MUSCULOSKELETAL PAIN
IASP Special Interest Group

FACT SHEET

An Update on Personalized Mechanistically Based Management of Musculoskeletal Pain

- **Kristian Kjær-Staal Petersen, dr.med., PhD, MSc:** Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, School of Medicine, and Center for Mathematical Modeling of Knee Osteoarthritis (MathKOA), Department of Material and Production, Faculty of Engineering and Science, Aalborg University, Aalborg, Denmark.
- **Lars Arendt-Nielsen, dr.med., PhD, MSc:** Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, School of Medicine, Aalborg University, and Aalborg University Hospital, Aalborg, Denmark.
- **Esther Pogatzki-Zahn, PhD, MD:** Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Muenster, Muenster, Germany.

The most common treatments of for musculoskeletal (MSK) pain are: 1) exercise-based therapy in combination with pain education (and weight loss if needed), 2) nonsteroidal anti-inflammatory drugs (NSAIDs) for short period of time, paracetamol, and 3) surgery. Exercise-based therapy in combination with pain education provide an average pain relief of 20-25% depending on the condition. Approx. 50-60% of patients will gain at least moderate pain relief (analgesic effect >30%) from NSAIDS and COX-2 inhibitors providing slightly better analgesic effects. Surgery reduces pain and analgesic consumption in most patients. However, 10-50% of patients are at risk of developing chronic postoperative pain following surgery of the joint.

Conclusively, it is evident that current standard pain management regimes work better for some patients versus others. One key aspect of personalized mechanistic pain management is to identify responders versus non-responders but also patents at risk for developing side-effects.

This fact sheet provides an update on current attempts to personalize MSK pain management.

Sensitization of central pain mechanisms

The nervous system transmits nociception can facilitate and/or impair the incoming nociceptive signals. The pain sensitization can occur in the peripheral, spinal, and descending pain pathways perpetuating each other and most likely lead to chronification.

Quantitative sensory testing (QST) is a semi-objective, psychophysically assessment technique to evaluate the sensitivity of the somatosensory system in general. Decades of research have linked QST assessed increased pain sensitivity to clinical MSK pain intensity [1]. Importantly, pain sensitivity is an umbrella term, but it can be broken down into subsets of assessments focusing on the peripheral nervous system pressure pain thresholds (PPTs) are often used), the spinal excitability (temporal summation of pain (TSP) is often applied), and the assessment of the descending pain inhibitory pathways (conditioned pain modulation (CPM) is often employed). A patient can be can be profiled as being more or less pain sensitive based on the beforementioned testing procedures [7], and studies suggest that more pain sensitive patients are less likely to gain pain relief from e.g. exercise based therapy and/or NSAIDs and are more likely to develop chronic postoperative pain following joint replacement surgery [8].

Inflammation

Inflammation can contribute to MSK pain, such as local inflammation (e.g., synovitis) or systemic (e.g., chronic low-grade inflammation). Systemic pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α) have been found upregulated in patients with MSK pain and associated with increased clinical pain intensity [4]. The first pilot studies suggested a role of predisposed immune malfunction in certain patients that may expose these individuals to a higher risk of developing e.g. chronic postoperative pain [5]. Hypothetically, biomarkers like

inflammatory networks might guide therapy and prevention of chronic postoperative pain [9]. A number of epigenetic markers have also indicated non-favorable changes involved in driving inflammation [6].

Mental Health Factors

Increased symptoms of anxiety and depression, and higher levels of a so-called "pain catastrophizing", an exaggerated or negative cognitive–affective response to anticipated or actual pain, are often associated to higher clinical pain in patients with MSK pain [3]. Poor quality of sleep is present in 50-75% of patients with chronic pain and poor quality of sleep is associated with higher levels of anxiety, depression and pain catastrophizing [2]. Higher levels of symptoms of anxiety, depression and pain catastrophizing have been associated with higher risk for developing chronic postoperative pain with catastrophizing having the highest predictive value [10].

The Future of Personalized Pain Medicine

The bio-psycho-social concept applies also to the field MSK pain and hence be implemented in the development of personalized MSK pain management. Several risk factors for poor treatment outcomes have been identified but currently, no evidence-based recommendations are available. Several randomized controlled trials have been conducted attempting to modulate e.g. preoperative risk factors for chronic postoperative pain but in general, these have so far not been successful. Future studies should explore the use of "enriched randomized controlled trials", which aims to apply a treatment to a patient population who are likely to respond to this treatment – examples of this could be 1) testing central acting compounds in patients with higher levels of pain sensitization, 2) testing anti-inflammatory treatments in patients with high levels of inflammation, 3) testing cognitive behavioral therapies in patients with negative affect or poor coping skills, or 4) assessing individualized multi-modal therapeutic strategies addressing the bio-psycho-social context of MSK pain.

References

[1] Arendt-Nielsen L, Morlion B, Perrot S, et al. Assessment and manifestation of central sensitisation across different chronic pain conditions. Eur J Pain;22:216–241 2018.

[2] Boye Larsen D, Laursen M, Simonsen O, et al. The association between sleep quality, preoperative risk factors for chronic postoperative pain and postoperative pain intensity 12 months after knee and hip arthroplasty. Br J Pain;15:486–496 2021.

[3] Edwards RR, Cahalan C, Mensing G, et al. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol;7:216–224 2011.

[4] Eitner A, Pester J, Vogel F, et al. Pain sensation in human osteoarthritic knee joints is strongly enhanced by diabetes mellitus. Pain;158:1743–1753 2017.

[5] Giordano R, Ghafouri B, Arendt-Nielsen L, et al. Inflammatory biomarkers in patients with painful knee osteoarthritis: exploring the potential link to chronic postoperative pain after total knee arthroplasty-a secondary analysis. Pain;165:337–346 2024.

[6] Giordano R, Petersen KK, Andersen HH, et al. Preoperative serum circulating microRNAs as potential biomarkers for chronic postoperative pain after total knee replacement. Mol Pain;16:1744806920962925 2020.

[7] Hertel E, de Andrade DC, Petersen KK-S. An attempt to identify nociceptive and nociplastic pain profiles using a clinical test for joint pain. Pain 2024.

[8] Petersen KK-S, Kilic K, Hertel E, et al. Quantitative sensory testing as an assessment tool to predict the response to standard pain treatment in knee osteoarthritis: a systematic review and meta-analysis. PAIN Reports;8:e1079 2023.

[9] Pogatzki-Zahn EM, Segelcke D. Searching for the rainbow: biomarkers relevant for chronic postsurgical pain. Pain;165:247–249 2024.

[10] Theunissen M, Peters ML, Bruce J, et al. Preoperative anxiety and catastrophizing: A systematic review and meta-analysis of the association with chronic postsurgical pain. Clin J Pain;28:819–841 2012.