

Pain: sex differences and implications for treatment

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FROM ABSTRACT

Women have a higher prevalence than men of several clinical pain conditions and of inflammation-mediated disorders.

There is 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 pro-nociceptive 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, serotonergic, and other pain-related systems have been documented; and some evidence suggests that differences are most pronounced during the peak reproductive years.

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.

Dr. MANSON NOTES:

1) Inflammation increases the incidence of pain. Both vitamin D and omega-3 fatty acids "have powerful anti-inflammatory effects."

2) "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's disease, fibromyalgia, osteoarthritis (OA), irritable bowel syndrome, and pain related to autoimmune disorders (rheumatoid arthritis and other collagen vascular diseases)."

- 3) Women are much more likely than men to suffer from chronic widespread pain (CWP).
- 4) Women also have increased sensitivity to pain and respond less to analgesic drugs.
- 5) "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." The sex ratio for pain syndromes parallel changes in sex hormone concentrations.
- 6) "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. A similar pattern has been found for temporomandibular disorders and other common pain complaints."
- 7) The severity of symptoms for headaches, fibromyalgia, and irritable bowel syndrome vary across the menstrual cycle in women. There is significant evidence for sex hormone influences on pain, especially estrogen.
- 8) "Women tend to have a heightened inflammatory response compared with men. 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 osteoarthritis (OA)."
- 9) Sex hormones can influence the opioid systems, dopaminergic and serotonergic activity, and other central pathways involved in nociception.
- 10) Dysfunction of dopaminergic neurotransmission may contribute to the clinical symptoms of fibromyalgia (chronic widespread pain and generalized hyperalgesia), which is much more prevalent in women than in men.
- 11) Two very promising nutritional interventions for pain management are moderate- to high-dose vitamin D and the marine omega-3 fatty acids (eicosapentaenoic acid + docosahexaenoic acid). These supplements are also promising in the prevention of cancer and cardiovascular disease.
- 12) Vitamin D and omega-3 fatty acids "reduce levels of circulating pro-inflammatory cytokines, decrease chronic joint pain, and may reduce the risk of autoimmune diseases."
- 13) "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."

- 14) Vitamin D, which is present in high levels in immune cells, regulates many genes involved in inflammation and acquired and innate immune responses.
- 15) Vitamin D reduces autoimmune disease susceptibility.
- 16) Vitamin D deficiency increases chronic widespread pain and/or fibromyalgia, especially in women.
- 17) A high level of vitamin D reduces knee and hip osteoarthritis and pain.
- 18) "Marine omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) reduce inflammation through the leukotriene and prostaglandin pathways, decreasing inflammatory mediators and cytokine production."
- 19) High-dose omega-3 fatty acids are associated with lower levels of biomarkers of systemic inflammation and "have promise for the treatment of various types of pain and arthritis, as well as the treatment of those with autoimmune disorders."
- 20) "Because of their cytokine-suppressing and anti-inflammatory effects, omega-3 fatty acids could have beneficial effects on the inflammatory processes involved in osteoarthritis and other chronic pain syndromes."
- 21) "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."
- 22) Omega-3 fatty acid supplementation for 3 to 4 months improves inflammatory joint pain relief in rheumatoid arthritis, inflammatory bowel disease, dysmenorrhea, and osteoarthritis.

CONCLUSIONS

- 1) "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."
- 2) Given the important role of inflammation and cytokines in mediating and modulating pain, there is a "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."

Cyclo-oxygenase (COX)/Lipo-oxygenase (LOX) Pathways

