Chronic Alcohol Consumption Increases Pain Hypersensitivity in a Preclinical Model of Post-Traumatic Osteoarthritis Independent of Structural Changes

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INTRODUCTION: Post-traumatic osteoarthritis (PTOA) remains one of the leading causes of chronic pain and disability worldwide. Available therapies such as NSAIDs, physical therapy, and corticosteroid injections may provide only transient pain relief for patients, leaving a significant treatment gap before possible joint replacement. This prolonged period may lead individuals to self-manage their pain, with some turning to alcohol for temporary relief. Consistent with this behavior, diagnosed osteoarthritis increases the risk of alcohol use disorder (AUD)-associated hospitalizations by approximately 10%.[1] Chronic alcohol exposure induces neuroadaptations that increase excitatory signaling and reduce inhibitory control within pain pathways, contributing to hyperalgesia and further negative affective states[2]. When combined with joint damage associated with OA, these neuroadaptations may amplify both the sensory and emotional dimensions of pain, reinforcing alcohol consumption and creating a self-perpetuating cycle of misuse. The interaction between AUD and musculoskeletal pain is thus complex and bidirectional, with chronic drinking potentially exacerbating nociceptive sensitivity while persistent pain promotes continued use. While clinical[3] and preclinical studies[4] have suggested a possible link between excessive alcohol use and progressive joint damage associated with OA, the mechanisms linking alcohol exposure to osteoarthritic pain sensitization remain minimally explored. We hypothesized that chronic alcohol use would exacerbate osteoarthritic pain behavior, inflammation, and joint damage in a PTOA model using young-adult male rats.

METHODS: All experiments were approved by the IACUC committee. Male Lewis rats (N=32), aged three months, were used in this pilot study. We focused initially on males due to their higher propensity for AUD, despite OA being more prevalent in females; studies including female rats are planned for the future. Rats were assigned to four groups: Sham, MMT (medial meniscus transection), MMT with 10% ethanol (EtOH), and MMT with 20% EtOH (N=8/group). Ethanol was gradually introduced into the drinking water of the 10% and 20% EtOH groups until target concentrations were reached, while the remaining groups received water only. Rats were maintained on their respective diets for three weeks prior to surgery and were weighed weekly throughout the study. OA was induced using MMT surgery, which included medial collateral ligament transection in all groups and medial meniscus transection in the MMT groups, while Sham rats received only the ligament transection. Pain and function were assessed longitudinally using gait analysis, von Frey testing, and pressure application monitoring at baseline and at 2-, 4-, and 6-weeks post-surgery. At the 6-week study conclusion, subchondral bone, cartilage, and osteophyte growth were imaged using contrast-enhanced microcomputed tomography. Cytokine and chemokine concentrations were measured in synovial fluid and serum using multiplex ELISA. Morphological, behavioral, and cytokine data were analyzed using mixed models. Group was used as a fixed variable, with time and time*group included for longitudinal measurements. Post-hoc tests of Tukey HSD or Wilcoxon were used when appropriate.

RESULTS: Fluid intake remained consistent and similar between control and 10% EtOH groups but remained depressed in the 20% EtOH group (Fig. 1A) with a corresponding drop in mass (not shown). We only intervened in the 20% EtOH group at week 3 by adding sucrose to the fluids, which increased consumption in two cages and resulted in elevated blood alcohol content at the study end (Fig. 1A), thus demonstrating the potential of this model in future studies; however, due to the low consumption and masses, this group was excluded from further analysis. Male rats that received MMT surgery displayed hyperalgesia as early as 1-week post-surgery, and some signs of allodynia by 6 weeks post-surgery (though this did not reach significance). Rats in the 10% EtOH group exhibited heightened hyperalgesia by 6 weeks post-surgery, with significantly lower median withdrawal forces compared to MMT rats receiving water ($p=0.019$) and Sham controls ($p=0.001$) (Fig. 1B). Similarly, ethanol intake led to allodynia compared to sham rats ($p=0.017$) (Fig. 1B). Despite these changes in pain behavior, ethanol consumption did not significantly alter joint pathology (Fig. 1C). Subchondral bone volume, cartilage lesions, osteophyte size, and cartilage attenuation were comparable between ethanol-consuming and water-consuming MMT rats. While there were no significant differences in serum cytokine levels among the groups, synovial fluid from ethanol-consuming rats revealed elevated cytokine levels relative to both the sham and MMT/water groups (Fig. 1D). Specifically, MMT/10% EtOH rats exhibited significantly higher IL-2 ($p = 0.035$) and IL-4 ($p = 0.035$) compared to MMT controls. Other cytokines, including IL-10 ($p=0.061$) and IL-6 ($p=0.094$), may also be higher due to ethanol consumption but did not reach significance in this pilot study. These results indicate that moderate ethanol intake amplifies pain behaviors and local (but not systemic) inflammation following MMT without exacerbating joint structural damage.

DISCUSSION: Preclinical AUD literature is extensive but dominated by addiction and psychology research using mice or rats selectively bred for alcohol preference, or outbred rats not commonly used for osteoarthritis research. Here, we developed a novel chronic alcohol drinking model within our PTOA model using male Lewis rats demonstrating two of the six required criteria for AUD models, including self-administration of ethanol reaching relevant blood alcohol concentrations. Our results demonstrate that 10% ethanol intake increases hyperalgesia and allodynia following MMT surgery despite no observable morphological changes. While ethanol intake did not lead to increased systemic inflammation, local inflammation was elevated with increased IL-2 and IL-4 levels in the synovial fluid of rats from the MMT/10% EtOH group. While typically considered to be anti-inflammatory, high levels of IL-4 in severe OA have been associated with greater symptoms and progression. As we did not observe any differences between the Sham and MMT controls, the elevated levels of cytokines in the ethanol drinking rats suggest a greater role of local inflammation in the presentation of pain-related behaviors of these rats. Pending histology and immunohistochemistry may provide further insight into this potential mechanism. As this was a pilot study, the study scope was limited and thus future studies will also need to evaluate different ethanol levels, presentation in female rats, and the effect of ethanol in Sham rats. Further, evaluating pain response in these OA rats to ethanol withdrawal remains a clinically relevant question to be addressed. Together, our initial results suggest that ethanol consumption increases local joint inflammation and exacerbates pain behaviors in PTOA without exacerbating joint damage.

SIGNIFICANCE: Osteoarthritic patients may seek self-medication through alcohol misuse for temporary pain relief; however, our findings reveal that chronic alcohol consumption can amplify joint hyperalgesia and allodynia potentially through elevated local inflammation.

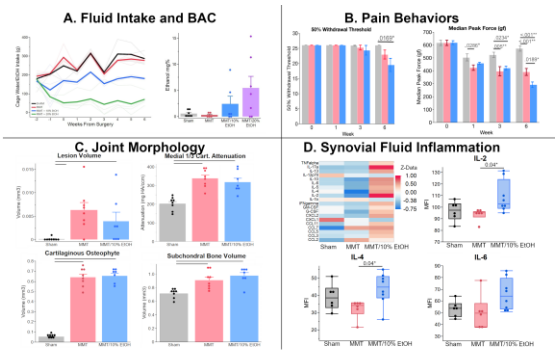

Figure 1. (A) Fluid intake and blood alcohol concentrations (BACs). Rats in the 20% ethanol group consumed less alcohol due to intolerance yet showed higher relative BACs. (B) Hind paw sensitivity measured with Von Frey filaments revealed lower withdrawal thresholds in 10% ethanol rats by six weeks post-surgery, indicating increased allodynia. Pressure application testing on the medial knee showed reduced withdrawal forces, consistent with heightened hyperalgesia. (C) Ethanol consumption did not significantly affect osteophyte size, subchondral bone volume, or cartilage attenuation (inversely correlated with proteoglycan content). Although ethanol-treated rats showed slightly smaller cartilage lesions, no structural differences in joint morphology were observed. (D) Multiplex Luminex analysis revealed significant increases in IL-2 and IL-4 in synovial fluid, with no significant changes detected in serum.

REFERENCES: 1. Singh JA et al. J Clin Rheumatol 2022. 2. Cucinello-Ragland JA et al. Int Rev Neurobiol 2021. 3. Liu T et al. OA Cart 2022. 4. KC R et al. Arth Rheum 2015.

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