

Chronic musculoskeletal pain; mechanisms and pain reports

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Doctoral Thesis

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Summary

Background: The knowledge of underlying mechanisms for the maintenance and spread of musculoskeletal pain is limited. Pain is a complex subjective experience influenced by a variety of factors. The focus of the present thesis is on possible mechanisms associated with chronic generalized musculoskeletal pain, and factors of importance for the variation in reports of pain intensity and sensory symptoms in subjects with localized and generalized musculoskeletal pain.

Aims: The specific aims were to investigate: 1) whether sympathoadrenal and cortisol responses were attenuated and associated with pain intensity and muscle fatigue during exercise in subjects with fibromyalgia (FM) compared with healthy controls; 2) the reliability and validity of two different pain assessment strategies of recalled pain intensity in subjects with localized (LP) and generalized (GP) musculoskeletal pain; 3) whether pain intensity, number of painful body areas and emotional distress were associated with neuropathic symptoms in subjects with musculoskeletal pain

Materials and methods: Sympathoadrenal and cortisol responses, pain intensity and muscular responses were compared between subjects with fibromyalgia and their matched healthy controls during dynamic bicycling and static repetitive contractions (papers I and II). Pain intensity, neuropathic symptoms (LANSS), and number of painful body areas were reported over the first week in four subsequent months and compared in subjects with LP and GP (papers III and IV). Pain intensity was assessed as recalls of pain intensity during the last 24 hours (daily recalls) (papers I-III) and the last seven days (weekly recalls) (papers I-IV). Real-time pain intensity was assessed moment by moment during exercise (papers I and II) and during one week in every day life (paper III).

Results: Compared with the healthy controls the FM patients exhibited lower peak oxygen uptake and lower MVC (papers I and II), similar physiological responses during dynamic exercise (paper I), but lower plasma adrenaline responses and higher relative EMG during static repetitive exercise (paper II). The catecholamine responses were not associated with real-time pain intensity and muscle fatigue during exercise (papers I and II). Real-time pain intensity increased during exercise, but no increase was reported in recalled pain comparing the week before and after exercise. Across four months the average of daily ratings of recalled

pain intensity conducted over a week were lower and corresponded better with the average of multiple real-time ratings than single ratings of weekly recalls. The GP group obtained lower reliability of pain intensity than the LP group and overestimated weekly recalled pain compared to real-time pain. The overestimation increased with increasing pain intensity (paper III). The LANSS scores were stable over time and positively associated with number of painful body areas, pain intensity, and emotional distress. In multiple regression analysis emotional distress and the diagnosis of fibromyalgia remained the final predictors of neuropathic symptoms (paper IV).

Conclusion: This study showed attenuated adrenaline responses in FM during static repetitive exercise, but no clear relationship between altered physiological responses and exercise related pain. Pain intensity varied considerably according to context and the assessment method applied. Generalized pain and emotional distress were the main factors influencing the reports of pain and sensory symptoms. In future studies, the causal relationship between emotional distress and development of generalized pain and associated symptoms need further exploration.

List of papers

This thesis is based on the following papers.

- I. L. Giske, C. Røe, S. Knardahl, N. K. Vøllestad: Pain and Sympathoadrenal Responses to Dynamic Exercise in Women With the Fibromyalgia Syndrome. *The Journal of Musculoskeletal Pain*. 2007 15(4): 25-38.
- II. L. Giske, N.K. Vøllestad, A.M.Mengshoel, J.Jensen, S.Knardahl, C.Røe. Attenuated adrenergic responses to exercise in women with fibromyalgia– a controlled study. *European Journal of Pain*. 2008 Apr;12(3):351-60.
- III. L. Giske, L. Sandvik, C.Røe. Comparison of daily and weekly retrospectively reported pain intensity in patients with localized and generalized musculoskeletal pain. *European Journal of Pain*. 2009 May. Under revision.
- IV. L.Giske, E. Bautz-Holter, L. Sandvik, C. Røe. Relationship between pain and neuropathic symptoms in patients with musculoskeletal pain. *Pain Medicine*. 2009 Apr 22. Accepted.

Abbreviations

Adr=Adrenaline

CI=Confidence interval

CV=Coefficient of variation

ICC=Intraclass correlation coefficient

EMG= Electromyography

FIQ=Fibromyalgia Impact Questionnaire

FM=Fibromyalgia

GP=Generalized pain

HPA-axis=Hypothalamic-pituitary-adrenal axis

HR=Heart rate

HSCL=Hopkin's Symptom Check List

La=Lactate

LANSS=Leeds Assessment of Neuropathic Symptoms and Signs

LP=Localized pain

MVC=Maximal voluntary contraction

NAdr=Noradrenaline

N=Newton

NRS=Numerical rating scale

SD=Standard deviation

VAS=Visual analogue scale

VO₂=Oxygen uptake

Errata

Paper II

1. In Figure 4, page 357, the score of pain intensity, shown by the box plot at "Midway" for the subjects with fibromyalgia, is incorrect. The correct score is median 57 (IR 44-74) mm on VAS.
2. At page 353, first paragraph: "On the day following the bicycle test," should be "On the day following the static repetitive exercise,"
3. At page 357, point 3.6, line 6, the p value is: $p > 0.21$, and not $p < 0.21$.

Paper IV:

1. Several specifications in Table 1, page 913, are incorrect. The corrections in Table 1 is shown below:

Table 1. Characteristics of participants and drop outs.

	Drop outs (N=12)	Participants (N=86)
Age (yrs), mean (SD)	44 (12)	48 (12)
Females, (n)	67 %	83 %
Pain duration (yrs), mean (SD)	10 (10)	12 (10)
Educational level, (n)		
<13 yrs, vocational	67 %	55 %
> 13 yrs, academic	33 %	45 %
Full/part time employment, (n)	42 %	49 %
Sick leave/disability pension (n)	58 %	51 %
No regular exercise (n)	58 %	65 %
Regular exercise (n)	42 %	35 %

1 Introduction

Musculoskeletal pain is common in the general population and may be looked upon as one of our daily life harassments. Most pain episodes from the musculoskeletal system resolve within a couple of weeks or months (18;159;170). However, in a large group of persons the condition is a severe, long lasting, and disabling problem implying substantial costs for the individual, the health care system, and the society (23;27). Estimates of the prevalence of chronic musculoskeletal pain vary widely, but is often reported between 15- 20 percent and even up to 50 percent in different European countries (92;136;185;196). From 2 to 10 percent report widespread pain (64;243). In Norway musculoskeletal pain is one of the most common causes of sick leave and receiving a disability pension (200).

Despite extensive research, the knowledge of the mechanisms involved in the maintenance and spread of musculoskeletal pain is incomplete, and further knowledge is needed. Aggravation of symptoms during physical and psychological stress is often reported, and altered responses from the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis have been indicated as being part of the pathogenesis in several musculoskeletal pain disorders (169;170;233). Pain is a multifactorial phenomenon and influenced by a wide range of personal and contextual factors. However, the relation between the underlying pain inducing mechanisms and the pain reported is complex. The focus of the present thesis is on possible mechanisms associated with chronic generalized musculoskeletal pain, and factors of importance for the variation in reports of pain and sensory symptoms in subjects with localized and generalized musculoskeletal pain.

1.1 *Musculoskeletal pain*

1.1.1. Pain definition

The International Association for the Study of Pain (IASP) define pain as “an unpleasant sensory and affective experience associated with actual or potential tissue damage, or described in terms of such damage” (155). According to the definition, pain is a complex and subjective experience comprising different dimensions of pain independent of the identification of tissue damage. Three main dimensions are proposed: the sensory-discriminative, affective-motivational and cognitive-evaluative (145). Pain intensity (how much it hurts), pain quality (the physical sensations), and pain localization are aspects of the sensory-discriminative dimension (100). The affective dimension is often described in terms of anxiety, depression, frustration, anger, and disgust, and the cognitive dimension is

evaluated by thoughts and beliefs about pain (225;241). Pain is influenced by a variety of psychological variables, previous experiences, is related to personal meanings, and influenced by cultural learning (46;147). Pain is a dynamic process demanding attention and a powerful motivational drive to avoid or handle threats (38;39;131).

1.1.2 Musculoskeletal pain, aetiology and classification

Musculoskeletal pain is not a well defined entity and may arise from different structures of the skeletal and muscular system. In a subsample of subjects, well defined medical diseases underlie the pain reports showing inflammation or other pathological tissue damage. In the vast majority no such causes are found. Nevertheless pain is assumed to originate from soft tissues such as tendons, ligaments, fibrous capsules, and muscles, the latter being the most common source (12;161;204). Muscle pain is difficult to localize and is often felt as diffuse pain in the affected area in addition to remote sites and other muscle or joint areas (151), and accompanied by muscle tenderness (4;193;244). Trauma, inflammation, and overload are causes of acute pain from the muscular system (151). After three months most injuries are healed, and pain exceeding this time period is often defined as chronic (156;226;238). The present thesis focus on chronic pain assumed to arise from muscles. In most subjects with chronic muscle pain objectively verified pathology has been difficult to identify (93;106), and the aetiology is unclear (12;60;130;161;191). Due to the lack of gold standards, pain is often used in the classification of muscle pain conditions (193;239;244).

According to Woolf (245), pain may be divided into nociceptive, inflammatory, neuropathic, and functional pain. Nociceptive pain is transient pain in response to a noxious stimulus, and inflammatory pain is when tissue damage or inflammation is present (245). Neuropathic arises “as a direct consequence of a lesion or disease affecting the somato-sensory system” (222), and functional pain is “abnormal operation of the nervous system” (245). Neuropathic and functional pain are thus uncoupled from a noxious stimulus to the peripheral sensory nerve endings (245). However, no diagnostic tool is available to identify the mechanisms involved and the patients must be evaluated on the basis of symptoms (247).

A criteria-based clinical classification often divides chronic muscle pain into two broad categories; regional pain including myofascial pain and widespread pain including fibromyalgia (89;130;161). Myofascial pain is a descriptive term used in two ways; generally to describe all regional pains of muscular origin, or specifically addressing the syndrome caused by myofascial trigger points (193). The most common regional pain site is the lower back, followed by head, neck, shoulder, and arm/wrist/hand (130;161). In the group with

widespread pain fibromyalgia represents the far end and is classified according to the American College of Rheumatology Criteria for fibromyalgia (ACR-criteria) (244) developed for research purposes. The ACR criteria definition of widespread pain is an accepted definition regarding the distribution of pain. Localized and generalized pain are often used synonymously with regional and widespread pain (89;161) although localized pain sometimes are referred to one or two painful sites (183). However, the localization of pain as regional or widespread does not necessarily remain unchanged (89). Some persons initially reporting localized pain (approximately 20 %), develop widespread pain later on (34;119;124). Eighty to 85 percent of subjects with fibromyalgia reported a localized onset (13;89). Several researchers suggest that there may be a continuum from localized to generalized muscle pain (44;159). The modulation of pain in the complex pathway between the periphery and the brain may indicate how pain may spread from one site to “all over” (131;153).

1.1.3 Nociception from muscles

Pain is the experience associated with tissue damage, but not necessarily tied to the stimulus. Nociception is the stimulus, generally perceived as pain, initiated by real or potential tissue damage (154;189).

The muscle nerves contain efferent fibres from motoneurons and sympathetic fibres, and afferent sensory thick myelinated A β , thin myelinated A δ , and unmyelinated C fibres. The A β terminate as organized endings in the muscle spindles and tendon organs and the A δ and C fibres as free nerve endings in the wall of the arterioles in muscle bellies and connective tissues. A β fibres are activated by low threshold non-noxious mechanical stimulation such as movement, vibration, and compression of the muscle belly. The A δ and C fibres are nociceptors responding to mechanical, thermal, and chemical stimuli intensities considered to be tissue threatening or having the potential to be tissue damaging. They respond to noxious squeeze of the muscle belly, non-physiological stretch, maximal contractions, and contractions during ischemic conditions (154). Receptors for various pronociceptive (facilitating) substances such as bradykinin, serotonin, substance P, potassium ions, histamines, adenosine triphosphate (ATP), protons (low pH), and prostaglandins, and also receptors for adrenaline and noradrenaline are sited at the nerve endings.

A cascade of events follows an injury of the muscle tissues. Pronociceptive substances are released from damaged cells facilitating an inflammatory process. Several of these substances produce vascular changes in the tissues, thus contributing to the inflammation process itself, and excite or change the chemo- and mechanosensitivity in the A δ and C fibres

(189). The nociceptors become sensitized (peripheral sensitization), that is; creating a stronger impulse at a lower pain threshold. It has also been suggested that sensitization of nociceptors appears during ischemic contractions with accumulation of various metabolic substances, such as potassium, ATP and lactate (5;78;154).

The muscular afferent nerves terminate at second order neurons, the nociceptive specific (NS) neurons and the wide dynamic range neurons (WDR), in the dorsal horn. The NS neurons only responds to nociceptive stimulation while the WDR neurons, which receive input from A β , A δ and C fibres, respond to both noxious and non noxious stimuli (131). The dorsal horn neurons receiving input from the muscle nociceptors most often also receive convergent input from cutaneous receptors and other deep somatic tissues which may be an explanation of the diffuse features of muscle pain (151). High and prolonged nociceptive activity in primary afferents may result in central sensitization defined as changed permeability of the WDR neuron membrane, increased excitability, spontaneous discharge, and expansion of the receptive fields (131;152). Normally these plastic changes diminish when the triggering stimulus ends. However, learning processes may contribute to long lasting, and under certain circumstances, also irreversible, neuroplastic changes (152;248).

From the second order neurons the nociceptive signals follow the spinothalamic and spinoreticular tract up to the brain (37;173). The axons send branches to neurons in the brain stem involved in descending pain modulation, project with neurons in the thalamus, and ascend to the somato-sensory cortex, the limbic system and brain areas involved in affect, and the hippocampus (37;116;135;173). Activation of network of the brain areas involved in acute pain has been shown by human brain imaging studies to include sensory, limbic, associative, and motor areas (33). Thus, nociception induces sensory sensations of pain, negative emotions associated with fear and aversion, arousal, motivational and behavioural responses (40), and is integrated with other sensory systems and learning and memory (33).

From the higher centres in the CNS, descending anti-nociceptive (inhibitory) or pronociceptive (facilitating) information influences most neurons in the spinal cord and modulates spinal cord activity. The responses from nociceptive deep input are much more strongly influenced by descending information than the responses from cutaneous input (154;189). Pathologically alterations of these antinociceptive or pronociceptive systems may contribute to increased activity and responsiveness of the neurons and lead to sensitization and chronic and widespread pain (153). The nociceptive pathways represent homeostatic networks and both painful and non-painful (such as A β fibre activity) somatic and visceral

stimuli as well as emotional and cognitive processes can activate this network (33;37;61;135;144).

1.2 Psychological and physiological stress.

The use of the term stress is ambiguous as it represents both a stimulus and a response. Stress, originating from the word “strain”, is used as a force applied on or disturbing the homeostasis of the body. The other meaning of stress originates from the word “distress” and is a reaction and a response (117;118). The term stressor is often used to distinguish the stimuli from the response (190). During physical and psychological stress the body must adapt in order to handle or escape the stressor or threat. Stress may be any environmental or internal stressor, such as injuries, pain, infections, physical exercise, mental challenges, and emotional distress. The two main systems activated during stress are the sympathetic nervous and adrenal (sympathoadrenal) system and the hypothalamic-pituitary-adrenal (HPA) axis. Activation of stress systems is complex and finely tuned with different regulation of body parts and effector cells (73;74). The biological responses to a stressor depend on type and intensity of the stressor and on characteristics of the individual, such as psychological and biological status, novelty, the perception of threat, and the perceived ability to control the stressor (73;74;170;172). Hence, the individual variations in response to a stressor are great. Noradrenaline is the main transmitter released from the sympathetic postganglionic nerve fibres which innervate smooth and cardiac muscles, glands, and gastrointestinal neurons, and adrenaline is the main hormone released from the adrenal medulla into the bloodstream (230). Initiated by the hypothalamus, cortisol is released from the adrenal cortex. A potent stimulus releasing noradrenaline is exercise, whereas emotional distress and pain are potent stimuli releasing adrenaline and cortisol (73;74;172). Not only emergencies but also activities of daily life, such as changing posture and locomotion, are associated with adjustments in sympathoadrenal outflow. Several compensatory mechanisms and multiple effectors interact to keep the internal milieu optimal during changing conditions, and “maintain stability through change” (138).

Muscle activity induced by psychological stress is low compared with that caused by heavy physical exercise (195). Thus, exercise used as a stimulus to challenge sympathoadrenal and muscle activity could elucidate pathophysiological mechanisms and differences in responses between subjects with muscle pain and healthy subjects.

During muscle activation and exercise the main functions of noradrenaline and adrenaline (catecholamines) are to induce blood vessel constriction and distribute blood flow

to active muscles, increase heart rate and blood pressure, and release glucose and fatty acid for energy mobilisation (65;151;170). The complex interaction between noradrenaline and adrenaline, which may have opposite effects on blood vessel constriction, and local metabolic factors, determines whether the blood vessels constrict or dilate (35). The main functions of cortisol are to participate in energy mobilisation and release glucose. Sympathetic activity increases through a central feed forward mechanism from higher motor centres and afferent feed back stimulation from contracting muscles (67;113;114). Similar control mechanisms are assumed for the HPA-axis responses (113). The increase in catecholamine and cortisol concentrations in the blood is dependent on intensity, duration, and mode of exercise (66;112;115). Fitness level, age, smoking, and medication are other factors of importance (73;110;111;142).

Under normal conditions- the catecholamines do not sensitize or activate nociceptors (97;152). A possible influence of sympathetic activity on muscle pain and sensitization of nociceptors is indirectly through the vascular bed and changes of tissue blood flow and changes of the micromilieu (97).

1.3 Hypotheses of chronic muscle pain

1.3.1 Alteration in muscle activity patterns

Several hypotheses on the relation between muscle activity and pain have been proposed. The “vicious circle” and the “pain adaptation” model are the two main hypotheses (104;105;129).

Hyperactivity and increased muscular tone was initially regarded as a possible source of muscle pain (221). This hypothesis has further been developed into the “vicious circle hypothesis” (105). It is thought that noxious stimulation of the muscle, for example by metabolites produced during static exercise, causes muscle spasms through activation of α and γ motor neurons in the muscle spindles. These muscle spasms would again cause further pain and contribute to a vicious circle of pain and muscle contractions. Through the spinal cord, via the dorsal horn cells and the connections with other muscles, the muscle activation and pain could spread to other areas and perpetuate itself by activating afferents in the muscle spindles in the homonymous and heteronymous muscles (104;105). The increased activity in nociceptors is thought to increase sympathetic activity and further contribute to the vicious circle of pain (104).

On the other hand, the “pain adaptation model” proposes that pain reduces agonist muscle activation and increases antagonist activation (129). This is thought to be an adaptive

response to pain as the muscle is protected from further damage. The “pain adaptation model”, however, does not propose a mechanism for the initiation of muscle pain, but explains the consequences of muscle pain.

Hypoxia, ischemia, and disturbed local microcirculation are suggested as being involved in the pathogenesis of FM and muscle pain disorders (12;89). Several findings, such as moth-eaten, ragged red fibres, mitochondrial abnormalities, and lower levels of ATP and phosphocreatine in the trapezius muscles (14), indicate an association with metabolic and muscle activity abnormality (12). However, several of the findings were believed to be due to secondary inactivity related changes, and have also been found in healthy subjects. It has been suggested that tension myalgia with sustained muscle contraction could be present (vicious circle hypothesis). Elevated muscle tension has not been found at rest (50;250). Some studies however, found that muscular tension persisted between muscle contractions, interpreted as that pain reduced the ability to relax (55;56). Conversely, if muscle pain inhibits agonist muscle activity (“pain adaptation” model) one would expect lowered muscle strength and oxygen uptake. Both normal (55;56;149;165;232) and reduced (7;20;94;197) muscle strength and fitness level are reported. Whether the lowered muscle strength and fitness level was due to lower central drive, for example as a result of inhibition by pain or lower effort, or pathological alterations in the muscle tissues, has not been clarified. In myofascial pain syndromes, dysfunction of the motor endplate, either as presynaptic, synaptic, or postsynaptic dysfunction related to release or uptake of acetylcholine, with muscle hyperexcitability and sustained contraction as a consequence, has been suggested (140;192;194). The causes of myofascial endplate dysfunction and muscle tension has, however, not been convincingly demonstrated (59). There is evidence that increased autonomic activity may also increase endplate noise (59;178).

1.3.2 Alteration of sympathoadrenal and HPA axis responses

In recent decades, altered responses from the sympathoadrenal system and HPA axis have been suggested as part of the pathogenesis of FM (7;41;169;228;229;233). Both elevated and decreased sympathoadrenal activation during resting conditions have been reported. Decreased pain was observed in FM patients after ganglion stellatum blockade, suggesting that increased sympathetic activity might contribute to the pain (7). On the other hand, attenuated sympathoadrenal and cortisol responses were reported after stimulation tests (43;81;164) and during exercise (54;149;167;229) suggesting decreased activation. Thus, the results seem contradictory, but it has been suggested that chronic sympathetic activation

induces increased levels of sympathetic activity at rest and attenuated levels after challenges (233). It is hypothesized that prolonged activation of the sympathetic nervous system and HPA-axis may overload the system resulting in diminished responses to acute stressors due to decreased responses from the cardiovascular and metabolic systems (7;41;169;228;229).

Fitness level is a known confounder of sympathoadrenal responses, and was seldom taken into consideration in previous studies. Furthermore, few of the above mentioned studies compared the catecholamine and cortisol responses with pain reported during exercise.

1.3.3 Peripheral and central sensitization

The peripheral and central sensitization processes are assumed to be important for the maintenance and spread of muscle pain (5;80;152). Muscle abnormalities may contribute to the sensitization process as input from muscle nociceptors is powerful in maintaining central sensitization (242). Alterations of sympathoneural responses and neuroendocrine abnormality may contribute, as well as the influence of emotional and cognitive factors on descending pain modulation pathways (61). The subjective response that is assumed to represent sensitization, either of the peripheral nociceptive receptors or that occurs within the CNS, is hyperalgesia, and is manifested by enhanced pain to noxious and non-noxious (allodynia) stimuli, and expansion of referred pain areas (79;153;154;246).

Hyperalgesia and abnormal nociceptive processing at the CNS level are mechanisms associated with the fibromyalgia syndrome (12;77;169), and also with low back pain and whip-lash associated disorders (71;76;89;205;209). Increased levels of substance P and nerve growth factor have been found in the trapezius muscle and in the cerebral spinal fluid in subjects with FM (72;184;227) Liu, 1995.

Increased sensitivity to innocent mechanical stimuli such as muscle contractions, touch, and thermal stimuli, has been found in fibromyalgia (77;120;121;244). Induction of hypertonic saline enlarged expansion of referred pain areas compared to healthy controls, and hyperalgesia was also present in non painful muscles (4;198). Furthermore, reduced effect on pain inhibition and alterations in descending pain modulation pathways have been found (120;203), and functional magnetic resonance imaging (fMRI) showed augmented central pain processing in subjects with fibromyalgia compared to healthy individuals (77). These response characteristics are suggested to be the result of sensitisation (5). Whether the sources that trigger the mechanisms of sensitization in fibromyalgia are of peripheral or central origin has not been clarified (12;141;201;233).

1.3.4 Psychological factors

There is little evidence of a psychological origin of pain in the absence of physical pathology (40;89). However, there is often a mismatch between objective findings and symptoms (49;158), and there is evidence for the importance of psychological factors in amplification and maintenance of pain (33;40;83;231). Substantial research has been conducted in order to gain better understanding of the psychological process contributing to pain.

Emotions, attention, interpretation, and learning can modulate pain perception (33;63;234). Catastrophe thinking, i.e. the tendency to overestimate the threat and seriousness of pain sensations, with increased attention to bodily symptoms and fear avoidance beliefs have been emphasized in recent years as an important perceptual characteristic and the behavioural dimension through which pain may be maintained over time (235;240). Attention to potentially painful events is suggested to be the mechanism by which catastrophizing influences pain experience (216). These thoughts and beliefs about pain may contribute to reduction of re-learning, correction of previous negative experiences, and lead to impaired functioning and maladaptive coping (63).

The neurological basis for the relations between emotions and pain remains unclear. Melzack (144) suggested that experience may modify pain processing, and factors that increase the sensory flow of pain signals may alter central thresholds of excitability and neural architecture over time. Several investigators have reported alterations of brain areas associated with pain sensation, motor control, and negative emotions and affect in chronic pain patients including low back pain, fibromyalgia, and tension type headache (3;9;37;134;173). Processes that were initially psychological in nature may become increasingly physiological and, in a bidirectional way, potentially self-sustaining (216). Learnt pain memories may be stored in several brain areas and affect future pain sensitivity (33;63;77). It has also been shown that neutral cues associated with a pain experience can evoke a painful sensation in the absence of a noxious stimulation (33).

Hypervigilance to pain, but also to other stimuli such as sound and light, has been shown in fibromyalgia (137;181). Catastrophe thoughts have been shown to induce increased emotional distress and more intense pain during painful stimulation both in healthy and in subjects with painful conditions (216). Increased emotional responses to pain, augmented pain processing, and cerebral activation were shown in subjects with fibromyalgia with a high degree of catastrophe thoughts compared to those with low (76). Subjects with chronic low back pain, who perceived that exercise increased pain, showed poor performance of exercise

tasks and avoided physical activity independently of actual reports of pain. Their rationale for avoidance was not pain but their learned expectation of heightened pain in response to activity (63).

1.4 Pain assessments

Because pain is a subjective experience it is only accessible through communication by verbal reports and /or behaviour from the person experiencing pain. In order to understand and evaluate pain and the mechanisms associated with the pain experience, it must be assessed, and self reports are the most common assessment tool (100;226). Reliable and valid assessment methods are essential for providing effective management of the musculoskeletal disorders and evaluating treatment effects. There is no gold standard in how to assess pain, and no single assessment method is able to capture the complexity of the experience. Pain may vary from moment to moment, and across different time intervals. The methods applied, the time intervals chosen, the state of the person, and the context, influence the reports.

Pain may be assessed in the actual situation (real-time pain) or retrospectively as a recall of previous pain. The ability to correctly retrieve previous episodes and whether the experience is consciously recalled or simply “known” have been questioned (58;223;224). The recall of pain is assumed to be retrieved from the episodic and/or the semantic memory (224). The episodic memory refers to unique personal experiences dependent on the particular time and place. The semantic memory is beliefs about one self, independently of retrieval of specific events, and refers to general facts and meanings shared with others (179;224). The ability to retrieve episodic information declines over time, while the semantic information is thought to be resistant to forgetting and interference (224). Studies investigating the involvement of episodic and semantic memory in recalls of pain intensity and pain quality indicate that the recalls are often based on the respondent’s beliefs about pain, i.e. involvement of the semantic memory, rather than consciously recalled (30;218;219).

It has been indicated that recalled and real-time pain (70;213), pain reported during activity and daily life (236), and experimental and clinical pain (58;175), may represent different aspect of the pain experience. The long term implications of having chronic pain compared to transient or acute pain episodes is thought to have different impact on a persons identity and life, with the affective component of pain being of greater influence in chronic pain (157;175;241). Hence, chronicity may have greater influence on recalls than real-time ratings of pain. It has also been suggested that contraction induced pain reported during exercise and chronic pain reported during every day life relate differently to function and

disability (236). The “contraction induced” pain was paralleled with transient acute pain, while persistent pain reported during every day life represented the chronic state (236). Furthermore, transient pain episodes induced in experimental settings are nonthreatening and probably less uncontrollable and open ended than clinical pain (175). Different contexts and assessment methods may therefore capture different aspects and mechanisms related to the pain experience.

1.4.1 Pain intensity

The pain intensity is the most common category to assess in musculoskeletal pain disorders, either by 100 mm visual analogue scales (VAS) or 0-10 numerical rating scales (NRS) (127). These scales, however, reduce a complex phenomenon into a single dimension. Although the VAS and NRS have shown acceptable validity i.e. closely related to other pain measures and pain behaviour, and reliability (100;174;175), the rating of an experience with linear properties is questioned by several authors (29;46;146). The number rated has been shown to incorporate a variety of internal and external factors related to complex personal meanings (46), and there was a lack of consistency between and within patients in the way they derived their ratings (29;46).

Pain intensity is often assessed by recall of previous pain during a certain time interval, often a week. However, the peak pain intensity during the recall period, the pain intensity and emotional state at the moment of recall, and pain closest in time to recall, are among factors influencing the reports (53;95;96;177). In recent years multiple ratings of the real-time pain intensity have gained increasing attention due to the lack of recall bias. In several studies this method has been used as a “gold standard” of the actual pain intensity experienced during a specified time interval (24). Acceptable concurrent validity between real-time and weekly recalled pain intensity has been reported (24;95;186), but overestimation of recalls was found in the majority of the studies (102;103;126;177;211).

A question of interest is whether shorter recall periods reflect the actual pain intensity during the recall period better than weekly reports. The reporting period has been shown to influence pain reports (28;212), and daily recalls were less influenced by “peak” and “end” pain intensity (101). Better accuracy in estimating previous pain has been reported in subjects with high pain intensity (96). Furthermore, subjects with a high number of painful body areas, such as fibromyalgia, have reported that pain often fluctuates between body areas with different intensity in different areas (89;244). The variability of pain accounted for a

substantial part of the variance in clinical pain (202). Thus, the magnitude of pain intensity and the distribution of pain might influence the recall of previous pain.

1.4.4 Pain quality

Only a limited aspect of the pain experience is captured by the assessment of pain intensity; i.e. how much it hurts. Another aspect is the pain qualities characterizing clinical pain. Pain quality is often assessed by verbal descriptors. However, the language used by different persons trying to describe the same pain phenomenon may have little in common. Thus, the assessment methods need to have a representative and common language, and a consistent way to evaluate pain in order to improve communication between persons with pain, health care workers, and researchers (225). For several years the McGill Pain Questionnaire (MPQ) (143) was the only questionnaire evaluating the pain quality by different sensory descriptors of pain (225). Several studies have shown that different kinds of pain have distinctive constellation of words used in the MPQ (146). However, the MPQ combines the sensory descriptors into a subscale, which may limit the information obtained of the specific pain qualities (52;100). Pain of nociceptive and neuropathic origin is thought to display different and specific pain qualities (10;246). In recent years several questionnaires have been developed in order to assess the pain qualities of neuropathic pain and to distinguish neuropathic from nociceptive pain (8;16;26;68;122). A cluster of symptoms such as hypersensitivity to touch, pain during muscle contractions, paresthesias, and burning sensations are frequent in muscle pain disorders (71;76;89;205;209;244) and partly overlap neuropathic symptoms. Similar or several mechanisms may operate within and between the different pain types (10;246). Thus, assessment of the pain quality may shed light on factors and mechanisms associated with these symptoms in muscle pain conditions.

1.4.1 Pain localization

Pain localization is often assessed by shading painful body areas on a pain drawing (100). The reliability of pain drawings is reported to be high (132), and they assess the sensory distribution of pain well (100). Several studies have reported an association between pain drawings and psychopathology with excessive marking as a sign of symptom amplification and somatization (100). However, it is emphasized that pain drawings are not the proper instrument to evaluate psychopathology, and one must be careful to extend the interpretation beyond the main purpose of the drawing by which it is known to be valid, i.e. the sensory distribution (100). Nevertheless, pain distribution and number of painful body areas have been

shown to be positively associated with somatic and psychological problems, functional limitations and problems in daily activities and social life, female gender, and work disability (45;107-109).

1.4.4 Affective aspects of pain

Pain affect may be defined as “the emotional arousal and disruption engendered by the pain experience” (100). The assessment of this dimension has been subordinated for many years compared to the extensive assessments of the sensory dimension (40;100;226), and is thus less explored. Pain affect is assumed to be more complex and less homogenous than pain intensity, and assessments of pain affect are less likely to be strongly related (100). In chronic pain states the secondary stages of pain affect, “suffering”, which is the long term and cumulative emotional and cognitive implications of the pain experience, are thought to be a dominating phenomenon (175;241). Evaluation of the emotional alterations in the person with chronic pain is therefore important, as reduction of this dimension might be a major target for treatment. Pain affect may be assessed directly by the intensity of the immediate unpleasantness or the secondary “suffering” on VAS (241), by the verbal affective descriptors in the MPQ (143) or by more general assessments of emotional distress or quality of life. The latter methods do not directly link the affect to pain. However, emotional distress as a consequence of pain or as a predisposing or perpetuating factor may influence the reports of pain in subjects with chronic pain.

2 Aims of the study

The first aim of the thesis was to investigate whether sympathoadrenal responses were attenuated and related to pain intensity in persons with generalized muscle pain. Another aim was to investigate factors of importance for the variation in reports of pain intensity and sensory symptoms in persons with localized and generalized musculoskeletal pain.

The specific aims were:

- To investigate whether sympathoadrenal responses during exercise were attenuated and associated with pain intensity, perceived exertion, and muscle fatigue, in subjects with fibromyalgia compared to healthy controls.
- To evaluate the reliability of two different pain assessment strategies of recalled pain intensity and their concurrent validity with real-time pain during every day life in subjects with localized and generalized musculoskeletal pain

- To investigate whether pain intensity, number of painful body areas, and emotional distress, were associated with neuropathic symptoms in subjects with musculoskeletal pain

3 Materials and methods

3.1 Designs

An experimental approach was used in papers I and II to investigate sympathoadrenal, pain and muscular responses during dynamic bicycling and statistic repetitive contractions to exhaustion, followed by descriptive recordings of symptoms one week after the day of the experiment. In papers III and IV a prospective longitudinal design was used to investigate reports and clinical presentations of recalled pain conducted across a four months period, and real-time registrations of pain intensity in the fourth month.

3.2 Subjects

Subjects comprising different diagnoses of musculoskeletal pain lasting for at least three months, recruited from the Fibromyalgia Association, primary health care in Oslo, and from Oslo University Hospital Ulleval, were included. Six of the women in paper I also participated in paper II, and one woman participated in papers I-IV. Matched healthy controls were included in papers I and II, and six participated in both papers I and II.

An overview of the participating subjects and some of the characteristics is given in Table 1. A more detailed description is given below.

Table 1. Study population in the separate papers; subjects with fibromyalgia (FM), healthy controls (C), and subjects with musculoskeletal pain (MP), including subgroups with localized (LP) and generalized (GP) pain.

	Paper I		Paper II		Paper III			Paper IV
	FM N = 15	C N=15	FM N=19	C N=19	MP N=90	LP N=40	GP N=50	MP N=86
Age (yrs), Mean (SD)	36(6)	36(7)	37(7)	37(7)	48(12)	46(13)	50(11)	48(12)
Employment (n)								
Full / part time	100%	100%	100%	100%	47%	63%	34%	49%
Sick leave /Pension					53%	37%	66%	51%
Education (n)								
Vocational<13 yrs	33%	0%	53%	21%	54%	40%	66%	55%
Academic>13 yrs	67%	100%	47%	79%	46%	60%	34%	45%
Pain duration(yrs) median (IR)	11 (6-13)	0 (0)	10 (6-8)	0 (0)	10 (4-20)	6 (2-10)	15 (8-20)	10 (5-20)
Tender points, median (IR)	14 (14-16)	1 (0-3)	16 (14-17)	0 (0)	11 (4-15)	4 (1-8)	14 (12-16)	12 (5-15)
Physical activity(n)								
Regular exercise	33%	33%	47%	47%	32%	30%	34%	35%
No regular exercise	67%	67%	53%	53%	68%	70%	64%	65%

In papers I and II, all subjects were working at least 50% or at home with small children attending kindergarten for less than four hours a day, and were between 18 and 45 years of age. Thirty four women with fibromyalgia fulfilling the ACR criteria of 1990 (244) were included. Subjects with any coexisting diseases were excluded. Healthy women were recruited by advertising or by inquiries at the National Institute of Occupational Health in Oslo and institutions localized nearby, and individually matched to the women with FM with respect to age (± 5 years), smoking habits, and self reported number of weekly exercise sessions. Healthy subjects who had been on sick leave due to musculoskeletal pain during the past three months were excluded.

In papers III and IV, 103 subjects with musculoskeletal pain were included. The inclusion criteria were age between 18 and 70 years and tender muscles on palpation. The exclusion criteria were surgery during the investigation period, inflammatory rheumatic disorders, and painful medical conditions apart from those affecting the musculoskeletal

system. The subjects included in paper IV did not have clinical and verified signs of nerve affliction. Twelve subjects were drop outs. Thirty nine of the subjects completing the protocol fulfilled the ACR criteria for fibromyalgia (244). Another ten subjects had pain distributed bilaterally, in the upper and lower part of the body, and axial pain. One subject had left side and axial pain. All had five or more painful body areas according to Natvig et al.’s description (123;160;162) and classified as generalized pain (GP) in paper III. The remaining 40 subjects had shoulder pain (n=23), low back pain (n=12), and neck pain (n=5), and were classified as localized pain (LP) in paper III. One subject fulfilling the ACR criteria was excluded due to missing data in paper III, and five other subjects (one with generalized pain, and 2 with shoulder and low back pain, respectively) were excluded in paper IV due to suspected nerve affliction. A subsample of 50 subjects (23 with LP and 27 with GP) completed real-time pain intensity registrations in month 4 (paper III).

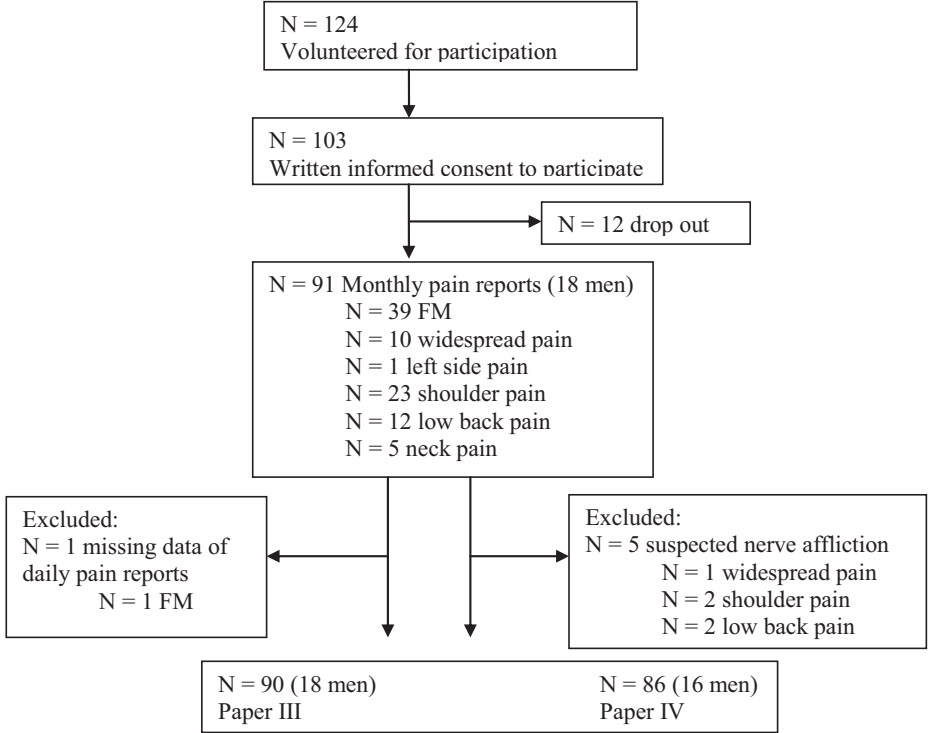


Figure 1. Flow chart showing subjects included in papers III and IV

3.3 Ethics

All participating subjects were informed by verbal instruction and written information about the project, and gave their written consent to participation. The project was approved by the Regional Committee of Medical Research Ethics.

3.4 Methods

3.4.1 Procedures

All subjects underwent a clinical examination including examination for the ACR criteria for fibromyalgia (244) and muscle tenderness. At inclusion, medical history, socio-demographic data, and current pain status were registered. Blood tests for rheumatic and thyroid dysfunction were taken, and anti-depressive medication was terminated 3 weeks before the experiments (papers I and II). Tender points were counted. Painful body areas were shaded on a pain drawing, and a Norwegian pain questionnaire after a model of the McGill Pain Questionnaire (NMPQ) (214), a Norwegian version of the Fibromyalgia Impact Questionnaire (FIQ) (31), and a musculoskeletal health complaint inventory (57;207) were filled in (papers I-IV). Emotional distress was registered in the Hopkins Symptom Checklist (HSCL), and pain intensity during the last seven days was recorded on VAS (papers III and IV). Sensory symptoms and signs were registered in the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (16) (paper IV). Thorough information and detailed protocol instructions were given. The subjects were divided into the GP and LP group after evaluation of medical history and counts of number of painful body areas shaded on the pain diagrams (paper III).

The questionnaires and scales selected for the specific investigations were answered and filled in as a baseline registration on the day of the experiment (papers I and II) or immediately before the first investigation week (papers III-IV).

Exercise protocols (papers I and II): When the subjects arrived at the laboratory a catheter was placed in an antecubital vein, and the selected questionnaires were filled in.

The subjects bicycled on an ergometer (paper I) with a pedal frequency of 60 revolutions per minute with an incremental increase of 22.5W in workload every second minute until exhaustion. The bicycling was terminated when the subjects could no longer maintain the pedal frequency despite verbal encouragement.

During the static repetitive exercise (paper II) the subjects were seated in a specially constructed chair (STAMI, Oslo, Norway) with the knees flexed 100⁰, and the trunk reclined against a backrest with a strap around the lower waist to reduce hip extensor contraction. Each

leg was connected to a strain gauge through a bar anchored around the leg above the malleoli. MVC was determined as the highest force, measured in Newton (N), obtained during three separate maximal contractions of 4 s duration. If the highest force was obtained in the third contraction, additional contractions were performed until stable force was achieved. Subsequently, the subjects carried out repetitive isometric contractions of both quadriceps muscles at 30% of maximal voluntary contraction (MVC). The 30% MVC was held for 6 s with 4 s rests between the contractions. Every sixth minute, a 4 s MVC substituted the 30% MVC contraction. Visual feedback of force was given on a computer display unit. Exhaustion was defined as the point when the subjects could no longer maintain the target force for 6 s. A staff member blinded to whether the subjects were patients or controls gave verbal encouragement, checked that the 30% MVC was held for 6s, and defined when exhaustion was reached. The repetitive isometric contractions were followed by a 30 minutes rest period, interrupted by attempted maximal knee extensions at one, five, ten, fifteen, twenty, and thirty minutes.

Blood samples were collected and pain intensity was recorded on VAS at baseline, at regular time intervals during exercise, and after one and five minutes of recovery. Oxygen uptake (VO_2) was determined by sampling expired air and perceived exertion was registered at Borg CR10 scale (25) at similar time points as pain intensity during exercise. Heart rate (HR) was recorded continuously every five seconds during dynamic exercise (paper I). During static repetitive exercise (paper II) HR, mean arterial pressure (MAP), bilateral electromyography (EMG) from the vastus lateralis and force were recorded and streamed to a hard disk for offline analyses. All measurements and registrations were obtained at least one minute after a MVC (paper II). For further information of the measurement procedure see papers I and II.

Pain and symptom registrations over 4 months (papers III and IV): Pain questionnaires were answered during the first week of the month for four consecutive months (Figure 1). Pain intensity during the last 24 hours (daily recalled pain) was recorded every day on 7 consecutive days (paper III). On the eighth day, pain intensity during the previous 7 days was recorded (weekly recalled pain), sensory symptoms were rated in the LANSS, and the subjects shaded painful body areas on a body pain diagram (papers III and IV). After three weeks without any data collection, this procedure was repeated. During the fourth month, multiple reports of the real-time pain intensity were collected during the week (paper III). For a more detailed description of the procedure see paper III.

3.4.2 Measurements

VO₂ and respiratory exchange ratio (R) (papers I and II) were estimated by standard procedures after measuring collection time and the content of O₂ and CO₂ (Ametek Carbon Dioxide Analyzer CD-3A and Sensor P-61B, and Flow Control D-2, Pittsburg, USA, AEI Technologies Oxygen Analyzer S-3A/1 and Sensor N-22M, Pittsburg, USA and K.L. Engineering Co, Flow Transducer K520, California, USA).

HR (paper I) was recorded every five seconds by Polar Advantage sport tester. During exercise the mean heart rate was calculated for the second minute of each workload.

HR, MAP, bilateral EMG from the vastus lateralis, and force (paper II) were recorded and streamed to a hard disk for offline analyses (paper II).

HR and MAP were measured by the Peñaz principle with a cuff on the third finger of the left hand (Finapres, Ohmeda, USA). The height difference between the third finger and the xiphoid process was measured in each individual, and the MAP values were individually corrected according to these differences.

EMG was recorded by bipolar surface electrodes (EMG, Blue sensor E-10-VS, 2 cm interelectrode distance Medicotest A/S, Ølstykke, Denmark A/S). The electrodes were placed on the belly of vastus lateralis, 1/3 of the thigh's length from the top of patella. The signals were amplified 1000 x (band-width 10-3000 Hz, CMRR > 100dB, input impedance > 5 GΩ, Preamplifiers, Premed, Oslo, Norway), and additionally amplified 2 x in an isolation amplifier (EMG-ISO-01, NIOH, Oslo, Norway), equipped with a first-order bandpass filter 10-1000 Hz.

Blood analyses (papers I and II): The blood samples were analysed for concentrations of adrenaline (Adr), noradrenaline (NAdr), cortisol and lactate. Glucose concentrations were measured to control for hypoglycaemic stimulation of the sympathetic nervous system. Plasma Adr and NAdr were measured by HPLC (91), and lactate and glucose were measured in full blood by enzymatic fluorometric methods (171). Plasma cortisol was measured by the RIA method (Coat-A-Count, Diagnostic Products Corporations, Los Angeles, USA).

Physical activity level (papers I-IV) was defined as number of weekly exercise sessions making the subjects sweat and short of breath lasting for more than 20 minutes. The alternatives were: below once a week, between 1 and 2 times a week, and above 2 times a week (papers I-IV).

Perceived exertion (papers I-II) during exercise was assessed by the Borg CR10 rating scale of perceived exertion ranged from zero (nothing at all) to 10 (extremely strong).

Standardized general and specific instructions following the CR10 scale were used (25) (papers I and II).

The Fibromyalgia Impact Questionnaire (FIQ) (31) contains 19 items. Pain intensity, fatigue, morning tiredness (papers I and II), and depression (paper IV), during the last seven days are scored on 100 mm visual analogue scales (VAS). The end points 0 and 100 mm represented “no pain” and “worst possible pain”, “no fatigue” and “completely exhausted”, “waking up completely refreshed” and “waking up completely exhausted”, and “not depressed” and “as depressed as possible” for pain, fatigue, morning tiredness, and depression, respectively. One and 7 days following the exercise tests, the subjects were asked identical questions about pain, fatigue and morning tiredness to those in the FIQ (papers I and II). Ten items contain the dimension of functioning last week, and are scored on a 4 level Likert scale from 0 (always) to 3 (never). These items are totalled in a score termed FIQf with a range from 0 to 30 (papers III and IV).

Recalled pain intensity (papers III and IV) was scored on a 100 mm VAS with end points “no pain” and “worst possible pain”. The subjects were asked to rate the “least”, “usual” and “highest” pain intensity during the last 24 hours (daily recalled pain) (paper III) and during the last 7 days (weekly recalled pain) (papers III and IV) by placing three marks on a VAS (241). Only recall of the “usual” pain intensity is considered in the data analyses in the thesis (papers III and IV). Weekly recall of pain intensity “during exercise” was scored on a VAS (paper IV). The average daily pain over one week (daily_w) was calculated as the mean of 7 daily ratings (paper III).

Real-time pain intensity (papers I-III) was rated on a 100 mm VAS with end points “no pain” and “worst possible pain” during exercise (papers I and II). The differentiation between pain intensity and perceived exertion was emphasised.

Real-time pain intensity during every day life was rated on an 11 point Numeric Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain) (paper III). Five coded text messages from a mobile telephone were sent at random time intervals between 9.00 am and 9.00 pm on five consecutive days. A coded answer was returned immediately. Reports returned more than one hour after sending were excluded from the data analyses. Subjects returning less than three reports per day across four days were excluded. The ratings were converted to a 0-100 scale and calculated as the mean of 25 ratings (5 ratings per day x 5 days), denoted average real-time pain (real-time_w).

A validated Norwegian version (214) of the McGill pain questionnaire (MPQ) (143) was used, including a pain drawing (papers I-IV). The questionnaire comprises pain

descriptive words representing the sensory, affective and evaluating components of the pain experience during the last week. A total score (range 0-112.5), and sensory (range 0-71.3), affective (range 0-32.9) and evaluative (range 0-8.6) subscales were calculated. The number of words marked (range 0-18) was counted.

Painful body areas during the last seven days were shaded on the pain drawing depicting the front and the back of the human body (papers I and IV). Number of painful body areas (range 0-10) was counted according to Natvig et al.'s description, and included pain in the head, neck, shoulders, upper back, elbows, hands/wrists, lower back, thighs, knees, and ankles/feet (123;160;162) (paper III). To obtain a more detailed count of affected body parts, the number of painful body areas was counted according to Staud et al.'s description (range 0-50) (206) (paper IV).

The ACR criteria (244) require eleven painful out of 18 defined points by palpation of a 4 kg pressure, and widespread pain for at least three months to fulfil the diagnostic criteria for fibromyalgia. Widespread pain is defined as pain on both sides on the body, above and below the midline, and axial pain.

The Musculoskeletal Complaint Checklist (57;207) includes 12 musculoskeletal complaints (head, neck, left and right shoulder/upper arm, respectively, left and right hand, respectively, upper back, lower back, legs, and chest) rated over the last 7 (paper III) and 14 days (papers I and II). A musculoskeletal complaint severity index (MSI – index range 0 to 9) was computed as a mean of an intensity score (range 0-3) and a duration score (number of days in pain, range 0-3) (papers I and II) (207).

Hopkins Symptom Checklist version 25 (HSCL-25) is a short version of the Symptom checklist (SL-90) (48) and a Norwegian translation was used (187;188) to register emotional distress (papers III and IV). It is scored on a 4 level Likert scale ranging from 1 (not at all) to 4 (very much), and contains 25 items, comprising the dimensions of somatisation, depression and anxiety. The scores of the items are totalled and then divided by 25. In women a mean symptom score of 1.75 or more has been reported to be a good predictor of current help-seeking, and is often used as a cut-off point (187).

Neuropathic symptoms and signs were assessed by the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (16). The LANSS was developed to assess the clinical signs of neuropathic pain, and to identify patients in whom the pain experience was dominated by neuropathic mechanisms. The questionnaire contains 5 items comprising questions of dysesthesia, autonomic dysfunction (altered appearance of painful area), hypersensitivity, evoked pain, and thermal qualities, and 2 items requiring testing for

allodynia and pin prick threshold. The item responses are weighted and the sum score ranges from 0 to 24. A score of 12 or more is the cut-off applied regarding diagnosing a neuropathic pain disorder. When the present study started the self-report questionnaire of the LANSS (S-LANSS) (17) was not available. Hence, the 5 first items were used as a self-report questionnaire. When only the self-reported items were used the maximum score was 16.

The LANSS did not exist in a Norwegian version, and was translated into Norwegian after accepted procedures (82). The questionnaire was translated into Norwegian by one professional translator with no health professional background and one Norwegian health professional who had been living and practising in the UK and Norway. The questionnaire was back translated into English by two bilingual translators, whose first language was English. The final Norwegian version was developed after reviewing and discussing the discrepancies with the translators at each step of the processes.

3.4.3 Data processing (paper II)

The force, HR, MAP and EMG data were converted from analogue to digital with a frequency of 2500 Hz (16 bit A/D card, AT-MIO16 x, National Instruments, Austin, TX, USA) and stored by Labview (National Instruments, Austin, TX, USA) for offline analysis. Force, HR, MAP, and root mean square EMG amplitude values were calculated over 0.2 s time periods.

Noise level for the EMG was defined individually for each subject as the lowest amplitude 0.2 s data point within the first baseline registration, and subtracted from all EMG data. The EMG amplitude during MVC was calculated as the highest mean of 5 consecutive 0.2 s values. Maximal voluntary electrical activity (EMG_{max}) was defined as the highest EMG amplitude obtained during the MVCs at baseline. The EMG amplitude during repetitive isometric contractions is given in per cent of the EMG_{max} values, but analyses from absolute EMG amplitude during contractions are also given.

During repetitive isometric contractions, the mean EMG amplitude during each contraction and rest period were calculated omitting the first and last seconds of all periods. The mean values over one minute for the contraction and for the rest periods were calculated for EMG amplitude, HR and MAP. Force and EMG amplitude during MVC and during repetitive exercise were similar in both legs, and hence only reported from the right leg.

3.4.4 Statistical analyses

The estimated sample size for the exercise tests (papers I and II) was calculated based on results from Van Denderen et al.'s study (229). A difference in plasma Adr concentrations of

about 25 % between FM patients and controls, which was reported in Van Denderen's study (229), required 15 subjects in each group (1) to achieve a test power of 80 % and a significance level of 5 %. The variance obtained in the present studies was comparable to the results of Van Denderen et al.'s study.

Lack of information of the variability of repeated measurements of daily and weekly pain intensity within subjects in the literature made it difficult to perform sample size calculations of the prospective study (paper III). A general recommendation of Altman is at least 50 subjects in a method comparison study (2). Test power was calculated post hoc using Sample Power in co-operation with professor Sandvik, Department of Epidemiology, Oslo University Hospital, Ullevål. The following estimates were used: The standard deviation of repeated measurements of pain intensity within a subject is denoted X . The standard deviations of the differences in X between daily and weekly measurements were 5.2 mm on VAS in the LP group and 3.6 mm in the GP group (paper III). We assume that these standard deviations represent the corresponding true standard deviations of our study. When comparing mean X for daily and weekly measurements a two-sided paired t-test was used with 5% significance level. The following may then be shown: In the LP ($n=40$) and the GP group ($n=50$) our study will have 80% test power to detect as statistically significant a true mean difference in X of at least 2.4 mm and 1.4 mm on VAS, respectively. These calculations imply that our study has 80% power to detect a true difference of at least 2.4 / 1.4 in mean X between daily and weekly measurements in the LP and GP group. As X is measured on a 100 mm VAS, we consider differences below 2.4 mm to be clinically insignificant, i.e. our study appears to be adequately powered to detect clinically significant differences in X between daily and weekly assessments in the two groups.

Statistical analyses were conducted using the Statistical Package of Social Science. All data was inspected by histograms, box plots and Q – Q plots, and by the Kolmogorov Smirnov test. In papers I and II the subjective reports were analysed by non-parametric tests. Otherwise parametric and non- parametric methods were used according to the distribution of the data sets. Continuous and normally distributed data were presented as mean values with standard deviations (SD) or 95 % confidence intervals (CI). Ordinal and skewed data were presented as median with interquartile range (IR) or range (minimum - maximum). Group differences were presented with 95 % CI or p values. Two-tailed significance level of 5 % was adopted.

Paired sample t-tests or Wilcoxon sign rank sum test were used when comparing matched subjects or when two measurements were obtained in the same subject (papers I-IV).

Independent sample t-tests were used when comparing different groups (papers III and IV). Chi-square tests were used comparing categorical data, and Fisher exact tests were used when $n < 5$ (papers III and IV).

Repeated Measure Analyses of Variance (repeated ANOVA) (General Linear Model (GLM)) were used for the repeated measures to assess temporal changes, group differences and temporal and group interactions over time for the continuous data (papers I-IV). Due to individual differences in endurance time (papers I and II), the measurements obtained at baseline, 2, 4, and 6 minutes bicycling were included in the analyses of the repeated measurements denoted “during exercise”. During the static repetitive contractions, the measurements obtained in the first minute, at 50% exercise time, and in the last minute were included. Huynh-Feldt corrected dfs (papers I, III, and IV) and Greenhouse Geisser corrected dfs (papers II), F, and p values are given.

The Milton Friedman test was used to assess temporal changes of the repeated measurements within each group for the pain intensity and skewed data of adrenaline concentrations (papers I-II). The area under the curve (AUC) for the repeated measurements was calculated (papers I and II) and compared. For the correlation analyses (paper II), AUC was calculated for the catecholamine and cortisol responses to exercise.

Spearman’s rank order analyses of correlation (r_s or σ) were used to examine bivariate associations (papers I-IV). Partial correlation analyses controlling for group or the influence of a third variable were used in papers II and III. As differences in MVC could influence the results in paper II, a univariate analysis of ANOVA with Adr and medication as dependent variables, and MVC as covariate, was used (paper II).

Backward multiple regressions (paper IV) were performed to investigate the effect of several predictors on a dependent variable. Predictors with inter-correlation coefficients above 0.7 were not entered in the same regression analyses.

Intraclass correlation coefficient (ICC), two-way random and mixed effect for single measures, (2,1) and (3,1), were used to estimate reliability (139) (papers III and IV). Absolute agreement or consistency definition was used according to whether systematic differences were considered measurement error or not. The ICC takes into account the variability between subjects in relation to the measurement error (215). Measurement error is the variation within subjects or the agreement between repeated measurements (47). In the present studies the within subject variability was obtained by calculating the standard deviations (SD) (papers III and IV) and the average coefficient of variation (CV) (paper IV) of the repeated measurements of pain intensity and the LANNS scores, respectively.

To find whether the differences between two measurements, and the standard deviations of the repeated measurements, increased with increasing scores, the method described by Bland and Altman (22) (“Bland –Altman” plots) was applied (paper III). The differences were plotted against the means of the two measurements for each individual, and the standard deviations were plotted against the mean of the repeated measurements, respectively. The graphs were visually examined, and the associations between the means and the differences or standard deviations, respectively, were determined.

4 Main results

4.1 Exercise capacity and sympathoadrenal responses (papers I and II)

During the dynamic exercise (paper I), the FM patients exhibited significantly lower peak oxygen uptake (18.9 (3.6) vs 24.4 (4.4) $\mu\text{mol/s/kg}$, $p<0.01$) but similar heart rates (182 (8) vs 182 (9), $p=0.99$) and catecholamine responses ($p=0.07$ - 0.65 , Table 2) at exhaustion compared with the matched healthy controls. The exercise could be assumed to be very close to maximal in both groups as the mean heart rates reached age predicted maximal values, the lactate concentrations exceeded 8 mM (above 8 mM for nine FM patients and 11 controls) and the R- values were above 1.10 in both groups indicating hyperventilation.

During static repetitive exercise (paper II), the endurance time was similar in both groups (50 (20) and 47 (27) minutes, $p=0.80$). The MVC force (407 (118) N) and EMG_{max} (175 (91) μV) was significantly lower in the FM compared to the control group (574 (99) N / 251 (108) μV) at baseline ($p=0.001$ - 0.02), but the decline in relative MVC and EMG during MVC was similar in both groups ($p=0.18$ - 0.36). During the repetitive submaximal contractions, the absolute EMG amplitudes were similar ($p=0.46$) and increased in both groups ($F(1.5,26)=5.2$, $p=0.02$). However, the FM group exhibited significantly higher relative EMG amplitude during contractions periods than the controls ($p<0.01$), and thus the EMG / force relationship was higher ($p=0.04$).

The increase in adrenaline concentrations during exercise and at exhaustion was significantly lower in the FM than the control group ($p=0.01$ - 0.03 , Table 2) (paper II). No influence of MVC force on adrenaline responses was found as evaluated by a regression analysis ($p=0.38$ - 0.40). The peak adrenaline concentrations were however skewed indicating a pattern of responders and non responders. Otherwise the responses in heart rate, MAP, noradrenaline, cortisol and lactate concentrations were similar in the FM and control group

during exercise ($p=0.07-0.92$). Partial correlation controlled for group showed no statistically significant association between catecholamine and cortisol responses versus decline in fatigue (endurance time and decline in MVC) and increases in EMG amplitude ($r: -0.30$ to 0.25 , p above 0.10 for all associations).

Table 2. Adrenaline (Adr) and noradrenaline (NAdr) concentrations during dynamic bicycling and static repetitive contractions in subjects with FM and their matched healthy controls. The concentrations at rest before exercise and peak values at exhaustion are given. The Adr concentrations at rest before the dynamic bicycling were under the detection limits for several subjects. For these subjects the Adr concentrations are set to the detection limit. $N=15$ matched pairs during dynamic and $n=19$ during static repetitive exercise, respectively.

		Rest		Exhaustion	
		FM group	Control group	FM group	Control group
Adr(nM)	Dynamic	0.16 (0.15-0.27)	0.15 (0.15-0.17)	1.24 (1.00-2.27)	2.26 (1.04-3.35)
Median(IR)	Static rep.	0.17 (0.11-0.21)	0.15 (0.10-0.24)	0.38 (0.34-0.96)	1.06 (0.72-1.85)
NAdr(nM)	Dynamic	2.03 (0.75)	2.45 (0.82)	15.41 (7.05)	19.42 (7.28)
Mean(SD)	Static rep.	2.89 (1.34)	2.72 (1.32)	7.12 (2.63)	6.58 (2.06)

4.2 Pain intensity during exercise (papers I and II)

The FM patients reported widespread and considerable pain in the FIQ at baseline. No increase was reported after exercise ($p=0.27-0.58$, Figure 2).

Real-time pain intensity increased substantially and linearly during exercise in the FM group, and decreased immediately after exhaustion (Figure 2). The control group reported almost no pain during dynamic exercise. A slight increase, but significantly lower than in the FM group ($p<0.001$), was reported during static repetitive exercise. Perceived exertion recorded on the Borg scale was significantly higher after one minute's exercise and at exhaustion in the FM (10 (IR 6)) than in the control group (9 (IR 3)) during static repetitive exercise ($p<0.02$), and slightly higher at exhaustion during dynamic exercise (9(IR 6) and 8.5 (IR 6), respectively, $p=0.06$).

The catecholamine concentrations were poorly associated with real-time pain intensity (papers I and II) and perceived exertion (paper II) at exhaustion in the FM group ($r_s: -0.15$ to -0.35 , $p=0.15-0.62$). Recalled pain intensity reported before dynamic exercise was poorly

associated with peak pain intensity during exercise in the subjects with FM ($r_s=0.23$, $p=0.40$, paper I).

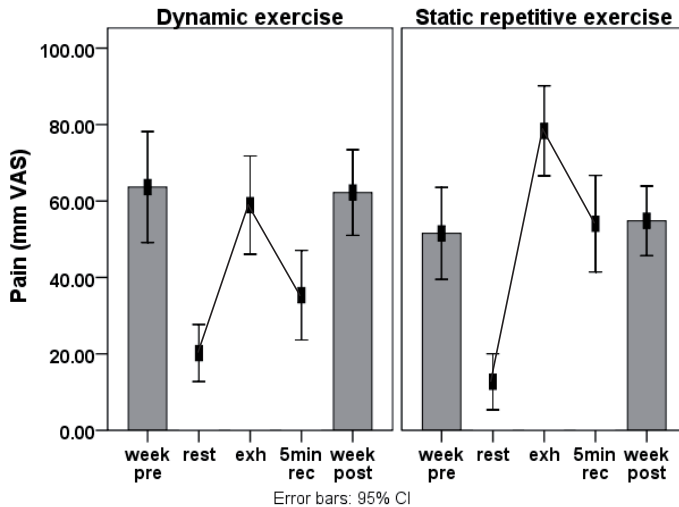


Figure 2. Weekly recalled (dark grey bars) and real-time (black lines) pain intensity reported on a visual analogue scale (VAS) during dynamic and static repetitive exercise in 15 and 19 subjects with FM, respectively. The x-axis represents the time axis. Weekly recalls are reported the week before (week pre) and after (week post) exercise. Real-time pain are reported at rest immediately before the exercise started (rest), at exhaustion of exercise (exh), and after five minutes recovery (5min rec). Mean and 95% CI are given.

4.3 Comparison of daily and weekly recalled pain intensity (paper III)

The GP group reported significantly longer pain duration, more emotional problems, exhibited lower educational level, and included more subjects out of work and fewer men than the LP group ($p=0.01-0.04$).

Recalled pain ratings were stable during the four-month period for the whole group, but weekly ratings were significantly higher than $daily_w$ ratings ($F=10.8$, $df=76$, $p=0.002$). Similar results were found in the GP group. $daily_w$ ratings decreased significantly ($F=4.7$, $df=2.7$, $p<0.01$) in the LP group, but from the second month the results were similar to those in the GP group.

The ICC was higher (better) for daily_w than for weekly ratings in the GP group (0.72 and 0.67, respectively), and a similar tendency was seen for the LP group (0.87 and 0.85). The SDs of monthly ratings of daily_w pain were significantly lower than the SDs of weekly ratings in the GP group (8(6) and 9(7) mm, respectively, CI: -2.2 to -0.2). No difference was found in the LP group (CI: -2.4 to 0.9). The SDs of both daily_w and weekly ratings were significantly higher in the GP than in the LP group ($p=0.04$), and the ICC were lower.

The SDs of recalled pain were poorly associated with emotional distress, educational level, and work situation (r_s : -0.09 to 0.14, $p=0.22$ -0.69). A weak association was found between the SDs of weekly recalls and number of painful body areas ($r_s=0.27$, $p=0.01$).

Neither the differences between weekly and daily_w recalled pain nor the SDs of the repeated measurements increased with increasing pain intensity (r_s : -0.17 to 0.25, $p=0.09$ -0.28).

Real-time $_w$ and daily_w recalled pain were similar in month 4 for both groups ($p=0.23$ -0.39, Figure 3), and the highest ICC was obtained between real-time $_w$ and daily_w ratings (0.91 and 0.87 in the LP and GP group, respectively). Weekly ratings were significantly higher than real-time $_w$ ratings in the GP group ($p<0.01$), and overestimation increased with increasing pain intensity ($r_s=0.59$, $p=0.001$).

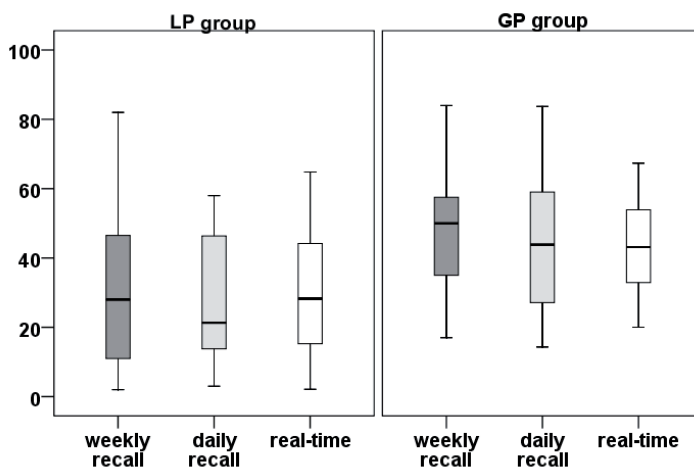


Figure 3. Weekly recalled (dark grey boxes), daily recalled (grey boxes) and real-time (white boxes) pain intensity reported on a 100 mm visual analogue scale (VAS) in Month 4 in 23 subjects with localized (LP) and 27 subjects with generalized (GP) musculoskeletal pain. The daily recalled and real-time ratings are averaged over the week. The vertical axis represents a 100 mm VAS. Percentiles (10th, 25th, 50th, 75th, 90th) are shown as box and error bars.

Four ratings were needed to obtain representative measures of the daily_w recalled pain over one week (difference from the reference mean of 7 ratings less than ± 10 mm on VAS for 95 % of the ratings). A description of the calculation is presented in paper III.

4.4 Neuropathic symptoms, pain intensity, and pain distribution (paper IV).

The mean score on the LANSS was 6.9 (SD 5.7). The frequency of sensory symptoms ranged from 9 % of the subjects reporting allodynia to 47 % reporting hypersensitivity to touch. The five self-reported items in LANSS were significantly associated with the two items representing signs. However, hypersensitivity was reported with a higher frequency than signs of allodynia and pin-prick threshold by clinical examination. Thirteen percent of the subjects scored above the cut-off of 12 in the LANSS, including 10 subjects with fibromyalgia, one subject with generalized pain, one with neck pain, and one with shoulder pain. Thus, in these subjects the sensory symptoms displayed similar features to neuropathic pain. Patients with fibromyalgia had significantly higher LANSS scores than the other diagnostic groups ($p < 0.03$), except compared to patients with neck pain ($p = 0.35$, $n = 5$). The LANSS scores were significantly and positively associated with pain duration, the diagnosis of fibromyalgia, number of painful body areas, recall of usual pain intensity and pain during exercise, emotional distress, and functioning and depression reported in the FIQ ($p = 0.01-0.04$). In backward multiple regression analyses, emotional distress and the diagnosis of fibromyalgia remained the final predictors for neuropathic symptoms. The LANSS self-report scores were stable over the four months period ($p = 0.21$), but the individual variations were large ($SD = 53\%$), and the variability increased with increasing LANSS scores ($r = 0.30$, $p < 0.01$).

5 Discussion

5.1 Methodological aspects

5.1.1 Study samples

The women with FM recruited in papers I and II were working at least part time and recruited from the Fibromyalgia Patient Association. The subjects were not older than 45 years because it was not known whether the catecholamine responses differed between pre- and post

menopausal women. The educational level in the FM group in papers I and II was comparable to that reported for women between 30-39 years in Oslo (199) (Table 1). It was however higher than reported in other studies (148;244) and than that found in subjects with GP in paper III. In addition, the subjects with FM were able to perform very close to maximal on the exercise tests. These persons therefore represent a less afflicted and younger group than persons with fibromyalgia in general. However, pain duration, pain intensity, fatigue and morning tiredness reported in the FIQ, and pain reported in the MPQ were similar to reports from other studies (86;148;150;244). Thus, the clinical symptoms were representative of the symptoms of fibromyalgia in general whereas secondary inactivity-related confounders of having the syndrome, such as lowered physical fitness and muscular strength, were reduced.

The controls, individually matched to the patients in papers I and II, exhibited higher educational level than reported in the general population. The study sample was selected, but was controlled for fitness level. We did not therefore expect any influence of educational level on the biological responses. The maximal oxygen uptake was similar to healthy untrained subjects in the general population (90;217), and the self reports of exercise frequency were probably therefore not a confounding factor in this group. Hence, the controls were representative of healthy subjects from the general population regarding the biological variables measured in papers I and II.

The persons with musculoskeletal pain participating in papers II and IV were recruited from the Fibromyalgia Association and from Ullevål University Hospital. We assume that the difference in recruitment were not the reason for the discrepancy in clinical and demographic variables found between the LP and GP group (paper III), as corresponding results have been obtained in survey studies (107;108). The proportion of subjects with fibromyalgia in the present sample was higher than that reported for subjects with chronic pain in the general population (64;185;243). However, the mean duration of pain and age distribution in the are in line with previous studies (161;185), and the low proportion of men may be explained by the high number of patients with fibromyalgia participating in our study. Individuals with LP reported low pain intensity, but a substantial number were receiving disability pension and had average pain duration of 7 years. Hence, the subjects with LP and GP represented individuals with long lasting musculoskeletal pain, with pain localization from one site to “all over”, and pain intensity from the lower to the upper end of a VAS.

5.1.2 Study designs

Pain was reported in experimental and clinical settings, during activity and every-day life, and as real-time and recalled assessments. Thus, we had opportunities to evaluate the influence of context, assessment strategy, and associated mechanisms on the pain reports.

An experimental controlled design with matched subjects was used in papers I and II, in order to measure and register biological and subjective responses during exercise. The strength of this design is that both patients and healthy subjects are investigated, several confounding variables are controlled, and the measurements are taken and analysed under similar conditions. In addition, in paper II a staff member blinded to whether the subjects were patients or controls guided the participants during the exercise and defined when exhaustion was reached. These factors strengthen the validity of the results. Furthermore, the correspondence between biological and subjective responses of pain intensity and perceived exertion can be evaluated, and possible explanations for discrepancies and similarities can be revealed. One problem of an experimental design is that it is time-consuming and fewer subjects can be evaluated, which may lead to small and probably not representative samples. The results may therefore not be generalized to all subjects with FM.

The strength of the prospective design in paper III and IV is the possibility to evaluate the variability of repeated reports of pain intensity and neuropathic symptoms over time. In a previous study, four monthly reports of subjective health complaints were representative of long term pain condition of 24 months in postal workers (207). Thus, we assume that the time frame used in the present study is sufficient to reflect the general variability.

5.1.3 Methods of data sampling

Two different exercise models were used in papers I and II. In both exercise models the intention was to compare the sympathoadrenal and pain responses at exhaustion and maximal performance. Incremental increase in work load until exhaustion was used during dynamic bicycling (paper I). Maximal or close to maximal responses in heart rate, oxygen uptake, and lactate may be obtained in this model (paper I). In paper II, static repetitive exercise a constant work load at 30 % of maximal voluntary force was used. At this force level no increase in lactate concentrations in the blood and only modest increases in heart rate and oxygen uptake were expected. Thus, different mechanisms related to sympathoadrenal responses were expected in the two studies. Further discussion of exercise protocols, methods for blood sampling, and EMG measurements are presented in the respective papers (papers I and II).

The selected questionnaires and pain intensity scales in papers I – IV are commonly used and reliability and validity tested. Subjective ratings are influenced by several internal and external factors, the variability is substantial, the correspondence with physiological measures is often limited, and the validity of the answers might be questioned. Biases such as being “eager to please”, the wish to verify the severity of a syndrome, misinterpretations, fatigue and learning effects, are potential problems. To reduce some of these common biases, all questionnaires and scales were thoroughly described, the reasons for overlapping and apparently repeated questions were explained, and they were filled in as a test with the test leader present. In a previous study a tendency to overestimate the first rating was reported, and they recommend omitting this rating from the analysis (207). Thus, for all subjective reports at least one rating was performed before the assessments were included in the analyses.

In the present thesis pain intensity was assessed by VAS in order to try to enable the subjects to remember the pain experience and not a number rated. Neither the VAS nor the NRS has proved consequently to be superior to the other (87;100), and the correlation between the two pain scales is reported to be high (100). The choice of scale therefore depends on the purpose of the study and characteristics of the sample.

The LANSS was used to assess the presence of neuropathic symptoms in the subjects with musculoskeletal pain (paper IV). It has been suggested that the sensory disturbances are considered to be “more or less” neuropathic (6;16;17) with overlap to conditions assumed to be nociceptive related. Neither pain intensity nor pain affect is included in the questionnaire, making it suitable for comparisons with pain intensity and emotional distress. Several other screening tools of neuropathic pain comprise these dimensions and these variables will thus be associated (8;26;68;122).

5.1.4 Data analyses and statistical methods

Parametric and non parametric methods were used in the present thesis according to distribution of the data sets. T-tests and Repeated Measure Analyses of Variance are robust tests, and parametric methods are recommended when the distribution of the data sets are sufficiently close to normal (1). It is, however, disputable whether non-parametric or parametric methods should be used when the construct of measurement might be considered ordinal. Pain intensity rated on VAS has showed ratio properties (174), and parametric methods can therefore be applied. However, in papers I and II non-parametric methods were used due to the low number of subjects participating.

In paper III, the variation of the repeated measurements of recalled pain intensity over 4 months was calculated as the standard deviation of the measurements for each individual. A common measure of the variation is the coefficient of variation (CV). However, the CV becomes misleadingly high in subjects with low pain intensity when the standard deviations are similar in subjects with high and low pain intensity, because the CV is given as the standard deviation in percent of the mean pain intensity. The absolute value, i.e. the standard deviation, was therefore chosen as a measure of the variability in paper III.

The calculation of sample sizes in papers I and II was based on previous reports of catecholamine responses. Substantial individual variations in catecholamine responses were found in the FM group. A multifactorial pathogenesis and differences in fitness levels may indicate that the FM group comprised subgroups with different patterns of responding. In future studies there is a need to control for these confounding factors. Post hoc calculations of power in the prospective study over four months (paper III) suggest that Type II errors in the comparisons of daily and weekly pain assessment strategies were of minor importance. The differences between the assessment strategies were statistically significant, but small, indicating that the clinical relevance should be interpreted with caution. In addition, the responsiveness of daily recalls was not conducted, i.e. “the ability to accurately detect change when it has occurred” (11), which is needed in the evaluation of daily recall.

5.2 Discussion of main results

5.2.1 Exercise performance and capacity

The subjects exhibited maximal or close to maximal exercise performance in papers I and II. Secondary criteria for reaching maximal performance were fulfilled during dynamic exercise (217), and similar endurance time, drop in MVC force and increase in heart rate and MAP strongly indicated similar exercise intensity in the FM and control group during static repetitive exercise. Thus, the variables were compared at similar relative intensity levels during exercise and at exhaustion.

Despite being matched on self reported exercise frequency, the FM patients obtained significantly lower maximal oxygen uptake (paper I) and muscle strength as evaluated by MVC_{max} (paper II) than the healthy subjects. The lower adrenaline responses found during static exercise could have contributed to lowered muscle performance. However, no increase in muscle fatigue development, as evaluated by endurance time and decline in MVC, were seen in the subjects with FM. Furthermore, the adrenaline responses were not associated with

muscle fatigue development and increase in EMG during exercise (paper II). Otherwise the physiological responses were normal. Hence, in keeping with most previous studies, lower fitness level and muscle strength were strongly indicated in the FM group (20;94;128;197).

Because the MVC was lower, the subjects with FM performed the static repetitive contractions at a lower force level than the controls, and similar EMG/force relationship would then be expected. However, the relative EMG (% EMG_{max}) was higher in the FM group, which could indicate reduced muscle efficiency. A possible explanation could be increased co-contractions of antagonist and agonist muscles as proposed in the “pain adaption” model (129). Increased hamstring coactivity would require higher quadriceps activity in order to maintain the required force. A recent study suggested that muscle pain was the main factor inhibiting muscle force and altering muscle coordination (5;36). In this study the lower force production was associated with lower central drive, and not with changes in the contractile properties of the muscles (5;36). Other studies have also indicated results as described in the pain adaptation model (163;180) rather than a vicious circle of increased activity in agonist muscles. Thus, substantial documentation exists for the “pain adaptation” hypothesis in chronic muscle pain, whereas the empirical support for the “vicious circle” hypothesis in humans is weak or lacking (151;152;170).

The lower exercise capacity found in the FM group could indicate that daily exercise was performed at lower intensity and possibly of shorter duration than in healthy subjects. Both pain and the perception of more strenuous exercise could contribute to lower effort during exercise. However, differences in reporting behaviour (19) and a generalized hypervigilance to stimuli, including muscle contractions (69;137), can not be ruled out.

5.2.3 Sympathoadrenal responses

Similar peak heart rates and catecholamine responses were found in FM and healthy controls during dynamic exercise (paper I), indicating normal responses from the sympathoadrenal system. In agreement with these results, the plasma noradrenaline concentrations were similar in FM patients and controls during static repetitive exercise (paper II). However, the adrenaline responses were significantly lower in the FM group (Table 3). Attenuated adrenaline responses, despite normal noradrenaline responses, are possible as these responses may only be moderately correlated (75). The attenuated adrenaline responses found during static repetitive, but not during dynamic exercise, could have several explanations. These two exercise modes trigger the metabolic, cardiovascular, and sympathoadrenal responses differently, and the regulation of adrenaline and noradrenaline are different in dynamic and

static exercise (35;115). A substantially higher sympathetic activity was seen during dynamic than static exercise due to general activation of the whole body and the activation of greater muscle masses. Thus, the afferent feedback mechanisms from working muscles were much stronger in the former (114). This could possibly have masked a lowered response from the adrenal medulla. During heavy dynamic exercise a substantial release of noradrenaline from the exercising muscle is seen. A small amount of adrenaline is also released from the postganglionic nerve fibres, which could have contributed to higher concentrations of plasma adrenaline during dynamic exercise despite a lowered contribution from the adrenal medulla. The rise in plasma adrenaline is larger, relative to that of noradrenalin, during static than dynamic exercise, and the sympathetic activity is increased in visceral organs rather than muscles (35). A blunted adrenaline response, possibly reflecting a blunted release from the adrenal medulla, might therefore have appeared during static, but not during dynamic exercise, in the FM patients. The regulation of noradrenaline and adrenaline are complex, however, and several systems interact, and we do not know the exact mechanisms.

The attenuated adrenaline response could indicate lowered sympathoadrenal activity and could represent a pathological mechanism related to FM. The difference in MVC between FM and controls could have affected the adrenaline responses, but this was not shown when evaluated by regression analyses. The exercise intensity was also probably similar as discussed above. However, differences in aerobic capacity between subjects with FM and controls cannot be ruled out as a confounding factor as this is known to attenuate adrenaline responses (111;112). Lower adrenaline responses have previously been reported in FM compared with age matched controls, but this was reported during dynamic exercise and accompanied by lower cortisol and noradrenaline responses (229). In addition, substantially lower heart rates were found in the FM group possibly indicating submaximal performance (229). Other studies have found normal catecholamine and cortisol responses (84;165). Differences in exercise modes and patient population between the studies could be an explanation of the discrepancy in results, as the FM patients in the present project represented a relatively active patient group. The adrenaline responses during static repetitive exercise were skewed indicating a pattern of responders and non-responders. A multi-factorial medical history, in addition to variable fitness levels, could indicate different subpopulations of the FM group, as has been suggested by several authors (12;169). At present, no unifying hypothesis based on the impact of sympathetic nervous and adrenal system in FM has been put forward (169;176;233).

5.2.4 Pain intensity during exercise

The FM patients reported a substantial increase in real-time pain intensity during exercise, but no long term effect was seen as no increase in pain intensity was reported the following week (papers I and II). The increase during exercise was probably not affected by the catecholamine responses as no associations between pain intensity and catecholamines were found. A possible explanation of the exercise-related pain might be sensitization and altered perception of mechanical stimulation. Increasing pain during exercise has previously been reported in subjects with shoulder myalgia, both in the afflicted and non-afflicted shoulder (180), indicating that similar mechanisms may be present in other groups of subjects with musculoskeletal pain.

Some of the controls experienced an increase in pain near exhaustion during static exercise, but no pain was reported during dynamic exercise. Epidemiological studies have indicated an association between static work and musculoskeletal pain. Sustained contraction above 20-30 percent of maximal force has been shown to cause ischemic condition and acute pain (98). At lower force levels, such as in the present study, the data are somewhat contradictory (125;210), but muscle pain is reported during repetitive and sustained contractions despite no accumulation of metabolites (195;237). Exhaustion of single muscle fibers being intensively active during contractions considered to be low for the muscle as a whole, have been suggested as a mechanism behind this pain (85).

The mean level of real-time pain intensity during exercise was substantially lower than the recall of pain prior to and after the exercise, and the baseline ratings of real-time pain were very low (from 10 – 20 mm on VAS). Several explanations for this discrepancy may be possible. Firstly, pain reports vary with context, expectations, and distractions (40;63). The participants' focus was probably on performing and not on pain at the moment of recording during exercise, and contextual factors and the experimental setting could have explained the low levels of real-time pain during exercise in general.

Secondly, exercise-induced pain may represent a different aspect of the pain experience than chronic pain reported during daily life (236). In keeping with this view, poor association was found between the real-time pain reported during exercise and the recalled pain intensity reported before the exercise (paper I). In a study by Baliki et al. (2006) two phases of spontaneous pain during every day life, “increasing pain” and “high sustained pain”, were compared in subjects with chronic back pain. “High sustained pain” activated brain regions which are involved in negative emotions, while “increasing pain” transiently activated

regions commonly observed for acute pain. During painful thermal stimulation similar brain areas associated with acute pain were activated in patients and healthy controls (9). Hence, muscle contractions were perceived as painful and the pain increased with time and intensity in the present studies, which might indicate that exercise-related pain could be paralleled with an acute pain experience.

Thirdly, differences in assessment strategies could be important. The ratings of recalled pain prior to exercise were conducted at approximately the same time as the baseline levels of real-time pain. Stable levels of recalled pain were seen in the exercise studies although subjects with fibromyalgia frequently report that strenuous exercise increases pain (21;150). This could indicate that the weekly recalls were either less susceptible to context and /or resistant to short lasting changes possibly involving the semantic memory and “known” (30;179;218;219).

In contrast to the discrepancy between real-time pain during exercise and recalled pain in papers I and II, considerable overlap between real-time and weekly recalled pain was seen during everyday life (paper III). However, in this study (paper III) weekly recalls were also overestimated. Hence, the assessment strategies of real-time and recalled pain were differently affected by context and might have captured different aspects of the pain experience.

5.2.7 Reliability of recalled pain intensity

The results of paper III showed that daily pain ratings were lower than weekly ratings and corresponded better with real-time ratings. These results were independent of the magnitude of pain intensity and whether the subjects exhibited localized or generalized pain. In agreement with the present results, lower daily than weekly recalled pain intensity and higher correlation between daily and real-time pain has been reported previously (28). However, higher daily recalled than real-time pain was also reported (28). The daily recalls were recorded on two different days and compared with the real-time pain for those two days (28). In contrast, subsequent ratings averaged over the week were used in the present study, and the different time frame used may explain the difference in results.

The reliability of recalled pain was lower in the GP than the LP group, but the SDs of recalled pain were only weakly associated with number of painful body areas. Magnitude of pain intensity, emotional distress, and pain duration were also of little influence. However, in a previous study, the number of painful body areas, the local pain intensity in the different body areas, and pain related negative affect, accounted for a considerable part of the variance of clinical pain in subjects with FM (202). We suggest that a high number of painful body

areas in combination with other symptoms as manifested in the GP group, may increase the variability of recalled pain.

In keeping with several other studies, weekly recalls were overestimated compared to real-time pain intensity, but only in the GP group (28;102;103;177;211). In contrast to a previous report (96), high pain intensity was associated with overestimation of weekly recalls in the GP group. However, the subjects with low pain intensity, who overestimated weekly pain in the previous study (96), exhibited a high degree of emotional distress and other symptoms often associated with symptoms reported in subjects with generalized pain (107;108;244). Differences in patient groups may therefore be a possible explanation of the difference in results.

Whether pain is localized or generalized seems to be the most important explanation of the discrepancy in reliability of recalled pain in the present study. High pain intensity was of importance only in estimating real-time pain by weekly recalls.

5.2.6 Neuropathic symptoms, pain intensity, and emotional distress

The mechanisms underlying the reports of neuropathic symptoms in subjects with musculoskeletal pain are unclear. In a previous study the neuropathic symptoms, as evaluated by reduced vibrotactile sense in subjects with persistent pain after computer use, were interpreted as nerve compression after repetitive use of the arm (99). Another possible explanation might be sensitization, as alteration in sensory perception may be clinical signs of abnormal pain processing (4;154;166;249). Despite no verified nerve lesion, 13 subjects with musculoskeletal pain, including 10 subjects with fibromyalgia, scored above the cut-off interpreted as neuropathic pain in the LANSS. The main predictors of neuropathic symptoms in the present study were the diagnosis of FM and emotional distress. Peripheral and central sensitization are mechanisms associated with the FM syndrome (12;77;141;169). In line with the increasing pain reported during exercise in subjects with FM (papers I and II), the positive association between neuropathic symptoms and recalls of pain during exercise might be due to sensitization. Furthermore, emotional distress is a strong predictor of chronic pain (83;231), related to sensory changes and altered pain processing (208), and a factor influencing the sensitization process. Emotional distress is associated with activation of the sympathoadrenal system and adrenaline release (74). The neuropathic symptoms' association with emotional distress is thus in line with our finding of attenuated adrenaline responses possibly indicating "wear and tear" of the stress systems. A possible mechanism for neuropathic symptoms in subjects with musculoskeletal pain and fibromyalgia may be sensitization.

The frequency of subjects with neuropathic symptoms was higher in the present study than previously reported in a population of subjects with chronic pain (220), but could be explained by the high number of subjects with FM in the present study. In agreement with our results neuropathic symptoms have previously been reported in FM (62;133). Whether FM has a neuropathic pain component, however, is a subject of controversy (15;42;51;168;182).

In accordance with previous reports, the reliability the sum scores of the five LANSS items were high (16;17). To our knowledge, the stability of individual items over time has not been investigated previously, and the highest reliability was found for altered touch sensation.

5.2.7 Clinical and research implications

The results from the present studies indicate that pain may induce reduced muscle efficiency and increased perceived exertion during exercise in subjects with FM. Similar relative exercise intensity might therefore be perceived as more strenuous in FM. This should be taken into account when designing interventions for increasing aerobic capacity and muscle strength in subjects with FM, and in expectation of results. An objective measurement of exercise intensity, for example heart rate measurement, could be useful and is a valid method according to our results. Dynamic exercise has several positive effects on general health indicating that this could be preferable as a training method in women with FM. Pain during exercise was transient and no deleterious effects were measured. However, the optimal training method regarding pain intensity, exercise mode, and pain tolerance is at present not known (32;88).

Subjects with generalized musculoskeletal pain exhibited more emotional distress and more subjects were out of work, indicating more severe affliction than in subjects with localized pain. Emotional distress was associated with neuropathic symptoms in subjects with musculoskeletal pain. In previous studies, sensory disturbances were associated with poor recovery (209). In clinical practice, emotional distress and neuropathic symptoms should therefore be taken into consideration in the diagnostic process in subjects with musculoskeletal pain and fibromyalgia, and attention to emotional distress in susceptible individuals may be an important treatment goal.

Generalized pain was associated with higher ratings of weekly recalled than real-time pain intensity and higher variability of pain intensity than localized pain, which is important to take into account when evaluating treatment effects for groups. Although daily pain ratings corresponded better with real-time ratings, the correlation coefficient between the weekly and

real-time ratings was moderately high, and mean difference between the SDs of daily and weekly ratings across four months was small. Single ratings of weekly recalled pain may therefore be just about as reliable as daily ratings for individual evaluations. The context's influence on pain intensity level should be taken into account when using real-time ratings or pain diaries of actual pain.

In research, physical fitness level in subjects with FM may be a confounding factor. Our results showed that self-report of exercise frequency is an incomplete evaluation tool of oxygen uptake and muscle strength compared with healthy subjects. Additional descriptions of intensity and duration of exercise habits are needed.

Caution should be exhibited when comparing pain intensity in different contexts and when different assessment strategies have been used. The present studies showed that reports of real-time pain intensity were heavily influenced by context when comparing the results obtained during exercise (papers I and II) and daily life (paper III). The average of daily recalls across a week was shown to be a more reliable and valid assessment strategy for evaluating previous pain than a single rating of weekly recall in subjects with musculoskeletal pain. Obtaining several assessments of daily recalls may be impractical in clinical practice, but for research purposes we suggest that the effort may be considered.

6 Conclusion and future perspectives

The results from the present thesis showed that the women with fibromyalgia obtained attenuated adrenaline responses to static repetitive contractions, but normal muscle fatigue and recovery responses, and normal catecholamine responses to dynamic exercise. Neither pain intensity nor perceived exertion was associated with the catecholamine responses, and exercise related pain could not be explained by altered physiological responses.

Using ratings of daily recalled pain, averaged over a week, improved the reliability of recalls of pain. This result was independent of the magnitude of pain intensity and whether the subjects exhibited localized or generalized pain. Weekly recalls were overestimated in subjects with generalized pain and the overestimation increased with increasing pain intensity.

Neuropathic symptoms were prominent features of chronic musculoskeletal pain, stable over time, and associated with emotional distress and the diagnosis of fibromyalgia.

In future research prospective studies evaluating sympathoadrenal responses are needed in order to reveal a causative relationship between sympathoadrenal responses and development of fibromyalgia. Prospective studies are also needed in order to understand the relationship

between emotional distress, generalized pain and associated symptoms in musculoskeletal pain. It seems as neuropathic symptoms are part of clinical symptoms in musculoskeletal pain, and the implication for prognosis would be important to clarify.

7 References

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Paper I

L. Giske, C. Røe, S. Knardahl, N. K. Vøllestad.

Pain and Sympathoadrenal Responses to Dynamic Exercise in Women With the Fibromyalgia Syndrome. *The Journal of Musculoskeletal Pain*. 2007 15(4): 25-38.

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Paper II

L. Giske, N.K. Vøllestad, A.M.Mengshoel, J.Jensen, S.Knardahl, C.Røe.

Attenuated adrenergic responses to exercise in women with fibromyalgia– a controlled study.
European Journal of Pain. 2008 Apr;12(3):351-60.

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Paper III

L. Giske, L. Sandvik, C.Røe.

Comparison of daily and weekly retrospectively reported pain intensity in patients with localized and generalized musculoskeletal pain. *European Journal of Pain*. 2009 May. Under revision.

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Paper IV

L.Giske, E. Bautz-Holter, L. Sandvik, C. Røe.

Relationship between pain and neuropathic symptoms in patients with musculoskeletal pain.

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