

15

Sex-Related Differences in Clinical and Experimental Muscle Pain

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This chapter deals with two issues: first, is there a sex difference in the presentation of muscle pain, and second, if so, how might we account for it? The first part of the chapter presents epidemiological evidence and discusses associated factors that might guide attempts to explain the evidence. However, satisfactory explanations also require evidence based on experimentally induced muscle pain, which will be reviewed in the second part of the chapter.

Epidemiological and Clinical Evidence

Epidemiological reports indicate that musculoskeletal pain is a major medical and economic problem. The pain and associated disability are linked with a significant loss of productivity and substantial health care expenditures for women. Leijon et al. (1998) observed that about 30% of all sick-leave days in Sweden are due to neck/shoulder or low back pain, which were defined as being of musculoskeletal origin. The authors

determined that leave due to sickness in general, and due to musculoskeletal pain in particular, was appreciably higher among women than men.

Wijnhoven et al. (2006a) conducted a Dutch population-based study and reported a prevalence of musculoskeletal pain of 45% in women and 39% in men, based only on self-report (responses to a questionnaire). Interestingly, the degree of sex differences varied between body locations. The highest female predominance was found in this Dutch population for the hip and wrist/hand, whereas the lowest sex differences, not reaching statistical significance, were found for the lower back and knee.

Age may affect the biological and psychosocial basis of sex differences, so it is worthwhile to study musculoskeletal pain in elderly women and men. Leveille et al. (2005) investigated a major sample of women and men aged 72 years and older. Among the women, 63% reported pain in one or more regions, compared to 52% of men. Widespread pain was more prevalent among women than men (15% vs. 5%, respectively). Rekola et al. (1993) found that women aged 55 to 64 years are more likely than women of any other age group to seek medical attention for musculoskeletal problems, particularly neck and shoulder problems. In men the frequency of visits was highest in the age group between 45 and 54 years, with low back pain being the most common complaint. These findings argue against a reduction of sex differences in musculoskeletal pain with increasing age.

The evidence presented so far suggests that sex differences in musculoskeletal pain vary among different body sites. Accordingly, varying sex differences for different diagnoses of musculoskeletal pain might be expected. LeResche (2000, 2006) has made the case that musculoskeletal pain syndromes confined to one body region are moderately more prevalent in females than in males, within a range known also for chronic pain originating from other tissues (see Table I). In particular, widespread chronic pain diagnosed as fibromyalgia is associated with an extremely strong female predominance.

Do physical risk factors account for all or at least some of these sex-related effects? A number of possible explanations have been offered, including differential exposure to risks in the work environment, dif-

Table I
Sex prevalence ratios in various pain conditions
for the adult general population

Pain Site or Condition	No. Studies	Range of F:M Ratio	Median of F:M Ratio
Headache (general)	15	1.1–3.1	1.3
Migraine	14	1.6–4.0	2.5
Burning mouth	2	1.3–2.5	1.9
Knee pain	4	1.0–1.9	1.6
Abdominal pain	4	1.2–1.3	1.25
Back pain	4	0.9–1.3	1.2
Neck pain	5	1.0–3.3	1.4
Shoulder pain	5	1.0–2.2	1.3
Temporomandibular pain	10	1.2–2.6	1.5
Fibromyalgia	4	2.0–6.8	4.3

Source: Modified from LeResche (2000).

ferences in muscle strength or excess body weight, work environments designed to male norms, or differences in the way injuries in men and women are evaluated, treated, or referred for rehabilitative services. Similarly, Fredriksson et al. (1999) noted that neck, shoulder, and lower limb disorders are associated with heavy lifting, monotonous work tasks, static work postures, vibrations, repetitive jobs, and a high work pace, and found that women may be at higher risk for all such disorders. They also pointed to psychosocial risk factors such as low work content, low social support, high perceived workload, time pressure, low job control, high perceived stress, and high psychological job demands.

In a 24-year longitudinal study conducted by Nordander et al. (1999), psychosocial factors such as monotony and high mental load at work were associated with increased risk for neck and upper limb disorders in women (who had a prevalence rate about twice that of men), whereas in men more physical factors related to work were associated with an increased risk. However, the authors noted that “these two aspects of the work environment are so tightly entangled that it is not possible to estimate their separate impact on musculoskeletal disorders in this kind of work.” The idea that women are vulnerable to psychosocial risk factors and men to physical risk factors would not be true. In fact, Wijnhoven et al. (2006b) observed almost the opposite tendency. Risk

factors with a sex-specific association were being overweight and older age, which only had an effect in women, as well as pain catastrophizing, which was more strongly associated with chronic musculoskeletal pain among men than among women.

Not only do the predisposing factors for musculoskeletal pain differ between the two sexes, but the consequences may also vary in a sex-specific manner, although data have been scarce so far. Wijnhoven et al. (2007), who investigated a sample of 2,517 individuals from the Dutch population, observed increased health care use in women with musculoskeletal pain compared to men. Men reported more work disability, but only when suffering from low back pain.

Clearly, understanding the causes and the consequences of these epidemiological findings is much more difficult than demonstrating their existence. Men and women differ in body size and functional capacity and, perhaps, in such factors as mix of fast-twitch and slow-twitch muscle fibers, cardiovascular endurance, and other physiological variables (Punnett and Berqvist, 1999). Endocrine influences, including menstruation, oral contraceptive use, pregnancy, and hysterectomy may increase the risk of musculoskeletal disorders (Unruh, 1996). The link between musculoskeletal pain and menstruation deserves more study; certainly, the literature on temporomandibular disorder shows that the use of estrogen by postmenopausal women significantly increases their odds of having orofacial pain (LeResche et al., 1997; Wise et al., 2000). On the psychosocial side, women may experience greater stress both in and outside the job setting, less control over the work process, fewer opportunities for advancement, and different implications of reporting musculoskeletal pain and seeking or accepting compensation. Future research must isolate which of these sex-specific biological and psychosocial factors are most critical. This quest may be supported by experimental approaches.

Experimental Evidence

This section discusses experimental findings in healthy subjects and patients and presents sex differences in experimental inductions of acute

musculoskeletal pain, in pressure pain sensitivity, and in temporal summation and inhibitory mechanisms relating to muscle pain (see Chapter 11, Graven-Nielsen and Arendt-Nielsen).

Experimental Induction of Acute Musculoskeletal Pain

Muscle pain can be induced by muscular overuse or misuse (see Chapter 11, Graven-Nielsen and Arendt-Nielsen). The question is whether the two sexes differ in the functional thresholds that determine the distinction between use and overuse or misuse. Karibe et al. (2003) investigated whether chewing bubble gum for 6 minutes triggers masticatory muscle pain in females and males to a similar degree. Sex differences in chewing-induced pain were found, with only women having critical levels of muscle pain. Accordingly, overuse appeared to occur in this study only in women; however, the painful effects were short-lived.

Exercise models of experimental muscle pain, which lead to longer-lasting muscle pain, are more comparable to clinical situations and thus more useful. From this perspective a phenomenon called delayed-onset muscle soreness (DOMS) has attracted interest (see Chapter 16, Dannecker). DOMS is muscle pain and soreness that is felt 12 to 48 hours after exercise, particularly after eccentric exercise (i.e., lengthening contractions) and at the beginning of a new exercise program, after a change in sports activities, or after a dramatic increase in the duration or intensity of exercise. This soreness is a normal response to unusual exertion and is part of an adaptation process that leads to greater stamina and strength as the muscles recover. DOMS can be experimentally induced very effectively by requiring the subjects to perform eccentric muscle contractions (movements that cause a muscle to forcefully contract while it lengthens). Investigations of sex differences in DOMS have produced equivocal results. Dannecker et al. (2003) found females reporting lower muscle pain intensity than males after DOMS had been induced in the elbow flexor. The decrease in pressure pain thresholds in the affected muscle, which is a regular accompaniment of DOMS, was similar in the two sexes. In a study by Nie et al. (2005b), DOMS was induced in the shoulder muscles by performing an eccentric shoulder

exercise. Pain intensity, pain area, and pain ratings on the McGill Pain Questionnaire were all increased after exercise. Pressure pain threshold was significantly decreased and reached its lowest values 24 hours after exercise. However, no sex differences were found in any of the parameters used to assess the development of DOMS. Nie et al. (2007) were able to mostly replicate the results of their first study regarding the lack of sex differences in subjective pain during DOMS. A significant decrease in exerted force during exercise was only found in males, despite similar ratings of perceived exertion in both sexes. This finding was paralleled only in males by increased EMG activity during eccentric exercise. The authors concluded that women have more prominent muscle fatigue resistance compared to men.

Injection of hypertonic saline (HS) into a muscle induces pain that strongly mimics clinical forms of musculoskeletal pain. Ge et al. (2004) injected HS twice in series bilaterally into the trapezius muscle of women and men. Only the maximum pain intensity differed between the sexes, with higher ratings in women. No sex differences were observed for mean pain intensity, referred pain pattern, or pain area. The same group replicated these findings in a second study (Ge et al., 2006). There was no statistically significant difference between men and women in mean pain, maximal pain, or area under the curve of VAS ratings after either the first or second injection. Moreover, referred pain patterns were similar for men and women.

A further method for inducing muscle pain was tested by Cairns et al. (2001) by injecting glutamate into the masseter muscle. This experimental pain model led to abundant sex differences; women perceived higher levels of muscle pain overall, higher levels of peak pain, and broader areas of pain. Furthermore, the duration of pain was significantly longer in women than in men.

Despite these impressive results regarding the use of glutamate-induced pain, studies using the other experimental models, which were also designed to induce acute musculoskeletal pain similar to clinical conditions, have failed to provide evidence that they are able to reproduce the pathophysiological mechanisms responsible for the reliable sex difference in clinical musculoskeletal pain.

Testing Pressure Pain Sensitivity

Women are often found to have greater pain sensitivity than men in laboratory settings, but the effects are particularly striking when pressure pain is applied. Reviews of these sex differences are found elsewhere (Riley et al., 1998; Fillingim, 2000; Rollman et al., 2000; Rollman and Lautenbacher, 2001), so this section will focus on the evidence that the experimental use of noxious pressure is an especially sensitive test for tracking the pathology of musculoskeletal pain and its underlying mechanisms.

Abundant evidence shows that mechanical pressure is the form of noxious input that is most likely to show altered pain thresholds in musculoskeletal pain conditions. For example, changes in responsiveness to experimental pain, which is often markedly increased in patients with fibromyalgia, are particularly noteworthy when pressure pain is used as the physical stressor (Kosek et al., 1996; Sorensen et al., 1998). Lautenbacher et al. (1994) found that the effect sizes for differences between fibromyalgia patients and pain-free volunteers were 1.53 for a tender point and 1.57 for a control point when pressure pain was applied. Effect sizes decreased to 0.65 and 0.84, respectively, for heat pain and to 0.22 and 0.91, respectively, for electrocutaneous pain. Although some of the differences between patients and controls for heat and electrocutaneous pain were significant, none of them reached the size obtained for pressure pain.

Similarly, patients with myofascial pain and temporomandibular disorder are exceptionally pain sensitive when pressure pain is used for diagnosis, especially within the region where clinical pain is most strongly experienced (Arendt-Nielsen et al., 2004; Rollman and Gillespie, 2004). Consequently, the use of pressure pain seems to tie into the processes underlying musculoskeletal pain more readily than the use of other pain induction methods. This assumption is corroborated by the observation of Lautenbacher et al. (1994) that a sizeable negative relationship was found between the magnitude of concurrent pain in fibromyalgia patients and the pain threshold for pressure, but not the threshold for heat or electrical current.

The question arises as to whether musculoskeletal pain reduces the pain threshold or whether a reduced pain threshold—because of a state of increased pain sensitivity of peripheral or central origin—predisposes the individual to have musculoskeletal pain. Musculoskeletal pain does not necessarily lead to a decrease in pressure pain threshold. Babenko and coworkers (1999) induced muscle pain by various chemical agents without changing local pressure pain thresholds. Similarly, Graven-Nielsen et al. (1998a,b) failed to decrease the local pressure pain thresholds reliably by inducing muscle pain by HS infusion. Recent evidence provided by Slade et al. (2007) in a longitudinal study also suggests that increased pain sensitivity belongs to the relevant risk factors for later development of temporomandibular disorder. Accordingly, decreased pressure pain thresholds in women might be indicative of a generalized state of increased pain sensitivity that may predispose women to experience symptoms of musculoskeletal pain.

Interaction of sex with age has not yet received sufficient interest. Two studies indicate that clear sex differences in pressure pain sensitivity may exist only in young persons. Pickering et al. (2002) found significantly reduced pressure pain threshold in females in a group of young adults but not among elderly individuals. In one of our studies, the effect sizes for differences between females and males in the usual direction were 0.79 for pressure pain thresholds and 0.57 for heat pain thresholds in a group of young adults (Lautenbacher et al., 2005). In contrast, in individuals over 70 years of age these classical differences were eliminated (effect size for heat pain thresholds: -0.06) or even reversed (effect size for pressure pain threshold: -0.50). Such findings point to critical limitations of the research on sex differences conducted so far, which has been strongly based on investigations in young persons.

Temporal Summation and Inhibitory Mechanisms Relating to Muscle Pain

The indication of a reliably increased sensitivity to pressure may suggest central hyperexcitability or a lack of sufficient pain inhibition, which becomes apparent when using this type of physical stressor. The paradigms

most often used to test such hypotheses are the assessment of temporal summation in pressure pain and the investigation of diffuse noxious inhibitory controls (DNICs) with pressure as the test stimulus.

Sarlani et al. (2004) investigated temporal summation by applying 10 repetitive, mildly noxious mechanical stimuli to the fingers of 25 women and 25 age-matched men. Temporal summation of pain intensity and unpleasantness ratings were more pronounced in women than in men. In addition, significant temporal summation occurred only with 2-second interstimulus interval in men but with 2- and 5-second interstimulus intervals in women. In a later study on patients with temporomandibular disorder, Sarlani et al. (2007) essentially replicated their findings.

We were interested in DNIC-like effects on temporal summation of pressure pain in females and males. For that purpose, we designed a study to examine the effects of tonic thermal stimulation of varying intensities (warmth, heat, and heat pain) used as a conditioning stimulus on the perception of single pulses of noxious pressure compared to the ratings of the last pressure stimulus of a series of five (0.5 Hz repetition frequency). Tonic heat (conditioning) and phasic pressure (test) stimuli were tailored to individual pain thresholds (thermal: -3°C , -1°C , and $+1^{\circ}\text{C}$ relative to pain threshold; pressure: 150% of pain threshold). VAS ratings for these stimuli did not differ between the sexes. As shown in Fig. 1, there was significant temporal summation, leading to much higher ratings for the last pulses of the repetitive series compared to those for single pulses (S. Lautenbacher et al., unpublished data). However, in contrast to Sarlani et al. (2004, 2007), in our study the two sexes did not differ in the amount of temporal summation of pressure pain. The DNIC-like reduction of the VAS ratings for pressure was generally weak because tonic heat pain did not have much more effect than warmth in this respect. Whereas the DNIC-like effects were at least visible in tendency in men, they were completely absent in women.

Our findings of no sex differences in temporal summation of pressure pain, which corroborate earlier results by Nie et al. (2005a), along with the data of Fillingim et al. (1998) showing a substantial sex difference in temporal summation of heat pain, suggest that temporal summation of pressure pain is not an especially sensitive test for sex differences.

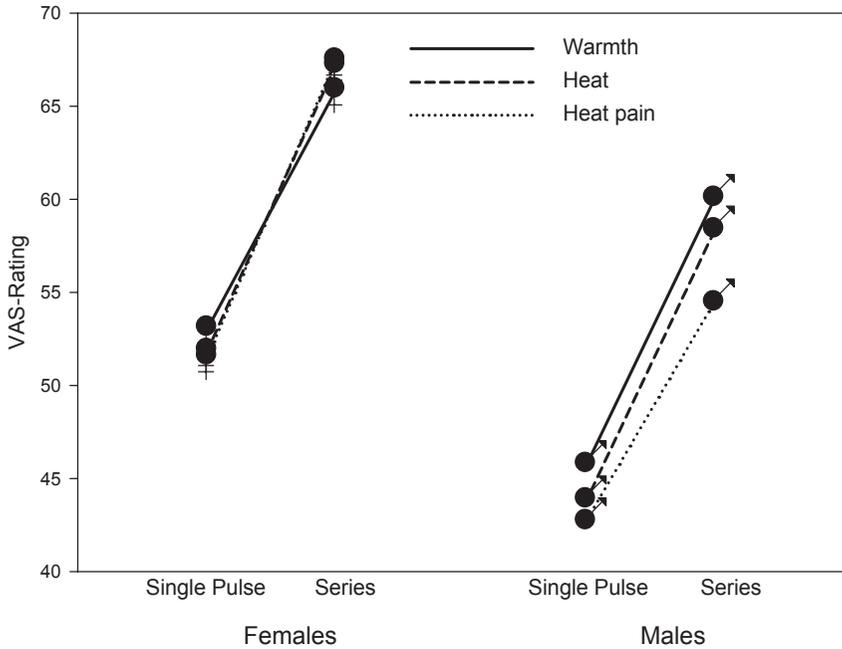


Fig. 1. Temporal summation of pressure pain in 20 women and 20 men. Mean ratings on a visual analogue scale (VAS, 0–100) of pain from single pulse stimulation were compared with those of the last stimulus in a series of five repeated stimuli with a repetition frequency of 0.5 Hz. Stimulations were applied to the fingertips of the left hand. The slopes indicate substantial temporal summation but without sex differences. Temporal summation was tested under concurrent application of tonic thermal stimuli (conditioning stimuli: warmth, heat, and heat pain) to assess diffuse noxious inhibitory controls. Only in men was there a tendency for reduced ratings when painful conditioning stimuli were applied. However, the comparison of the two sexes failed to reach significance in this respect (S. Lautenbacher et al., unpublished data).

Therefore, the studies of Sarlani et al. (2004, 2007) by themselves do not give convincing evidence of a particularly pronounced central hyperexcitability when applying repetitively noxious pressure. Furthermore, our very weak evidence for stronger DNIC-effects in men than in women when painful pressure was applied as the test stimulus discredits the hypothesis that deficient DNIC mechanisms are a critical cause of the strong sex differences in pressure pain sensitivity.

The formulation of the latter hypothesis was based in part on observations by Mense (1998, 1999). The author suggested that the descending antinociceptive systems exert a more powerful influence on the input from muscle nociceptors than on that from skin nociceptors.

Accordingly, a weakening of these antinociceptive systems should result in a lowering of pain thresholds for stimulation of muscles (because pressure stimulation activates both skin and muscle nociceptors) and in an increased likelihood of spontaneous muscle pain. Lautenbacher and Rollman (1997) and Kosek and Hansson (1997) found deficiencies in the pain inhibitory systems of fibromyalgia patients, which were especially prominent when they used pressure pain as the test stimulus compared to using heat pain.

What further evidence, other than our findings (see Fig. 1), is available for the hypothesis that sex differences in DNIC effects are especially prominent when pressure is used as the test stimulus? Ge et al. (2004) investigated sex differences in DNIC by measuring pressure pain thresholds over time in the trapezius muscles and the posterolateral neck muscles following repeated bilateral injection of hypertonic versus isotonic saline into both trapezius muscles. Significantly higher pressure pain thresholds in men than in women were shown 15 minutes after the first bilateral injection, and 7.5 and 15 minutes after the second bilateral injection. These results showed sex differences in the temporal characteristics of DNIC, with longer-lasting hypoalgesia in men than in women.

Pud et al. (2005) investigated healthy volunteers to examine the effect of tonic immersion of the fingers in ice-cold water as a conditioning stimulus on pain intensities produced by mechanical punctuate stimuli, applied both adjacent and contralateral to the cooled area. There was a significant decrease in mechanical pain intensities at both sites when stimulation was applied immediately after the cold immersion. However, the extent of pain reduction was similar for males and for females. Furthermore, there are also reports of sex differences in DNIC effects when electrical current (France and Suchowiecki, 1999) or heat (Staud et al., 2003) were used as test stimuli.

In conclusion, there is no sound empirical basis so far to assume that the descending inhibition of nociceptive input from deep tissue, i.e., from muscles, is particularly subject to sex-related factors or that it is weaker in women. However, the assessment of DNIC-like inhibition does not cover all descending inhibitory systems, and therefore sex differences in DNIC cannot be excluded by the findings to date.

Concluding Remarks

There is no doubt that there are sex differences in susceptibility to musculoskeletal pain and in pain sensitivity, with women—as a rule—being more often affected and more sensitive to pain. The question is whether such sex differences are stronger in clinical and experimental musculoskeletal pain compared to types of pain originating from other tissues. As far as the available evidence goes, at present we can be confident that chronic widespread musculoskeletal pain, specifically fibromyalgia, is outstandingly frequent in women and that sensitivity to pressure pain is more reliably increased in women compared to sensitivity for other types of noxious stressors. In regard to all other forms of clinical muscle pain and experimental methods of simulating, summing, and inhibiting muscle pain, sex differences are in the usual range known for pain in general. This evidence does not mean, however, that the experimental paradigms set up to investigate musculoskeletal pain—models such as DOMS, HS injection, temporal summation of pressure pain, and DNIC effects on muscle pain—fail to address critical aspects of muscle pain pathophysiology. It only means that they do not address those aspects that are critical for understanding the particularly strong effects seen in women in certain forms of chronic musculoskeletal pain.

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