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SEX DIFFERENCES IN CHRONIC WIDESPREAD PAIN AND FIBROMYALGIA: DO THEY EXIST AND WHY?

Chronic musculoskeletal pain of unknown etiology and fibromyalgia (FM) illustrate the pain discrepancy between men and women and raise important questions as to the reasons for this sex difference.

Chronic pain (CP) and chronic widespread pain (CWP) are common in both developed and under-developed countries (1). The same is true for fibromyalgia (2), which, by definition, is associated with CWP as well as other symptoms (3). FM also appears to have a significant impact on society, directly in terms of health care costs and indirectly via loss of productivity (4,5).

Initially felt to be a female disorder, at least one large general population study has found FM to occur in 1-2% of adult men (6). To date, scant data exist to explain potential gender differences in the expression of FM. There is also a limited understanding with respect to the underlying causal mechanisms of FM, though such mechanisms are felt to be largely multi-factorial (7). An improved understanding of sex differences in the prevalence and expression of CWP and FM may provide impetus for improved understanding of these causal mechanisms.

In the outpatient subspecialty setting, a significant majority of patients reporting CWP and meeting the case definition for FM are female; the ratio of females to males among subspecialty clinic patients where FM has been reported has been as high as 9 to 1 (8). However, caution must be exercised when interpreting these data because women utilize health care services to a greater extent than men (9,10). More recently, several general population studies have demonstrated that a greater proportion of women report pain, CP, and CWP (11). There have been a few exceptions. Male gender may be a risk factor for chronic back pain among adults, as are advanced age and a variety of other disease- and occupation-related factors (12). Andersson et al. (13) found no difference between the sexes in the overall prevalence of CP, but did find that a greater percentage of women reported pain in the neck, shoulder, forearm, hip and hand; men did not experience pain to a greater extent than women in any location.

However, the majority of general population studies have shown statistically significant sex differences in the prevalence of CP and CWP. Reviewing data from

Correspondence to: Kevin White, MD, PhD, FRCP(C), Division of Rheumatology, 268 Grosvenor St., London, ON N6A 4V2, Canada
E-mail: kevin.white@sjhc.London.on.ca

the National Health and Nutrition Examination Survey (NHANES-1) and from the National Health and Nutrition Examination Follow-Up Study (NHEFS), Magni et al. (14) found that 57% of adults reporting CP were female. In a survey of 3605 adults in Scotland, Elliott et al. (16) demonstrated an odds ratio for CP of 1.24 for women (15). The odds ratio for CP among 1051 Hong Kong adults was 1.5 for women (16). Interestingly, CP is more common in females even among children and adolescents (17, 18).

The sex differences for CWP and FM appear to be even greater than for CP. In a cross-sectional population survey of 2210 adults in southern Israel, 14% of women reported CWP compared to 3% of men (19). In a survey of 1340 adults in Northern England, 15.6% of women reported CWP compared to 9.4% of men (20). In Wichita, Kansas, women were four times more likely to report CWP and threefold more likely to report fatigue and sleep disturbance (two other prominent symptoms of FM). Women also were nine times more likely to have tenderness at 11 or more FM tender points. The overall prevalence of FM in Wichita was 2.2% in women and 0.5% in men. In a general population survey of 3395 non-institutionalized adults in London, Ontario, Canada, 9.0% of women reported CWP versus 4.7% of men (21). Women were also more likely to report general and debilitating fatigue. The overall prevalence of FM was found to be 4.9% in women and 1.6% in men (6). In Finland, FM appears to be twice as common among women (22).

Interestingly, while FM clearly is more common in women than men, in an examination of 86 women and 14 men, all meeting the published case definition for FM and all recruited in a general population survey, there was little difference in the clinical severity or range of symptoms between women and men (23).

Why women are more likely to report CP and CWP and more likely to have FM is not known. There is evidence that women in general have a higher degree of body tenderness than men. However, not all individuals with 11 or more FM tender points have pain (24).

It appears that men and women differ in their perception of pain. Riley et al. (25) reviewed differences in the perception of noxious stimuli and conducted a meta-analysis of 17 studies on pain threshold and 9 studies on pain tolerance. Both pain threshold and pain tolerance were significantly higher in men. This was true with the use of various nociceptive agents including mechanical pressure, electrical stimuli, and thermal stimuli. These authors (25) pointed out that those studies which failed to show such differences, do not have sufficient power. Unruh (26), in a review of the literature on the prevalence of chronic and/or recurrent pain conditions, found a higher female prevalence of migraine, tension headaches, musculoskeletal pain, facial pain, and abdominal pain.

Paulson et al. (27) conducted an interesting study involving 10 young men and 10 young women. Thermal stimuli of 40°C and 50°C were applied to the sub-

jects and regional cerebral blood flow measured by positron emission tomography (PET). Both men and women rated the 50°C stimuli as painful, but women rated it as more intense than men; both groups showed a bilateral activation of the premotor cortex as well as activation of a number of contralateral structures including the posterior insula, anterior cingulate cortex, and the cerebellar vermis during heat pain, but women had a significantly greater activation of the contralateral prefrontal cortex when compared to males (27). Thus both sexes showed similarities in brain activation patterns but there were also neurophysiologic differences demonstrated by the PET scan.

The role of ovarian hormones in modulating pain perception has been of considerable interest. In a meta-analysis of pain perception across the menstrual cycle, Riley et al. (28) found that pressure stimulation, cold pressor pain, thermal heat stimulation, and ischemic muscle pain gave rise to a clear pattern with the follicular phase demonstrating higher thresholds for pain than later phases. Electrical stimulation was different from other stimulus modalities showing the highest thresholds for the luteal phase. It should be noted that the production of 17 beta estradiol, estrone, and estriol is lower in the follicular phase than in the luteal phase (29).

The role of estrogen and progesterone in modulating pain during pregnancy has also been of interest. There is an elevated threshold to pain during pregnancy (30). This seems to be mediated in part by an interaction between dynorphin and kappa opiate receptors (30). Dynorphin is an opioid neuropeptide that binds to kappa-opioid receptors and has analgesic effects (31). Delta-opioid systems are also involved in increased pain thresholds seen in pregnancy (32). On the other hand, the predominant mu-opioid system does not appear to participate; indeed there are sex differences in the activation of the mu-opioid system. Zubieta et al. (33) induced deep tissue pain in 14 healthy young men and 14 healthy young women; the women were in the early follicular phase of their menstrual cycle; men demonstrated larger magnitudes of mu-opioid system activation than women in the anterior thalamus, ventral base ganglia, and amygdala (33). Women also showed a reduction of the basal state of activation of the mu-opioid system in the nucleus accumbens.

Hapidou and Rollman (34) studied tender points during the menstrual cycle in normally menstruating women. They found that there was an increase in the number of tender points in the follicular phase of the cycle as compared to the luteal. This increase in response to a noxious stimulus was similar to those reported with electric shocks to the skin, but in the opposite direction to those found with cold pressor pain, ischemia, and radiant heat (34). It has been suggested that pain due to mechanical pressure is more likely to show sex differences (35). Thus, there is a need to study further the relationship between various noxious stimuli and hormonal factors.

Fillingim and Edwards (36) studied a group of women on hormone replacement therapy (HRT), women on no HRT, and men. There was no difference between the groups in self-reported pain complaints.

However, women on HRT had a significantly lower heat pain threshold and tolerance than women not on HRT and men.

Responses to analgesia and anesthesia also vary between men and women. Nalbuphine is an analgesic which acts predominantly at kappa-opiod receptors. It was used in postoperative pain in men and women (37). Women showed a significantly greater analgesic response than men; interestingly, men who received a lower dose of the drug, experienced significantly greater pain than those receiving placebo.

A group of healthy young men and women were subjected to painful continuous electrical stimulation of the ear lobe, and given ibuprofen as an analgesic. Ibuprofen was significantly less effective in women than in men (38). Men and women, however, do not seem to differ in their analgesic responses to placebo (37, 39).

It is not clear whether psychosocial factors differ in their effects on pain perception in men and women. It has been suggested that anxiety may differentially affect men and women perceiving and reporting pain (40). In a community study it was found that interference of pain had a greater impact on the threat appraisal of pain for women than for men (41). Thus, in addition to neuropsychologic and neurohormonal effects, psychosocial factors such as gender roles, pain-coping mechanisms, and social support likely also play an important role in the way men and women perceive and react to pain (42).

We have begun to understand better the pathophysiology of acute pain, largely due to advances in functional brain imaging. The study of CP will present greater challenges as the modulating factors involved are more complex. The contribution of sex and gender to the perception of pain will continue to be an important area of research.

Kevin P White, MD, PhD[1,2]
Manfred Harth, MD[1]
[1]*Dept. of Medicine, Division of Rheumatology*
[2]*Dept. of Epidemiology and Biostatistics*
University of Western Ontario
London, Ontario, Canada

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