GABA, glutamate, glutathione, and central pain in people with knee osteoarthritis: a pre- and post-knee replacement study

Mataea Armstrong, University of Calgary, Cumming School of Medicine, mataea.armstrong@ucalgary.ca

Abstract: KOAPAIN2 is a multimodal clinical study that aims to elucidate the pathophysiology of chronic pain in knee osteoarthritis using advanced imaging methods. We will collect structural, neurochemical, psychological and sensory data to study this pain. Our primary aim is to analyze neurochemical concentrations in pain-processing centers of the brain in people with and without knee osteoarthritis from 40-75 years old. These data will also be collected following knee replacement at 3- and 6-month follow-ups.

Knee osteoarthritis:

Knee osteoarthritis (KOA) is a degenerative joint disease affecting over 250 million individuals worldwide (1). KOA involves degradation of both bone and cartilage health, ultimately resulting in chronic pain and decreases in freedom of mobility and quality of life (2). Currently, available treatments for KOA allow for pain management and slowed disease progression. However, there are no available treatments to stop or reverse the deterioration of joint tissues and the associated symptoms. Knee replacement is the final treatment option for KOA, with total knee arthroplasty (TKA) involving the removal of affected bone and cartilage and replacement with orthopedic hardware. Unfortunately, 15-40% of TKA patients continue to experience chronic pain despite the removal of these damaged joint tissues (3). This persistent pain effect suggests that the pathophysiology of KOA extends beyond localized joint damage and involves the development of maladaptive central pain processing mechanisms.

KOAPAIN2:

To study these mechanisms of central pain in KOA, our study employs advanced magnetic resonance imaging (MRI) of the brain and knee, weight-bearing computed tomography (WBCT) of the knee, questionnaire data, and quantitative sensory testing (QST). This multimodal study, called KOAPAIN2, will provide us with insight into structural, psychological, and neurochemical differences between people with KOA and age- and sex-matched controls. We will also be collecting longitudinal data in people with KOA before TKA, and at 3- and 6-months post-TKA. This will empower the study to analyze the effects of recovery from KOA symptoms and chronic pain. The primary aim of this study is to use magnetic resonance spectroscopy (MRS) to quantify neurochemical concentrations within pain processing centers of the brain, allowing for comparisons both between KOA patients and normative controls, and in pre- and post-TKA recovery analyses. Our study will evaluate four regions of the brain associated with pain signalling and emotional response: the primary somatosensory, anterior and posterior insular, and anterior cingulate cortices (4). Our neurochemicals of interest are gamma-aminobutyric acid (GABA), the brain's primary inhibitory neurotransmitter, glutamate, the brain's primary excitatory neurotransmitter, and glutathione, which acts as a marker of oxidative stress in the brain (5, 6). The KOAPAIN2 study also aims to uncover relationships between our neurochemical analyses, questionnaire data, and QST. By quantifying individual pain thresholds, sensitivity, and modulation using QST (7), we will be able to assess the impact of KOA on pain perception and integration. Combining advanced imaging methods, QST, and questionnaires to assess central pain, sensitization, and psychological factors, our study is uniquely positioned to uncover a pathophysiological framework of KOA pain.

Significance:

By uncovering the pathophysiology of KOA pain and its disintegration from joint tissue damage, we hope to identify factors impacting patient response to TKA and uncover potential targets for subsequent treatments. This body of work could also be impactful for other chronic pain disorders involving the dysregulation of central pain processing networks. Our work aims to understand why KOA pain persists in 15-40% of people following TKA (3), and how we can identify, treat, and prevent this pain.

References

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