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Pain: sex differences and implications for treatment

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Abstract

Women have a higher prevalence than men of several clinical pain conditions and of inflammation-mediated disorders. There is also increasing evidence for sex differences in sensitivity to experimental pain and in the response to analgesics. Estrogen, progesterone, and other gonadal hormones have a complex role in inflammatory processes and the pain response. Microglia cells in the central nervous system, which have sex hormone receptors, become activated in response to inflammatory stimuli, releasing cytokines and other mediators that are pronociceptive and can amplify the pain response. Although the mechanisms underlying sex differences in pain and analgesia have not been fully elucidated, both peripheral and central nervous systems pathways may be involved. Sex differences in the opioid, dopaminergic, serotoninergic, and other pain-related systems have been documented; and some evidence suggests that differences are most pronounced during the peak reproductive years. Psychosocial factors also play an important role. Given the important role of inflammation in mediating pain, nutritional factors that modulate the inflammatory response offer a promising and exciting new avenue for the prevention and treatment of chronic pain disorders. Of particular interest is the potential role of moderate- to high-dose vitamin D and omega-3 fatty acid supplements, both of which have powerful anti-inflammatory effects. These nutritional interventions, which influence cytokine, leukotriene, and prostaglandin pathways, may be of particular benefit to women due to their higher prevalence of inflammatory chronic pain disorders. The recent launch of a new large-scale randomized trial of these nutritional supplements provides an opportunity to assess their potential antinociceptive role. Additional research is needed to clarify the mechanisms for sex differences in pain and to develop new treatment modalities that improve pain management for both men and women.

1. Introduction

A recent consensus report on sex and gender differences in pain and analgesia [1] concluded that important differences in pain and analgesia exist between the sexes and that attention should be directed to the following 3 areas: (*a*) conditions that lead to the expression of sex and gender differences in pain experience and reactivity, (*b*) mechanisms that underlie these differences, and (*c*) how these differences can inform clinical pain management. The present article summarizes the state of knowledge concerning sex-based differences in pain and explores promising new interventions for the prevention and treatment of chronic pain, including vitamin D and omega-3 fatty acids, both of which have powerful anti-inflammatory effects.

2. Prevalence of pain in men vs women and evidence for sex-based differences

It is well established that women have a higher prevalence than men of several clinical pain-related conditions, including migraine headaches, temporomandibular joint disorders, carpal tunnel syndrome, Raynaud disease, fibromyalgia, osteoarthritis (OA), irritable bowel syndrome, and pain related to autoimmune disorders (rheumatoid arthritis and other collagen vascular diseases) [1,2]. In a recent survey of chronic pain, women were much more likely than men to be suffering from chronic widespread pain (CWP) [2] (Table 1). In addition, there is

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Table 1
Prevalence of widespread pain in representative samples

Study	Country	Prevalence	Female	Male
Bergman	Sweden	Chronic	**15%**	**8%**
Buskila	Israel	Chronic	**14%**	**3%**
Gerdle	Sweden	1 wk	**34%**	**22%**
Hardt	United States	1 mo	4%	3%
Thomas	United Kingdom	1 mo	5%	3%
Winjhoven	Netherlands	Current	**12%**	**6%**
Winjhoven	Netherlands	1 y	**20%**	**11%**
Winjhoven	Netherlands	Chronic	**4%**	**1%**

Bolded numbers reflect significant sex differences in prevalence. Source: Fillingim et al (*J Pain* 2009;10[5]:451).

increasing evidence of sex differences in sensitivity to experimental pain and response to analgesics [3,4]. Despite these findings, most animal research on pain and analgesia has included male subjects only; and few studies have been designed to assess sex differences [1,5]. The consensus report has highlighted the need to fill this research gap [1].

In contrast to the sex differences in the prevalence of pain-related conditions, reported sex differences in experimental pain responsiveness have been more subtle and may vary by stimulus modality. A meta-analysis reported that sex differences in threshold and tolerance measures were largest and most consistently found for pressure pain and electrical stimulation, and were smallest and least consistent for thermal pain [6]. Regarding temporal summation of heat pain, commonly used to evaluate differences in the central processing of nociceptive signals, most studies have suggested a more robust response among females than males [1].

Recent research indicates that psychological and social variables powerfully influence pain and may even explain more of the variance than do biological variables [7,8]. More research is needed to address how the relevant psychosocial variables differ in men and women, and how these variables interact with biological sex or sociocultural aspects of gender to influence the experience of pain.

3. Hormonal influences on pain

The influence of gonadal hormones on sex differences in the pain experience, although a subject of great interest, has received limited study. Levels of sex steroid hormones, including estrogens, progesterone, and testosterone, differ substantially between the sexes at different life stages and have diverse effects on the peripheral and central nervous systems. Hormone levels fluctuate widely in women across the life span, including changes during the menstrual cycle, pregnancy, and following menopause [2]. In contrast, men experience much less pronounced fluctuations in hormone levels, aside from changes pre- and postpuberty and some reduction in testosterone levels with aging.

Several lines of evidence suggest hormonal contributions to many clinical pain conditions [1,2]. One line of evidence is that changes in the sex ratio for pain syndromes parallel changes in sex hormone concentrations. For example, prepubertal girls and boys have a similar prevalence of migraine; however, the lifetime prevalence of migraine becomes 3-fold higher in women than men (18% vs 6%) after puberty, suggesting a hormonal link [9,10]. A similar pattern has been found for temporomandibular disorders [11] and other common pain complaints [2]. Another observation is that the severity of symptoms related to several pain conditions, including headaches, fibromyalgia, and irritable bowel syndrome, appears to vary across the menstrual cycle in women, although findings have not been entirely consistent [2]. A third line of support is that pregnancy and the postpartum state are associated with changes in the frequency and severity of certain pain conditions, including migraine and temporomandibular joint symptoms [1,2]. Moreover, exogenous hormone use, such as oral contraceptives and menopausal hormone therapy, has been linked to several pain syndromes, including carpal tunnel syndrome and temporomandibular joint syndrome [12,13]; but the research is inconsistent. Finally, a study of transsexuals undergoing hormonal treatment suggested a greater prevalence of chronic pain in male-to-female patients undergoing estradiol/antiandrogen treatment than in female-to-male patients treated with testosterone [14]. In aggregate, these studies provide evidence for sex hormone influences on clinical pain, with both administration and withdrawal of estrogens increasing the risk for pain.

Regarding changes in pain perception across the menstrual cycle, a meta-analysis concluded that pain thresholds tended to be higher during the follicular phase of the menstrual cycle (low to moderate levels of estradiol and progesterone) than during perimenstrual phases of the cycle (lower levels of these hormones) [15]. The effect sizes were small, however; and other studies have had conflicting results [2,16,17]. Additional evidence for hormonal contributions to pain sensitivity according to sex hormone levels and/or use of menopausal hormone therapy have been inconsistent [18-20]. The mechanisms by which hormones may influence pain perception remain poorly understood, but Fillingim and colleagues [2,20] recommend a broad categorization into peripheral and central nervous system effects, as summarized below.

4. Peripheral vs central nervous system effects of sex hormones

The peripheral effects of sex hormones include their effects on disease pathophysiology and pathways associated with pain. A key factor is the role of hormones in inflammation and the evidence that women tend to have a heightened inflammatory response compared with men [21]. This enhanced inflammatory response may contribute to the substantially higher risk of painful inflammatory autoimmune conditions in women compared with men, including

rheumatoid arthritis, lupus and other collagen vascular disorders, and OA. The effects of estrogens on inflammatory responses are highly complex and depend on the level of estrogens, the time course of the inflammatory process, and several other factors [21,22]. For example, very high estrogen concentrations tend to inhibit inflammation, whereas lower levels of estrogens may produce either no effect or a proinflammatory effect [21,23]. Furthermore, estradiol administered systemically vs centrally may have divergent effects [24-28].

Sex hormones can influence multiple central nervous system pathways, including effects on endogenous opioid systems, dopaminergic and serotonergic activity, and other endogenous components involved in nociception. Sex differences in neurotransmitter levels, receptor binding, and responsiveness to medications acting through these pathways have been identified [2,29-35]. For example, it has been proposed that dysfunction of dopaminergic neurotransmission may contribute to the clinical symptoms of fibromyalgia (ie, CWP and generalized hyperalgesia), which is much more prevalent in women than in men, and that dopamine may represent an important target for the treatment of fibromyalgia [33]. This is a promising hypothesis, but additional research is needed to elucidate the role of dopamine and other systems in sex-related influences on pain. Moreover, an improved understanding of the contribution of psychosocial factors and gender roles will be critically important to advance knowledge and improve clinical pain management in both men and women.

5. Implications for treatment

As noted by Greenspan and colleagues [1], a key goal of research on sex differences in pain and analgesia is to use knowledge about sex-specific mechanisms to improve pain management in both sexes. One avenue to pursue in developing new preventive and therapeutic modalities for pain syndromes is research on nutritional agents with anti-inflammatory properties. Two very promising nutritional interventions are moderate- to high-dose vitamin D and the marine omega-3 fatty acids. The recent launch of the large-scale VITamin D and OmegA-3 TriaL (VITAL) will provide an exceptional opportunity to assess the role of these agents in the prevention and treatment of pain syndromes, such as chronic knee pain due to OA and exacerbations of migraine or other headaches, as well as effects on biomarkers of inflammation and the incidence of autoimmune diseases in the cohort.

VITAL is a large-scale randomized trial, funded by the National Institutes of Health, to test the role of vitamin D (in the form of vitamin D_3 [cholecalciferol], 2000 IU/d) and marine omega-3 fatty acid (eicosapentaenoic acid + docosahexaenoic acid, 1 g/d) supplements in the prevention of cancer and cardiovascular disease. The trial will randomize 20 000 US men and women men, aged at least 60 years and at least 65 years, respectively, to the 2 nutritional interventions in a 2 × 2 factorial design, allowing for the study of the agents' effects both independently and jointly. A recently funded ancillary study will assess the effect of the 2 interventions on autoimmune disease incidence, biomarkers of systemic inflammation, and chronic knee pain in VITAL. Given the much higher prevalence of autoimmune disorders and OA-related joint pain in women than in men, the findings may have particular relevance to women and offer a means to reduce sex-related disparities in these outcomes. If efficacy is established, these popular nutritional supplements could be useful for reducing pain and other morbidity related to inflammatory disorders.

Vitamin D and omega-3 fatty acids have been shown to have anti-inflammatory, immune-modulating, and some pain-modifying effects [36,37]. Data from laboratory studies, observational epidemiologic research, and small prevention trials suggest that these nutritional agents reduce levels of circulating proinflammatory cytokines, decrease chronic joint pain, and may reduce the risk of autoimmune diseases. However, large primary prevention trials in general populations have not been previously conducted. Autoimmune diseases, including rheumatoid arthritis, autoimmune thyroid disease, inflammatory bowel disease, and other conditions, are associated with autoantibody production and systemic inflammation. They are associated with significant morbidity, and no preventive therapy is currently available. Inflammation and immune activation also contribute to the development of chronic knee pain, one of the most common causes of pain and disability in the elderly.

6. Vitamin D

Vitamin D, in addition to its role in calcium homeostasis, has powerful effects on the immune system, inhibiting proinflammatory cytokines such as interleukin-6 and tumor necrosis factor–α and reducing C-reactive protein [36]. Through binding to the vitamin D receptor, which is present in high levels in immune cells, the active $1,25(OH)_2D$ regulates many genes involved in inflammation and acquired and innate immune responses [38,39]. Laboratory studies and observational epidemiologic studies suggest a role for vitamin D in reducing autoimmune disease susceptibility, but large randomized trials of high-dose vitamin D supplements have been lacking.

In addition, although vitamin D appears promising for chronic musculoskeletal pain [40,41] and pain related to arthritis, more rigorous testing of its effects on joint and other musculoskeletal pain is needed. Vitamin D deficiency is known to be associated with pain due to osteomalacia, and several studies suggest an inverse association between 25-OH vitamin D levels and CWP and/or fibromyalgia, especially in women [40,42,43]. In a British study, low vitamin D levels were correlated with CWP in women but not in men (P value for interaction by sex = .03) [41]. An inverse association

between serum vitamin D level and knee pain also has been observed in several studies. In a study of elderly men, those with low serum 25-OH vitamin D levels were twice as likely to have prevalent hip OA [44]; and in another study, older women with symptomatic OA had lower levels of 25-OH vitamin D than women with asymptomatic disease [45]. Two large prospective cohort studies of serum 25-OH D levels and progression of radiographic knee OA have yielded conflicting results, however [46,47]. Moreover, in the only randomized trial to directly test vitamin D's effect on joint pain, 3 months of treatment with high-dose vitamin D (50 000 IU ergocalciferol per week) did not reduce musculoskeletal pain [48]. However, 3 months may have been an insufficient duration of therapy to assess treatment efficacy. Additional study of a potential role for vitamin D supplementation in treating chronic pain, including fibromyalgia, is indicated [40,42,43].

7. Marine omega-3 fatty acids

Marine omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) reduce inflammation through the leukotriene and prostaglandin pathways, decreasing inflammatory mediators and cytokine production [37]. High-dose omega-3 fatty acids are associated with lower levels of biomarkers of systemic inflammation in large observational studies and have promise for the treatment of various types of pain and arthritis, as well as the treatment of those with autoimmune disorders. However, again, no large-scale randomized controlled trials of these supplements have ever tested their effects on systemic inflammation, prevention of autoimmune diseases, or treatment of chronic pain disorders.

Because of their cytokine-suppressing and anti-inflammatory effects, omega-3 fatty acids could have beneficial effects on the inflammatory processes involved in OA and other chronic pain syndromes. In addition, omega-3 fatty acids may have important central nervous system–related effects involving cognition, mood, and behavior, which are central to pain processing [49]. In a meta-analysis of 17 small randomized trials of omega-3 fatty acid supplementation for inflammatory joint pain relief in rheumatoid arthritis, inflammatory bowel disease, or dysmenorrhea, Goldberg and colleagues [50] found that supplementation for 3 to 4 months reduced joint pain intensity, number of painful and/or tender joints, and nonsteroidal anti-inflammatory medication consumption. In a small open-label study, marine omega-3 fatty acid supplementation for 6 months reduced OA pain as assessed by a visual analog scale [51]. Large-scale randomized trials of omega-3 supplementation with longer duration of treatment are needed.

8. Conclusions and future directions

Important sex and gender differences in the pain experience and response to analgesics have been demonstrated. Several lines of evidence suggest that sex steroid hormones contribute to these differences, but the relationships are complex and are likely to be multifactorial. Both the peripheral and central nervous systems, including opioid, dopaminergic, serotoninergic, and other systems, demonstrate sex-related differences and may be affected by gonadal hormones. Psychosocial factors also influence pain and analgesia. Given the important role of inflammation and cytokines in mediating and modulating pain, the potential benefits of nutrients with anti-inflammatory effects should be fully explored. Of particular interest is the promising role of moderate- to high-dose vitamin D and omega-3 fatty acid supplementation in preventing and treating inflammation and chronic pain disorders. These nutritional interventions may be of particular benefit to women due to their higher prevalence of inflammatory chronic pain disorders. The launch of a new large-scale randomized trial of these nutritional supplements provides an opportunity to test these hypotheses. Additional research is needed to elucidate the mechanisms for sex differences in pain and to develop new prevention and treatment options that improve pain management for both men and women.

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