Cannabinoid-Induced Gene Expression Changes in a Spinal Fusion Model

Kaveh Momenzadeh, MD*; Diana Yeritsyan, BS; Nadim Kheir, MD; Mohammadreza Abbasian, MD; Edith Martinez Lozano, MD; Caleb Yeung, MD; Harold Fogel, MD; Ara Nazarian PhD, DrSc*

Purpose: The rising opioid epidemic is a public health crisis affecting orthopaedic care and pain management. Medical marijuana is a potential non-opioid analgesic yet to be studied in the surgical setting, since its effects on fracture repair are not fully understood. Studies have demonstrated analgesic and potentially osteoinductive properties of cannabinoids with endocannabinoid receptor expression in bone tissue. This study aims to understand the molecular, tissue, and cell responses to the administration of tetrahydrocannabinol (THC) and cannabidiol (CBD) compounds in a fracture repair model.

Methods: L4-L5 posterolateral, inter-transverse lumbar spinal fusion was performed utilizing allogenic bone grafts. Treatments of saline, THC, CBD, or CBD+THC dosed at 5 mg/kg were delivered intraperitoneally. Callus tissue were harvested 2 and 8 weeks post-surgery for qPCR (quantitative polymerase chain reaction) assessment to quantify changes in expression of osteogenic genes. Micro-CT (μCT) image-based callus analysis and histology were performed. One-way analysis of variance followed by post hoc comparisons were performed.

Results: μCT demonstrated significantly higher mineralized bone volume fraction (BV/TV) for the CBD and THC groups compared to saline. Quantitative PCR at 2 weeks indicated downregulated RANKL/OPG ratios skewing towards osteogenesis in the CBD and CBD+THC groups, with the THC group demonstrating a downward trend ($P>0.05$). ALPL, BMP4, SOST, and CTNNB1 were all significantly higher in the CBD group, with CTNNB1 also showing an upregulating trend in the THC and CBD+THC groups. Data at 8 weeks show no change in expression of CTNNB1, MMP13, or Col1A1. Osteoblast activity markers ALPL and RUNX2 at 8 weeks were downregulated for all treatment groups, while SOST was downregulated for CBD and THC. In the CBD+THC group, RANK, RANKL, and OPG were downregulated. OPG downregulation reached significance for the CBD+THC group compared to saline. Interestingly, RANKL/OPG ratio showed upregulation in the CBD and CBD+THC groups. RANKL showed upregulation in the CBD and THC groups.

Conclusion: Osteogenic factors were upregulated in the cannabinoid-treated groups at 2 weeks, which indicates a potential for bone regeneration. The RANKL/OPG ratio as an indicator for the metabolic state of bone is showing downregulation at 2 weeks and upregulation at 8 weeks, in line with physiological expectation of a lower ratio in the early phases and higher in the later remodeling phases; thus, cannabinoids showed enhanced effects with no adverse effect on bone regeneration outcome.

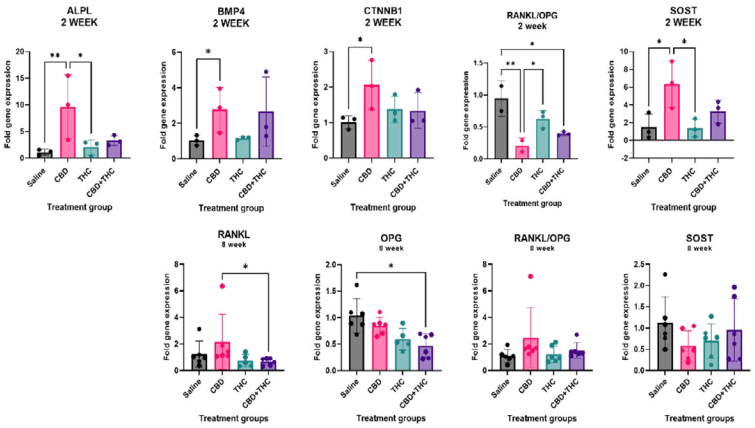

Figure 1. 2 week and 8 week qPCR data representing gene expression fold changes compared to Saline control and B-actin.
ALPL: Alkaline Phosphatase
BMP4: Bone Morphogenetic Protein 4
CTNNB1: Beta-Catenin
SOST: Sclerostin
RANKL: Receptor Activator of Nuclear Factor Kappa B Ligand
OPG: Osteoprotegerin
* represents P <0.05
** represents P <0.01

See the meeting website for complete listing of authors' disclosure information. Schedule and presenters subject to change.