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Editorial

The muscle in fibromyalgia

The main symptoms in fibromyalgia are muscle pain, stiffness and muscle fatigue. In 1981, when we started our fibromyalgia studies, we had a lot of patients with such symptoms at our clinic. None of them had arthritis or laboratory signs of inflammation, which is the key that opens the door to the rheumatology unit. Fibromyalgia patients in our own studies were all diagnosed according to the Yunus criteria from 1981 to 1990 and according to the ACR criteria since 1990 [1, 2].

The first questions that should be asked are these: When do we feel pain in the muscles? What kind of changes in the muscle tissue produce pain? Is there any evidence that such changes exist in the muscle in fibromyalgia?

Muscle fibres are not provided with nociceptors [for reviews see 3–5]. Chronic degenerative muscle disorders are not painful. Inflammation can cause sensitization of pain receptors, but on the other hand polymyositis can exist without pain. Hypoxia in combination with muscle work causes pain as well as energy depletion.

In the late 1980s we carried out several studies to find out if there was any peripheral contribution to the pain of fibromyalgia. An epidural catheter was inserted in the patients. According to the method introduced by Cherry *et al*. [6], the patients were given physiological saline twice followed by an opioid, given naloxone intravenously, and finally a local anaesthetic (lidocaine) [6]. The nine patients were placed on a bicycle ergometer and were asked to exercise to an intensity of 40 and 80% of their maximal oxygen uptake [7]. These studies showed that the patients did not respond to placebo, they were able to work without any increase in pain during administration of the opioid, and when they were given the local anaesthetic they were all free of pain. The conclusion was that there probably is a peripheral component in fibromyalgia.

Because the main symptoms in fibromyalgia (pain, stiffness and fatigue) are located in the muscles—at least according to the patients—muscle biopsies, mostly from the trapezius muscle, have been studied [8]. Biopsies have also been taken from the deltoid, the brachioradial, anterior tibial and quadriceps muscles. Light microscope, histochemical and electron microscope studies have been done, as well as specific analyses of, for example, the content of substance P in muscle biopsies, which is increased in fibromyalgia muscle. Serotonin has been measured by the use of microdialysis in the masseter muscle and found to be higher in patients with fibromyalgia than in controls.

Muscle biopsy studies have been made by our group as well as by Yunus *et al*. [9], Bartels and Danneskiold-Samsoe [10], Kalyan Raman *et al*. [11], Pongratz and Spath [12] and Drewes *et al*. [13]. Drewes *et al*. studied the quadriceps muscle by electron microscopy, and in most cases they found empty sleeves of basement membrane, cellular damage manifested as lipofuchsin inclusions, and mitochondria with irregular patterns of cristae. Electron microscope studies have also been done by Kalyan Raman *et al*. [11], Fassbender and Wegner [14], Yunus *et al*. [15] and Lindman *et al*. [16, 17], and these studies have shown minor mitochondrial abnormalities.

In general, there has been no sign of degeneration or regeneration or inflammation. Atrophy of type 2 fibres has been reported in several studies. The frequencies of type 1 and type 2 fibres have been determined in patients and controls, as has mean cross-sectional area of the fibres, and no differences have been found. Most of the studies have been made in the upper part of the trapezius muscle. Studies of the normal trapezius indicate a relatively poor supply of capillaries as well as low mitochondrial volume density compared with limb muscles [17]. In the normal trapezius there are some differences between men and women, females having smaller cross-sectional areas of both type-1 and type-2 fibres. As the mitochondrial volume density of a muscle is directly related to its endurance capacity, our results might indicate a relatively low oxidative capacity of the muscle fibres and thus little ability for endurance work.

The presence of moth-eaten and ragged-red fibres indicates uneven distribution and proliferation of mitochondria. Accumulation of mitochondria is seen in Gomori trichrome staining, and this gives the ragged appearance. Mitochondrial proliferation may be a compensatory phenomenon in disorders or pathophysiological states affecting oxidative metabolism. Ragged red fibres appear to be related to insufficient blood supply, as shown by Heffner and Barron in 1978 [18].

Ragged red and moth-eaten fibres are not specific to fibromyalgia, but are often seen in chronic neuromuscular disorders. They have also been found in controls. Ragged red fibres are also found in localized chronic shoulder pain, predominantly on the painful side and if the patient has been exposed to static loading. They can also be found in polymyalgia rheumatica, mitochondrial diseases and experimental ischaemia.

Muscle microcirculation can be measured in different ways. Lund *et al*. [19] used an oxygen multipoint electrode on the muscle surface in 10 patients and eight controls. The trapezius and brachioradial muscles were studied. A pathological distribution of tissue oxygen pressure values was found in all patients but in only one of the controls. These results indicate

abnormal capillary microcirculation, at least in the tender point area. Blood flow in the tender point area has also been examined using an intramuscular needle electrode, and lower values were found in the patients.

Capillary density was examined in the trapezius muscle in 10 patients and nine controls, and no differences were found between the two groups [8]. Lindh *et al*. [20] examined the vastus lateralis muscle and found a lower density of capillaries (numbers of capillaries per fibre and per mm^2) in fibromyalgia patients. Lindman *et al*. [21] found a greater thickness of the endothelium of the capillaries of fibromyalgia patients. Similar changes had been observed by Fassbender and Wegner in 1973 [14]. These changes are either caused by or are the cause of localized hypoxia. These findings are similar to those of Gidlöf *et al*. [22], who observed derangement of limb muscle capillaries after tourniquet-induced ischaemia. The endothelial changes were also found in controls, but they were more frequent in fibromyalgia. Muscle blood flow has also been examined by Bennett *et al*. [23] using xenon 133 clearance, and lower values were found in fibromyalgia.

The microcirculation in the muscle is controlled by locally produced metabolites, the sympathetic nervous system and humoral factors. When eight patients received a stellate ganglion blockade with the local anaesthetic bupivacaine, patients with total sympathetic blockade were free from pain and tender points in the arm. Sham blockade did not have this effect [24]. Larsson *et al*. [25] studied blood flow with a laser Doppler technique in the trapezius muscle in patients with shoulder pain on only one side. On the pain-free side there was an increase in blood flow as the load increased. On the painful side, however, blood flow did not increase on increasing the load. This also indicates disturbed local regulation of the microcirculation.

Levels of ATP and phosphocreatine were analysed in muscle biopsies from the trapezius [26] and the tibialis anterior muscle in patients with fibromyalgia and in the trapezius muscle of healthy controls, and lower values were found in the patients than in the controls.

Studies using magnetic resonance spectroscopy (MRS) have produced results different from studies of muscle biopsies. The MRS studies were all carried out under different circumstances and in different muscles.

At our clinic, fibromyalgia patients and controls were studied during rest and under different work loads. At rest and under submaximal loading there were no differences between the two groups, but under maximal load the patients produced only half as much work as the controls (A. Bengtsson *et al*., submitted for publication). The pH reduction was the same in controls and patients, as, for example, Vestergaard-Poulsen *et al*. have also found [27]. The patients thus reached the level of pH reduction at which pain and fatigue inhibit work after a much shorter time and under a lesser work load compared with the controls. Park *et al*. found lower ATP values at rest in patients with fibromyalgia [28]. Oxidative enzymes were studied by Lindh *et al*. [20], who found that 3-hydroxy CoA dehydrogenase and citrate synthase were lower in patients than in controls.

Maximal voluntary contraction has been examined in fibromyalgia in several studies, and all of these found a reduction in muscle strength, but when the muscle was stimulated electrically normal values were found. Jacobsen *et al*. [29] found a significant reduction in isometric and isokinetic strength in the quadriceps muscle. Mengshoel *et al*. [30] tested grip strength in the dominant hand and found a significant reduction in muscle endurance, tested by repeated maximal grip pressure, dynamic endurance work and static endurance work.

Bäckman *et al*. [31] presented evidence that the reduced strength was due to an impaired central activation of motor units. In one study by Elert *et al*. [32], patients and controls were asked to do 100 repeated shoulder flexions. EMG was controlled simultaneously. Pain and perception of effort were not recorded. However, this study showed that patients with fibromyalgia had EMG activity between muscle contractions. One hypothesis is that this was due to the prolonged relaxation time recorded in fibromyalgia [31]. When the muscle is not relaxed between contractions, the microcirculation of the muscle might be affected.

When the microcirculation and metabolism of the muscle are affected, muscle pain can arise in work, but fibromyalgia patients have pain at rest as well as widespread pain and allodynia that cannot be explained by the results of muscle biopsies. Pain cannot be explained by the findings of muscle biopsies if a state of central sensitization does not exist [33].

Pharmacological analyses of pain in fibromyalgia showed that patients were all pain-free after epidural blockade [7]. Resting pain disappeared, as did the tender points.

The effects of intravenous infusion of morphine, lidocaine, ketamine and placebo were analysed in 18 patients. Only two patients responded to placebo [34]. Thirteen responded to one or several drugs but not to placebo. Only three patients did not respond to any drug or to placebo. Thirteen patients responded to ketamine, which blocks NMDA (*N*-methyl-D-aspartate) receptors. This points to central sensitization as an important factor in fibromyalgia and the likelihood that different fibromyalgia patients probably have different pain mechanisms [35].

Sörensen *et al*. [33] studied experimentally induced muscle pain by infusion of hypertonic saline and showed that hyperalgesia in fibromyalgia is present in fibromyalgia muscle without pain. In the cerebral fluid, the concentration of substance P is higher in fibromyalgia patients than in controls, and these findings have been confirmed by Russell [36].

The muscle biopsy studies show that there are no specific changes conclusively for fibromyalgia. However, moth-eaten fibres, ragged red fibres and type 2 fibre atrophy indicate that the muscles are involved in the pathogenesis of fibromyalgia. The studies mentioned above indicate that the regulation

of the microcirculation is disturbed in fibromyalgia in a way that might lead to sensitization of the intramuscular nociceptors. My conclusion from the studies on muscle metabolism in fibromyalgia is that there is a defect that is not seen at rest and when the patient is working at a submaximal load, but is seen under maximal loading and under static contraction.

The mechanisms of pain are not the same in all patients with fibromyalgia. It may be that this confuses us all because different fibromyalgia patients are seen according to whether we work in a rheumatology unit, a general practice or a psychiatric clinic.

However, in the majority of patients there is a state of central sensitization. In these patients, changes in the muscles, such as mitochondrial changes, a change in the microcirculation and/or a change in muscle metabolism, might sensitize muscle nociceptors and thereby cause pain, fatigue and muscle weakness.

It is important for us to understand the influences of other chronic pain mechanisms, such as pain-inhibitory and pain-facilitating pathways, and the cortical and subcortical processes involved in the establishment of chronic pain. Studies of both peripheral and central factors will be necessary before we achieve a full understanding of pain in fibromyalgia.

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