Myofascial pain in females and personalized care: the key role played by sex hormones

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Running Title: Sex hormones and myofascial pain in females

It is well established that the prevalence rate of musculoskeletal pain is significantly higher in women with respect to males, with even greater onset of chronic conditions (Ceccarelli et al., 2021). There are data indicating that mechanisms of pain may be different in the two sexes: hypersensitivity to mechanical pain is mediated in male mice by the signaling pathway from the microglia to neurons, and instead by T-lymphocytes in female mice (Sorge et al., 2015). Likewise, male mice lacking testosterone showed a switch to the pain pathway normally noted in females. Conversely, females lacking T-lymphocytes or those that are pregnant, showed a switch to the pain pathway normally observed in males. This sexual dimorphism may be influenced by sex hormones.

Some researchers have recently reported that fascia can be a possible source of pain: if the connective tissue is altered, the behavior of the fascial tissue and the underlying muscle may become compromised causing myofascial pain. The comprehension of how this tissue is remodeled according to physiological and pathological parameters is fundamental for the comprehension of the pain mechanism and for the development of personalized treatment strategies. Sex hormones, just as aging, pathologies, and surgical interventions, may have a direct influence on connective tissues: relaxin inhibits fibrosis and inflammation, and estrogen deficiency is associated with an increase in fibrosis and pain. At the same time, an elevation in estrogen

levels during ovulation has been associated with increased ligament and ankle laxity, and some studies reported a clear analgesic action with high estrogens concentrations.

Knowledge about how sex hormone disorders can dysregulate the fascial tissue is an important step for understanding gender differences in myofascial pain, helping clinicians to diagnose and treat patients. Sex hormone receptors are expressed by fascial fibroblasts, with a lower expression with the decrease in hormone levels in post-menopausal women (Fede et al., 2016). The cells of the fascia can moreover modulate the synthesis of extracellular matrix components depending on hormone levels: when β-estradiol levels are low, fascial tissue becomes enriched in collagen-I (from 5.2% of control sample to 8.4%), with a parallel decrease in collagen-III (from 2.4% to 1.5%) and elastic fibers (from 0.5% to 0.2%) (Fede et al., 2019). Consequently, the tissue becomes less elastic and more rigid, something that normally occurs during menopause. Conversely, when hormone levels are high, as they normally are during the ovulatory peak or during pregnancy, the opposite takes place: collagen-III rises to 6.8% during ovulation and 6.7% during pregnancy as does Fibrillin-1 (from 0.2% in menopause to 3.6% during pregnancy) while collagen-I falls to 1.9% (Fede et al., 2019). The result is softer, more elastic tissue.

These results highlight how hormonal disorders in women can dysregulate the extracellular matrix synthesis, modifying the biomechanical properties of tissue and evoking the sensitization of fascial nociceptors. Reports from clinicians have demonstrated that fluctuations in estradiol are associated with musculoskeletal and joint pain, stiffness and depressed mood during the menopause transition, and oral administration of estrogen can contribute to reducing myofascial pain. But the decrease of estrogen in menopausal women affect the tissues not all in one direction (better or worse): some studies suggested diverse involvement of estrogens in the various pathophysiological mechanisms. Moreover, in postmenopausal women, the differences in pain thresholds disappear, suggesting a switch to a process pain more like men (Ceccarelli et al., 2021).

Also age seems to affect myofascial tissue remodeling: in fact, connective tissues become thicker with aging in favor of collagen I, with a consequent reduction in their gliding properties (Pavan et al., 2020). No differences were found in resistance to the elongation of single muscle fibers in young (~21 years) and elderly (~67 years) subjects. Instead, the contribution of the extracellular matrix significantly increased in the elderly (from 3.3% to 8.2%): the passive stiffness and the reduction in muscle function linked to aging are caused by a stiffening of the extracellular matrix resulting from an accumulation of collagen fibers (Pavan et al., 2020). Hansen et al. demonstrated that together with a decrease in estrogen levels, this mechanism can be linked to the up-regulation

of IGF-1 (insulin growth factor 1), which enhances collagen synthesis. Estrogen replacement therapy can block this mechanism and counteract the degenerative changes helping to maintain muscle strength and reducing stiffness (Hansen 2018). On the contrary, tamoxifen, a non-steroidal anti-estrogen drug used in anti-tumor therapy in breast cancer patients, induces the secretion of TGF-beta, which seems to be associated to the pathogenesis of radiotherapy-induced lung fibrosis. Further studies on how sex hormones have complex and multifactorial effects into fasciae and pain mechanisms are certainly warranted. They will permit to correlate any dysfunctions in hormonal levels linked to pathologies, aging and period of the cycle, to the onset of myofascial pain, thus making it possible to find out a targeted gender therapy.

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