

Skeletal Muscle Abnormalities in Patients With Fibromyalgia

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ABSTRACT:

Widespread muscle pain and tender points are the most common complaints of fibromyalgia patients, and the underlying mechanisms responsible for these symptoms have been studied intensively during the past decade. It has been suggested that fatigue and pain may lead to decreased levels of physical activity in many patients. The resulting deconditioned state may itself contribute to muscle abnormalities. Associated symptoms such as disturbed sleep, anxiety, depression, or irritable bowel also may have a negative impact on muscle function and level of daily activities. The important interactions between the central nervous and musculoskeletal systems may involve another element, the neuroendocrine stress-response system. This review will consider both the current state of knowledge and also future studies which might be designed to answer more effectively the outstanding questions regarding the underlying pathogenesis of fibromyalgia.

The most common complaints of fibromyalgia (FM) patients are widespread muscle pain and tender points. These symptoms, along with the fatigue, muscle weakness, and stiffness reported by many, are of great concern to the patients. The underlying mechanisms responsible for these symptoms have been studied intensively during the past decade. Considerable progress has been made in identifying morphologic and biochemical abnormalities in these painful, dysfunctional muscles. Most if not all of the observed anatomical and metabolic defects are consistent with symptoms of weakness, fatigue, and pain.

It has often been suggested that fatigue and pain may lead to decreased levels of physical activity in many patients, and the resulting deconditioned state may itself cause muscle abnormalities. However, deconditioning is not usually associated with generalized pain, indicating that a much more inclusive rationale is required to explain the problems of this multidimensional disease. Associated symptoms such as disturbed sleep, anxiety, depression, or irritable bowel syndrome also may have a negative impact on muscle function or level of daily activities. The important interactions between the central nervous system and the musculoskeletal system may involve yet a third player, the neuroendocrine stress-response system. As an example, growth hormone and somatomedin-C deficits in the sleep-deprived patient may prevent adequate repair of muscle tissue following exertion and exercise.¹

In this review, we will consider both the current state of knowledge and also future studies which might be designed to answer more effectively the outstanding questions regarding the underlying pathogenesis of FM. Improved approaches to treatment for these patients are ultimately dependent upon unraveling the complex pathophysiology of this disorder.

Evidence for Muscle Abnormalities in Fibromyalgia

Histologic Studies of Muscle Structure. Serum levels of muscle enzymes such as creatine kinase and aldolase are normal in most patients with FM, as are electromyography findings.^{2, 3} However, numerous biopsy studies have demonstrated histologic changes in skeletal muscle tissues (Table 1). These investigations merit detailed examination with particular attention to clinical characteristics of the study groups, the muscles selected for biopsy, and techniques applied to the examination of tissues. Histologic findings are important because the data often relate to metabolic abnormalities and clinical symptoms.

Table 1. Histologic Studies of Muscle Tissue in Patients With Fibromyalgia

Muscles Studied	Microscopic Findings	Author, year
Various, including trapezius	Moth-eaten fibers, ragged red fibers, abnormal mitochondria	Henriksson, 1982 ⁵
Trapezius	Mild changes; not different from controls	Yunus, 1989 ⁸
Quadricep muscles	Rubber band morphology	Bartels, 1986 ⁹
Quadricep muscles	Rubber band morphology	Jacobsen, 1991 ¹⁰
Quadricep muscles	Duplication of membranes, abnormal mitochondria, thickened capillary endothelium	Drewes, 1993 ¹¹
Quadricep muscles	Reduced numbers of capillaries	Lindh, 1995 ¹⁵
Trapezius	Compromised capillary circulation	Bengtsson, 1989 ¹⁶
Trapezius	Abnormal mitochondria, reduced number of capillaries, thickened capillary endothelium	Lindman, 1993 ¹⁷

Trapezius Muscle Biopsies. In a 1982 study of 15 patients who satisfied the Yunus criteria for FM,⁴ open muscle biopsies of tender areas in various muscles were obtained.⁵ Using light microscopy, 11 of the 15 patients (73%), had samples containing fibers with a moth-eaten appearance. These changes were seen in all nine of the trapezius muscle samples and in two of the four deltoid biopsies, whereas the two quadricep samples did not show abnormal fibers. In addition, tissues from five of the 15 patients contained ragged red fibers, which is a pathologic change usually associated with mitochondrial myopathies.⁶ The presence of abnormalities was further confirmed by electron microscopic studies of five patients who all demonstrated mitochondrial changes such as electron-dense inclusions and lack of inner membranes, myofibrillar Z-streaming, and cytoplasmic bodies. Because normal controls were not included in this study, specificity of the findings for FM could not be ascertained. In fact, abnormalities such as moth-eaten fibers have been described in normal trapezius muscles from women,⁷ suggesting that at least some of these findings are not unique for FM.

Major criticisms of this and other studies had included the fact that they were not carefully controlled or blinded. In order to address these problems, Yunus et al designed a study using a carefully characterized FM group of 21 patients.⁸ Findings were compared to 11 normal controls with similar demographic features. Patients with potentially confounding comorbidities such as cervical spine arthritis or hypothyroidism were excluded. Open biopsies of tender points in the trapezius muscle of the patients and from corresponding sites in the controls were obtained. Electron microscopic examination was carried out by a blinded assessor. Most abnormalities were classified as mild, and more important, no statistically significant differences were observed between the patient and control groups. The findings of numerous, although mild, abnormalities in the trapezius muscles of normal subjects were consistent with a previous report.⁷ The usual tensions exerted upon this muscle group during daily activities may contribute to such changes even in normal individuals. The results of this controlled study, published in 1989, threw some doubt on the significance of the previously described abnormalities in FM trapezius muscles.⁵ Of greater importance, however, was the study's controlled experimental design, which set the standard for future investigations.

Quadricep Muscle Biopsies. Histologic studies of the quadricep muscles in FM patients have been reported by several other groups of investigators.⁹⁻¹¹ In the first of these studies, the diagnostic criteria of Smythe and Moldofsky were used for the selection of patients.¹² Needle biopsies from all 13 FM patients

showed bandlike structures, which were wrapped around glycerinated muscle fibers at irregular intervals, and an interfibrillar network of connective tissue. The bands were associated with some constriction of the underlying fibers. Extra contractions in adjacent fibers could be induced by the connecting reticular network. No bands were observed in the tissues of any of the seven normal control subjects, suggesting relative specificity of this finding for FM. Because the control group was not described in detail, differences in age, sex, or activity level might afford possible explanations for the results. Nevertheless, these findings are strongly suggestive of a relatively specific muscle abnormality in FM patients.

A subsequent study in 1991 confirmed the finding of so-called "rubber-band" morphology in the quadricep muscles of FM patients.¹⁰ These studies by Jacobsen et al included 84 patients who had FM according to a blended set of criteria derived from both Smythe and Yunus.^{4, 12} These patients were compared to a group of 26 individuals classified as having chronic myofascial pain (CMP) syndrome, with symptoms localized predominantly to the neck, shoulders, and back. No normal controls were available for this investigation. Single glycerinized fiber preparations from needle biopsy samples were scored by two blinded examiners using a quantitative scale to grade any observed abnormalities. Differences in biopsy score between the FM patients and the CMP patients were statistically significant ($P < .002$). The previously described rubber-band morphology⁹ was the most striking difference between the two groups, being observed in 63% of the FM patients but only 29% of the CMP patients. These authors also hypothesized that the rubber-band morphology with reticular threads connecting neighboring cells may lead to a state of prolonged contractions in adjacent fibers, inducing a low-energy state within the muscle cell. This abnormal morphology also correlates with increased pain and stiffness after exercise, as reported by FM patients.

More recent studies lend further support to the existence of anatomic muscle abnormalities in FM. Drewes et al¹¹ used needle biopsies to study the quadricep muscles of 20 female patients with FM as defined by the Yunus criteria.⁴ A control group of five women of comparable age was also examined. Light microscopic examination of the biopsy tissues failed to show any significant abnormalities in the FM patients or in the controls. Ultrastructural studies were performed on either patients, and all samples revealed abnormalities of muscle cell membranes, including empty or partly empty sleeves of basement membranes and duplication of membranes. Other cytoplasmic, nuclear, and mitochondrial abnormalities were observed, including lipofuscin inclusions, nuclear aggregates, and mitochondria with irregular cristae. The mitochondrial abnormalities may relate to reductions in the high-energy phosphate compounds adenosine triphosphate (ATP) and phosphocreatine (PCr), and decreased total oxidative capacity in FM muscles, as noted in metabolic investigations.^{13, 14} None of the controls showed any of these abnormalities. The previously described rubber-band morphology^{9, 10} was not observed, possibly due to differences in fiber preparation or fixation techniques. The authors state that the observed abnormalities in FM patients are probably not the result of immobility because the patients functioned normally in daily activities, although they tended to exercise less due to pain and stiffness.

Carefully controlled examination of the vastus lateralis muscle of the quadricep group has demonstrated that the number of capillaries per square millimeter and also the fiber area in relation to the capillaries were lower in FM patients than in normal controls.¹⁵ Similarly, in the trapezius muscle the capillary microcirculation over tender points was compromised in all of 10 FM patients studied and in none of the eight controls.¹⁶ A second study of the tender points in the trapezius confirmed the findings of reduced capillary circulation, and with electron microscopic examination, also showed thickening and structural derangement of capillary endothelium.¹⁷ In addition, small muscle fibers showed altered distribution and structure of mitochondria. These small fibers, which may be related to "ragged red" fibers, were found only in the patients and not in the control subjects. Decreased capillary bed volume, thickened capillary endothelium, and structurally abnormal mitochondria may contribute to poor oxygen diffusion, decreased oxidative phosphorylation, and lower ATP synthesis in the dysfunctional muscles.

Summary of Histologic Studies. The various histologic studies of FM muscle allow several conclusions to be drawn. The first is that the site chosen for biopsy is very important. Although the trapezius is generally more symptomatic in FM, the numerous abnormalities observed in normal biopsy samples may confound

the pathologic evaluation of muscles from FM patients. By contrast, the quadricep muscles in normal individuals demonstrated a minimal number of abnormalities. The quadricep muscles are utilized only intermittently in normal activities, with intervening periods of rest that may help preserve the fiber morphology. For these reasons, this muscle group may be a more useful site for the detection of differences between FM patients and normal subjects.

A second important conclusion is that abnormalities of muscle mitochondria and thickened endothelium may be involved in the pathogenesis of FM. Other findings, discussed below, suggest the presence of changes in oxidative metabolism, which would be consistent with this hypothesis. Using what is known about classical mitochondrial myopathies, it would follow that ultrastructural examination of FM muscle biopsies may be more sensitive to the presence of abnormalities in FM muscles than examination by light microscopy alone.⁶

Studies of Muscle Strength and Function. Studies of muscle strength and aerobic endurance in FM patients have generally found a reduction in muscle performance as compared to normal controls. Muscle strength and endurance have been evaluated in many ways, ranging from simple grip strength to aerobic exercise regimens.

Strength Studies in Upper Extremities. In FM patients, the grip strength was found to be reduced by 40% ($P < .01$) as compared to normal control values in reports by Mengshoel et al and Nordenskiold et al.^{18, 19} The maximal voluntary contractile force of the hand was also significantly decreased by 26% ($P < .05$) in FM patients, as demonstrated in studies of Bengtsson et al.² In this same study, however, electrical stimulation of the adductor pollicis in the forearm generated equal force in patients and controls when measured by force transducers and electromyographic recordings.² This result was interpreted as suggesting that fatigue in FM patients may be, at least in part, of central origin. These central factors could include inhibition of the motor drive due to pain or negative feedback from muscles with abnormal metabolism, or it could be of psychological origin.

Strength Studies in Shoulders and Lower Extremities. In a static endurance work test for the shoulder, FM patients showed a 63% decrease ($P < .004$) in performance as compared to controls.¹⁸ For FM patients, and maximum isometric and isokinetic strength of knee extension was significantly lower by 58% to 66% and 41% to 51%, respectively, compared to a group of well-matched controls ($P < .01$).²⁰ These results were subsequently confirmed by a second group of investigators.²¹ Strength in the quadriceps muscles of FM patients was measured using an isokinetic method and was also reported to be significantly less than in normal controls.⁹ By contrast, several groups have suggested that differences in muscle strength or performance between FM patients and controls are not significant. For example, the maximal voluntary contraction (MVC) of trapezius and tibialis anterior muscles of FM patients was found to be normal.²² Shoulder flexion using an isokinetic dynamometer was also normal in patients; however, the relaxation between contractions was curtailed, suggesting a mechanism for induction of pain and stiffness.²³ Nonetheless, the majority of the data demonstrated reproducible and statistically significant decreases in the strength and performance of FM patients as compared to control subjects.^{2, 9, 18-21} The percentage of reduction range rather widely from 26% to 63%, depending upon the muscle groups tested and the type of exercise used.^{2, 18} The investigators who did not observe significant differences may have valid results for the particular conditions used in the exercise protocols.^{22, 23}

Energy Consumption. The overall level of physical activity in FM patients and controls was measured by Norregaard et al using a graded scale which quantitated the amount of time spent each day in various activities.^{24, 25} The levels were used to derive an estimate of daily energy consumption, which was expressed as metabolic equivalents (METs). Patients with FM were found to have significantly lower MET values than sedentary controls ($P < .01$). This suggests that endurance for the cumulative effort of daily activities is reduced in FM patients. Consistent with this observation are the data of Bennett et al, who determined that levels of aerobic fitness were markedly reduced in FM patients compared to a carefully matched control group.²⁶ Reduced aerobic fitness is compatible with two important findings: (1) the

abnormal distribution of oxygen in FM muscles as measured with an oxygen-sensitive electrode,²⁷ and (2) significantly lower blood flow in exercising muscles of FM patients as compared to age- and sex-matched controls.²⁶

Aerobic Fitness. In order to improve aerobic endurance in patients with FM, McCain et al designed and tested a 20-week supervised training program.²⁸ Enhanced cardiovascular fitness was achieved in 15 of the 18 patients (83%) in the cardiovascular training group. Significant improvement was observed in the pain threshold measurements over the tender points, but not in the visual analog scores for pain. Similar results were obtained by Mengshoel et al, who evaluated the effects of 20 weeks of physical fitness training.²⁹ Improved dynamic endurance work performance for the upper extremities was found in the training group of FM patients in comparison to the FM control group not training ($P < .01$). Statistically significant changes were not seen, however, in general pain, pain coping, or fatigue. In a subsequent pilot study, Mengshoel and coworkers selected 26 FM patients for a 10-week multidisciplinary program, consisting of both cognitive and exercise components.³⁰ After 10 weeks, this pilot study showed a significant reduction in pain intensity as compared to baseline ($P < .05$). Exercise programs for individual patients with varying degrees of functional impairment have been described in detail by McCain.³¹ Overall, these results show that some FM patients are able to participate in rather vigorous training programs, which may lead to significant symptomatic improvement.

Summary of Muscle Strength and Function Studies. These investigations suggest that muscle strength and endurance are most likely reduced in the majority of patients with FM. However, the training investigations indicate that it is possible for FM patients to achieve higher levels of fitness and that such training may translate into clinical improvement. Whether physical training also translates into changes in underlying biochemical abnormalities remains to be determined.

Studies of Abnormalities in Muscle Metabolism. Most studies of patients with FM demonstrate that their muscles show decreased contractile force and endurance. Muscle dysfunction usually correlates with abnormal metabolism, which can be readily investigated by determining the levels of critical metabolites. Measurement of intracellular metabolites has been classically achieved through direct chemical measurements performed on muscle biopsy specimens. More recently, magnetic resonance spectroscopy (MRS) has provided a technique for noninvasive determination of metabolites which can be accomplished during exercise as well as at rest. Levels of the high-energy compounds required for muscle contraction, namely, ATP and PCr, can be quantitated using P-31 MRS. Both biopsy and P-31 MRS approaches have been applied to the study of FM patients.

ATP and PCr in Muscle Biopsies. In 1986, Bengtsson et al reported results of a study in which biochemical analysis of muscle biopsy tissues was used to measure levels of high-energy phosphate metabolites PCr and ATP, as well as ADP, AMP, creatine lactate, pyruvate, and glycogen. All 15 patients fulfilled the FM criteria as defined by Yunus.⁴ A normal control group of similar age and sex distribution also was examined. Open surgical biopsies obtained from the trapezius or anterior tibialis muscles were frozen, and the various metabolites of interest were extracted and quantitated. Levels of PCr and ATP were significantly lower in the trapezius samples from the FM patients as compared to the controls ($P < .001$ for PCr and ATP). Since creatine levels were increased in the FM trapezius, the synthesis of PCr, which is the most important store of high-energy phosphate in the muscle cell, was clearly defective. The abnormalities were present only in the trapezius muscle tender points and not in the anterior tibialis.

P-31 Magnetic Resonance Spectroscopy. The technique of P-31 MRS has been shown to be useful in the characterization of metabolic abnormalities in a number of muscle diseases, including glycogen phosphorylase deficiency,³² mitochondrial myopathies,^{33, 34} and dermatomyositis.^{35, 36} For fibromyalgia, five different P-31 MRS investigations revealed no abnormalities in the measurements of P-31 metabolites during rest or exercise.^{22, 37-40} In all of these FM studies, the data were reported as metabolite ratios, that is, Pi/PCr or β -ATP/PCr. By measuring ratios of compounds rather than determining their absolute levels,

significant abnormalities may go undetected because the ratios of important metabolites can be normal while the actual concentrations are reduced.⁴¹

We recently examined 12 fibromyalgia patients using P-31 MRS and compared the results to a corresponding group of 11 normal controls.^{14, 42} Visual analog scales for pain, fatigue, and weakness showed significant elevations in the FM patients compared to the controls ($P < .0001$ for each). Most of the patients were active homemakers or were employed outside of the home. P-31 MRS data were acquired from the quadricep muscles at rest and during exercise at 25% MVC. PCr and ATP levels in the resting muscles of the patients were 15% lower than those for the control group ($P < .001$). During exercise, PCr and ATP concentrations were also significantly lower (15%) in the patients' muscles ($P < .03$). These data are in rather close agreement with the biopsy determinations, which showed reductions in PCr and ATP of 21% and 17%, respectively, in the tender sites of the trapezius muscle.¹³ The reduced levels of PCr and ATP in the patients' muscles correlate with clinical observations regarding weakness and pain during activities involving the quadriceps and the trapezius muscles.

There are several reasons for the differences among our findings^{14, 42} and those reported in previous P-31 MRS studies.^{22, 37-40} First, we measured absolute levels of Pi, PCr, and ATP, whereas other investigators reported ratios of these compounds; a ratio may be similar in patients and controls although concentrations of both compounds may be substantially reduced. Second, we examined the quadricep muscles, while other groups utilized the trapezius, calf muscles, anterior tibialis, or wrist flexors. The histologic data suggest that differences between FM patients and normal controls may be more easily detected in the quadriceps. Third, the type of exercise used in our studies differed from that in all other protocols.

The energy reserve or so-called phosphorylation potential (PP) and total oxidative capacity (V_{max}) for the FM and control groups were calculated using the P-31 MRS data. The mean PP was significantly less in the FM group than in the controls (145 mmoles^{-1} and 378 mmoles^{-1} , respectively; $P < .01$). Likewise, V_{max} was statistically lower in the patients as compared to the controls (124 and 220, respectively; $P < .0007$). These data are consistent with an impairment in oxidative phosphorylation and ATP synthesis in the muscles of FM patients, and may translate into the commonly observed clinical symptom of fatigue.

An interesting MRS observation by Jubrias et al was the frequent appearance of a phosphodiester (PDE) peak in the exercising forearm muscles of FM patients.⁴⁰ This PDE peak is heterogeneous in composition, consisting of several different phosphodiesters associated with muscle cell membranes. Although normal controls also showed PDE peaks, the appearance was significantly more pronounced in the FM patients. In evaluating the quadricep muscles, Park et al confirmed the finding of greater amounts of PDE in FM muscles.⁴² The abnormal appearance of PDE may be associated with the disruption of the cell membranes, as observed in microscopic examinations.^{5, 11, 17} Various other myopathies have also shown excess amounts of PDE, further indicating an important correlation between abnormal membranes and muscle disease.^{43, 44}

The P-31 MRS data have been utilized in an artificial neural network analysis to examine differences between FM patients and normal controls.⁴⁵ The neural network is a computerized pattern recognition process which has been applied to various clinical problems.⁴⁶ Indeed, the neural network successfully distinguished FM patients from normal controls, thereby confirming the presence of abnormalities in FM.

Summary of Metabolic Abnormalities. The poor bioenergetic status of FM muscles may be due to reduced levels of ATP and PCr, lower energy reserves (PP) and oxidative capacity (V_{max}), and abnormal PDE levels, all of which could result from impaired oxidative phosphorylation in mitochondria. In simple terms, mitochondrial function may be impaired by decreased availability of oxygen due to the compromised capillary microcirculation and thickened endothelium. Decreased levels of ATP also have been demonstrated in erythrocytes,^{47, 48} suggesting that this defect may be a more general and systemic

problem than originally perceived. Because FM is a multidimensional disease, these metabolic abnormalities may very well impinge on other organ systems.

Discussion

Hypotheses to Explain Pathophysiology of Muscle Abnormalities and Symptoms in FM patients.

The presence of numerous abnormalities in FM muscle structure and biochemistry has been well established by the work of many investigators. The abnormalities are not isolated entities but show multiple interactions that may impact upon the clinical symptoms (Table 2). Five major histologic abnormalities and four major physiologic or biochemical problems are listed. It is likely that each anatomical defect is related to at least two biochemical problems. For example, the constricting "rubber band" morphology may lead to lower ATP through prolonged fiber contraction and to decreased oxidative capacity via reduced blood flow. Both compromised capillary circulation and thickened capillary endothelium will decrease oxygen diffusion, thereby impairing oxidative phosphorylation, leading to lower levels of PCr and ATP and decreased Vmax and PP. Abnormal mitochondria are very likely to impact on all four biochemical defects. The case also could be made in the opposite direction, and each of the biochemical defects could be seen to induce morphologic problems. These cycles of interactions can be seen as promoting and even amplifying the factors responsible for muscle pain, weakness, and fatigue.

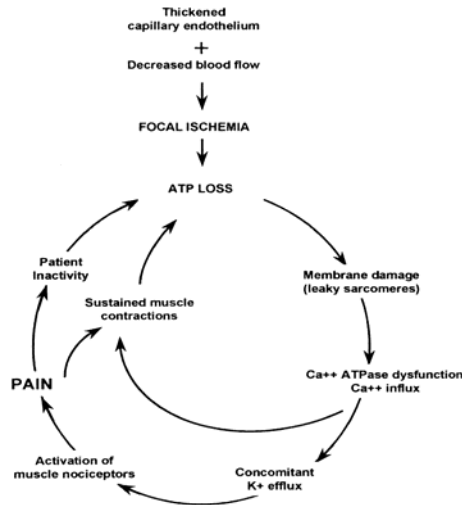
Table 2. Potential Muscle Factors Contributing to Clinical Symptoms in Patients With Fibromyalgia

Histologic Abnormalities	Clinical Symptoms	Biochemical Abnormalities
Rubber band morphology		Low levels of ATP and PCr
Decreased capillary numbers	Pain	Decreased oxidative capacity (Vmax)
Thickened capillary endothelium	Fatigue	Decreased oxygen delivery (diffusion)
Abnormal mitochondria	Weakness	Increased membrane phosphodiesterases
Sarcolemmic membrane damage		

When considering how the two columns of muscle abnormalities affect the major clinical symptoms, interactions become even more complex and entwined. Once again, each abnormality can be logically related to one or more of the major clinical symptoms. Pain itself may induce weakness and fatigue along with reduced daily activity levels. Indeed, the reduced level of daily activities, which relates to the much-discussed deconditioning, may impact on the overall picture of anatomical and biochemical defects. It should be noted that the scientific data on muscle abnormalities are internally consistent with the clinical symptoms of the dysfunctional muscle.

An expanded picture of causal factors in FM has been proposed particularly to include important central problems such as sleep disturbance (Figure 1). Because growth hormone is produced predominantly during stage 4 sleep, the nonrefreshing sleep of many patients may produce a growth hormone and somatomedin-C deficit. Because exercise promotes growth hormone secretion, the decreased daily activity levels of patients may further augment hormone deficits. Thus repair processes for the exercised muscle may proceed at lower rates, leaving the muscle in a suboptimal state following exertion. The aberrant microfibrillar structure and abnormal sarcolemmal membranes provide evidence of prevalent damage in FM muscle. Sarcolemma damage results in an influx of calcium into the sarcomeres, which itself results in sustained contractions that may be responsible for clinical symptoms of pain and stiffness as well as reductions of ATP, with substantial metabolic consequences. Calcium influx evokes a counter-current of potassium efflux from the sarcomeres. Potassium, as an activator of nociceptors, would likewise promote sensations of pain. Other central mechanisms relevant to pain may involve abnormalities in tryptophan metabolism, which relates to sleep disturbances and enhanced perception of nociceptive pain. All of these experimental data are consistent with the picture of a multidimensional disease with close interrelations between organ systems.

Figure 1. Diagram of proposed interactions of various muscle abnormalities leading to pain and muscle dysfunction.



Areas for Further Study. Since deconditioning is often discussed as a possible explanation for musculoskeletal abnormalities in patients with FM, it would be of some importance to report quantitatively the level of activity for patients in any study of muscle function or metabolism. This could be achieved through interview or by a self-report questionnaire. A normal control group with similar levels of activities and strength may be difficult if not impossible to find. By carefully quantitating levels of activities in both patients and controls, however, meaningful correlations could be established.

One very important approach would be to determine the role of deconditioning in the musculoskeletal manifestations of FM. McCain et al²⁸ and Mengshoel et al^{29, 30} have demonstrated that at least some FM patients can participate in rather intensive exercise programs. Interestingly, the work capacity improved, but by most measures the pain level remained constant. Therefore, the work/pain ratio was improved, and the patients became more efficient as individuals. Quantitative measures and correlations between work, daily activities, pain, fatigue, ATP, PCr, and PDE before and after exercise programs may provide insight into the pathogenesis of FM.

The availability of enzyme analysis of muscle tissue for diagnosis of metabolic myopathies offers the possibility of investigating FM patients for such abnormalities. Such a study would be of interest from a biochemical and possibly genetic viewpoint because many of the histologic and electron microscopic data suggest changes reminiscent of mitochondrial disorders.

Use of additional in vivo spectroscopic (MRS) techniques many provide further insight into metabolic changes in resting or exercising muscle. Such techniques are currently the only way to measure changes in metabolites during exercise. Proton spectroscopy (H-1 MRS) offers the possibility to measure levels of important muscle metabolites including creatine, choline, and lipids, while carbon spectroscopy (C-13 MRS) provides the extraordinary potential to evaluate intermediates in the glycolytic cycle and also determine kinetics parameters.

Clinical investigations of FM in muscle must be correlated with studies in other areas, such as neurology with endocrinology. Until the etiology of FM is known, awareness of various scientific endeavors is essential for design of new experimental approaches and formulation of therapeutic protocols.

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Table 1. Histologic Studies of Muscle Tissue in Patients With Fibromyalgia

Muscles Studied	Microscopic Findings	Author, year
Various, including trapezius	Motheaten fibers, ragged red fibers, abnormal mitochondria	Henriksson, 1982 ⁵
Trapezius	Mild changes; not different from controls	Yunus, 1989 ⁸
Quadriцеп muscles	Rubber band morphology	Bartels, 1986 ⁹
Quadriцеп muscles	Rubber band morphology	Jacobsen, 1991 ¹⁰
Quadriцеп muscles	Duplication of membranes, abnormal mitochondria, thickened capillary endothelium	Drewes, 1993 ¹¹
Quadriцеп muscles	Reduced numbers of capillaries	Lindh, 1995 ¹⁵
Trapezius	Compromised capillary circulation	Bengtsson, 1989 ¹⁶
Trapezius	Abnormal mitochondria, reduced number of capillaries, thickened capillary endothelium	Lindman, 1993 ¹⁷

Table 2. Potential Muscle Factors Contributing to Clinical Symptoms in Patients With Fibromyalgia

Histologic Abnormalities	Clinical Symptoms	Biochemical Abnormalities
Rubber band morphology		Low levels of ATP and PCr
Decreased capillary numbers	Pain	Decreased oxidative capacity (Vmax)
Thickened capillary endothelium	Fatigue	Decreased oxygen delivery (diffusion)
Abnormal mitochondria	Weakness	Increased membrane phosphodiesterases
Sarcolemmic membrane damage		

Figure 1. Diagram of proposed interactions of various muscle abnormalities leading to pain and muscle dysfunction.

