackled with sleep 'hygiene' principles.

Physical exercises

Graded daily physical exercise seems to be the key therapy for patients with fibromyalgia to prevent progression of physical deconditioning and to enhance functional capacities; it may also improve fibromyalgia symptoms. Physical fitness training seems feasible and beneficial (Martin et al. 1996; Gowans et al. 1999), but long-term effects of exercise require further evaluation. Not all studies on physical fitness training report positive results. Exercise should initially be of a low-impact type and gradually intensified. Some patients benefit from additional regular stretching and relaxation exercises. Exercises in warm water and balneotherapy may give additional symptomatic relief. Patients often argue that they are busy the whole day and that exercises are not necessary. It should be explained that activities in daily life are essentially different from whole body exercises. Adherence to physical exercise will be improved if this treatment is embedded in an educational package aimed at tackling incorrect notions (e.g. that exercise will worsen the condition), at enhancing coping skills and increasing motivation.

To explain the negative downward spiral or vicious circle of pain at physical activity → avoidance of physical activities → deconditioning → more pain at physical activities, Fig. 4 can be used.

Another often-heard objection against physical exercise is that it is not possible to perform them because they will increase pain. It should be made clear that exercises start off at a very low-level, and that in general there is and should be no increase in pain following an adequate scheme. Overdoing exercise should be avoided, because as a consequence of increased pain, motivation could be lost. In clinical practice, it is helpful to ask a physiotherapist to plan and demonstrate slowly intensifying exercise to the patient, to encourage adherence to the programme and, if necessary, to adapt the exercise-programme in follow-up contacts. Though there is no evidence-based, long-term programme for physical exercises for patients with fibromyalgia, patients who perform physical exercise of the whole body, for example, during 20 min a day, are likely to benefit. A slowly progressive scheme should be tailored to the needs and possibilities of the individual patient.

Other non-pharmacological therapies, psychobehavioural management

The effect of biofeedback, hypnotherapy, relaxation response training, and many other complementary and non-pharmacological therapies has not

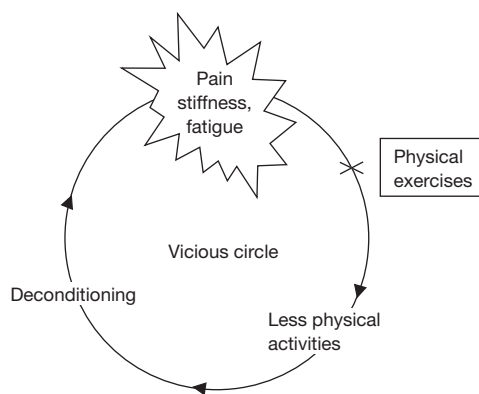


Fig. 4 Simple model to educate patients and motivate them for daily physical exercises. The physician can draw this model in front of the patient on a piece of paper and illustrate it with a little story about the different chances a triathlon athlete and a lazy princess have of pain in muscles after the same physical activity, solely based on the different levels of conditioning, fitness of muscles. The negative vicious circle of pain at physical activities, therefore less activities followed by deconditioning and thus more pain at physical activities can be broken by daily physical exercises.

been properly investigated (Simms 1994). The multifaceted nature of problems in fibromyalgia with its profound influence on physical, psychological, and social aspects of quality of life, warrant a multidisciplinary team approach, including cognitive-behavioural intervention. The aim is to help patients manage symptoms and consequences of fibromyalgia and assist them in realizing individualized realistic goals in life and in defining the steps that have to be taken to achieve these goals. If treatment is tailored to individual patients' psychosocial needs, patients are likely to benefit in the short run (Turk et al. 1998), but long-term benefits of cognitive-behavioural interventions are not proven (Rossy et al. 1999). Patients with concomitant psychiatric illness or severe psychological disorders need to be treated by a psychiatrist or clinical psychologist.

Pharmacological treatment

Drug treatment should be part of a therapeutic strategy encompassing education and physical exercises. In a meta-analysis the latter treatment appeared to be at least as efficacious as pharmacological treatment alone in improving fibromyalgia symptoms (Rossy et al. 1999).

Analgesics like tramadol and non-steroidal anti-inflammatory drugs only partially improve symptoms. Two weeks after local injection therapy with 0.5 per cent xylocaine of trigger points in the upper trapezius muscle in patients with fibromyalgia, there was improvement in pain and range of motion, but at the expense of significant post-injection soreness (Hong and Hsueh 1996). Glucocorticoids should not be used in patients with fibromyalgia.

The effect of antidepressants, particularly tricyclics such as amitriptyline, has been studied frequently in patients with fibromyalgia. Most tricyclics have a mean moderately beneficial effect (Arnold et al. 2000), but many patients do not respond: the percentage of responders ranges from 25 to 37 (Arnold et al. 2000). It is not possible to predict the response to antidepressants in individual patients. Long-term effectiveness has not been proven: in the only study with a follow-up longer than 3 months, the percentage of patients clinically responding at 6 months in the amitriptyline group did not differ significantly from the percentage in the placebo group (Carette et al. 1994). Whether the beneficial effect is independent of depression needs further study, but response to some antidepressants in patients with fibromyalgia, for instance amitriptyline, occurs at doses lower than those used in major depression, suggesting an independent mode of action. Another argument for this hypothesis is that not all antidepressants are equally helpful in patients with fibromyalgia, for instance moclobemide lacks the beneficial effect of amitriptyline (Hannonen et al. 1998). A third argument is the finding that fluoxetine decreased depression scores, but not fibromyalgia symptoms (Wolfe et al. 1994).

Based on the hypotheses of pathophysiological mechanisms discussed above, antidepressants and other drugs with specific and theoretically appropriate modes of action have been tested in fibromyalgia, showing for most drugs disappointing results. The conclusion is that as adjunct to education and physical exercise, drug treatment may have a place in the management of fibromyalgia, but that it is only a modest place. Analgesics and non-steroidal anti-inflammatory drugs can be tried to diminish pain, if necessary with pain modulating drugs such as the tricyclic agents amitriptyline (start 25 mg at bedtime, if ineffective after 6 weeks 50 mg, maximally 75 mg) or cyclobenzaprine (10 mg at bedtime). Adverse effects of tricyclic agents are dry mouth and drowsiness. Not all patients respond; medication that is not effective should be stopped.

Directions for further clinical trials

Because of the multidimensional nature of fibromyalgia, is not to be expected that cure will be found in the near future. Pharmacological therapy should preferably be investigated for its additional effect to the basic, non-pharmacological therapy. To determine which (sub-groups of) patients benefit from adjunctive therapy and whether the effect can be predicted merits future investigation. The Fibromyalgia Impact Questionnaire is a responsive measure to assess perceived clinical improvement and its inclusion as a primary endpoint in clinical trials is recommended (Dunkl et al. 2000).

Prognosis, social consequences, cost

In the long-term, most patients have a poor prognosis regarding morbidity. After a mean follow-up of 4 years following diagnosis, 97 per cent of 72 patients still had symptoms typical of fibromyalgia (Ledingham et al. 1993). In another study, after 5 years, 50 per cent of 56 patients with fibromyalgia reported that pain, fatigue, and sleep problems had increased, less than 20 per cent reported improvement, and in more than 30 per cent there was no change (Henriksson 1994). Patients followed for as long as 7 years showed that their high scores for pain, functional disability, fatigue, sleep disturbance, and psychological status did not change substantially over time.

Fibromyalgia also has negative social–economic consequences. In a multicentre survey in 1988 in the United States, more than 16 per cent of patients with fibromyalgia reported receiving social security disability payments (highest centre rate 36 per cent; lowest 6 per cent) compared to 2.2 per cent of the US population and 29 per cent of patients with rheumatoid arthritis seen at one centre. Overall, 27 per cent reported receiving at least one form of disability payment (Wolfe et al. 1997a). In Brazil, there was a decrease in family income for 65 per cent of 44 female patients with fibromyalgia and for 75 per cent of 41 patients with rheumatoid arthritis. Fifty-five per cent of patients with fibromyalgia and 67 per cent of those with rheumatoid arthritis received social security aid (Martinez et al. 1995). Thus, work disability is a serious problem, but most patients with fibromyalgia can work, if adaptations are made.

In the United States, the hospitalization rate for patients with fibromyalgia was 1 every 3 years and almost half of admissions was related to fibromyalgia-associated symptoms. In addition, patients had more surgical interventions in their medical history compared with patients with other rheumatic disorders. The mean yearly per-patient cost of fibromyalgia in 1996 was US\$ 2274. Some patients with high costs skewed results; many patients used few services and had limited costs. Total costs and utilization were associated independently with the number of self-reported comorbid or associated conditions, functional disability, and global disease severity (Wolfe et al. 1997b). In Canada, direct health care cost associated with fibromyalgia within a representative community sample was estimated to be Canadian \$493 yearly per patient (White et al. 1999).

Litigation, medicolegal aspects

Because of its perceived subjective nature and the absence of well-defined criteria for diagnosis and severity of the condition, fibromyalgia creates problems in litigation, and the determination of rehabilitation costs and disability payments. For a rheumatic disease like rheumatoid arthritis, in most cases the diagnosis is indisputable; in case of litigation, the issue is disability. In fibromyalgia, key litigation issues are the diagnosis, is the claimant faking or exaggerating pain, and the grade of disability. Among subjects giving true responses or deliberately exaggerating pain at assessment of tender points (fakers), exaggeration was difficult to detect but accurate discrimination of fakers was possible. The detection of fakers was improved by also assessing pain behaviour (Smythe 1997). In a similar study, fakers could not be discriminated on the basis of tenderness at ‘control points’. Using the classification criteria for fibromyalgia and bedside observations, fakers were misidentified as fibromyalgia patients in 1/3 of judgements, and fibromyalgia patients as simulators in 1/5 of judgements (Khostanteen et al. 2000).

A diagnosis neither reflects the degree of disability nor the severity of the condition. Verifying the diagnosis would be less important, if disability could be objectively assessed. For fibromyalgia this would require detailed observation in the non-clinical setting, conversations with family and co-workers and psychological and comprehensive physical testing. In most cases, this is not feasible. Frank malingering is probably rare. Litigation can be a major source of stress in fibromyalgia and other pain patients, rarely aggravating symptoms, though.

Conclusions

Fibromyalgia is a common, chronic generalized musculoskeletal pain syndrome, characterized by multiple symptoms and tender points, that has a severe impact on the daily life of the patients. The origin of the syndrome probably is multidimensional. For groups of patients, several dysfunctional central neurohormonal and pain processing systems are found, but at an individual patient level, there is no diagnostic laboratory test. Research findings have broadened our insight into the mechanisms of fibromyalgia, but have not led to an effective therapy. Because of its multidimensional nature, effective pharmacological therapy is unlikely to be available in the near future. Management of the syndrome needs to be tailored to the individual patient’s symptoms and needs. Therapy, which always should include education and physical exercises, is only symptomatic.

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