

Weight-Bearing Locomotion Mitigates Knee PTOA Progression in Rodents: A Systematic Review and Meta-Analysis

Sydni V.W. Whitten¹, Michael Jones¹, Marin Plemmons², Young Hui Chang², Jarred Kaiser^{3, 4}, Liang-Ching Tsai¹

¹Department of Physical Therapy, Georgia State University
²School of Biological Sciences, Georgia Institute of Technology
³Department of Orthopaedics, Emory University
⁴Atlanta VA Medical Center

swhitten4@student.gsu.edu

Disclosures: Sydni V.W. Whitten (N), Michael Jones (N), Marin Plemmons (N), Young Hui Chang (N), Jarred Kaiser (N), Liang-Ching Tsai (N)

INTRODUCTION: Post-traumatic osteoarthritis (PTOA) of the knee has been associated with abnormal knee joint loading post-injury. However, no standardized weight-bearing (WB) activity guidelines exist to delay the progression of PTOA following knee injuries. Examining the effects of WB parameters can be challenging in human subject testing. Animal models provides an alternative to investigate the causal-effect of WB exercise interventions on PTOA. This systematic review and meta-analysis evaluated the impact of WB locomotive exercises on knee PTOA outcomes in rodent models to better understand regenerative rehabilitation strategies for patients with traumatic knee injuries.

METHODS: Studies that were published up to January 2025 were reviewed and included if it met the following criteria: (1) rodent models of knee PTOA, (2) comparison of WB locomotive exercises (i.e., treadmill or wheel running) vs. no exercises, and (3) outcome measures evaluating the severity of PTOA, including composite knee OA scores (OARSI and Mankin), cartilage morphology (thickness, volume, roughness, or lesions), cartilage quality based on chondrocyte, proteoglycan or type II collagen content, and/or osteophyte morphology. A total of 22 studies that involved 606 rodents were included. Seventy-eight Cohen's d effect sizes (ES) were calculated. If significant heterogeneity was observed for a PTOA outcome measure across studies, subgroup and meta-regression analyses were used to explore potential moderator variables, such as different animal species, PTOA model used, intensity and duration of the intervention, frequency, and time of exercise initiation, that may influence study results.

RESULTS SECTION: WB locomotion had a significant positive effect on overall knee joint health quantified using the OARSI or Mankin composite scores (ES=1.14, $p<0.001$) with substantial heterogeneity across study ESs ($I^2=78.8$, $p<0.001$; Figure 1). Follow-up analysis revealed that greater knee composite scores (less PTOA) were significantly associated with longer intervention durations ($r=0.600$, $p<0.001$; Figure 2). Although the ES for cartilage quality was not statistically significant ($p=0.07$), high heterogeneity was also observed ($I^2=56.4$, $p=0.014$). Follow-up analyses revealed that greater locomotion speed was associated with lower cartilage quality ($r=0.700$, $p=0.04$). Locomotive exercises did not have a significant effect on the remaining PTOA outcome variables (all $p>0.051$).

DISCUSSION: Findings from this meta-analysis suggest that WB locomotion has the potential to serve as a protective strategy against knee PTOA progression in rodents. Composite knee OA scores may be more sensitive markers for preserving post-injury knee joint health with WB exercises than individual morphological and/or histological variable. Moreover, the association between increased intervention duration and better knee joint health indicates that engaging in long-term WB activities may be essential to gaining the therapeutic benefits of WB exercises. However, WB locomotive exercises at a high intensity/speed may diminish cartilage quality.

SIGNIFICANCE/CLINICAL RELEVANCE: Although early WB restrictions are often prescribed to patients after traumatic knee injuries in hopes of promoting tissue healing, this meta-analysis indicates that WB locomotion may prevent/delay knee joint degeneration after trauma knee injuries in rodent models. These results suggest that rehabilitation following traumatic knee injuries may need to emphasize safe and prolonged WB activity rather than restricting activity participation. Further work establishing an optimal timing and dosing threshold for WB exercise interventions is warranted to maximize the therapeutic benefits of WB activities.

REFERENCES: 1. Primorac D, et al. Genes (Basel). 2020;11(8):163-179; 2. Dilley JE, et al. Bone Rep. 2023;18; 3. Kaiser J, et al. Osteoarthr Cartil. 2024;32:912-921; 4. Oka Y, et al. Osteoarthr Cartil Open. 2023;5(2):100359; 5. Lin Y, Christiansen B. Connect Tissue Res. 2025.

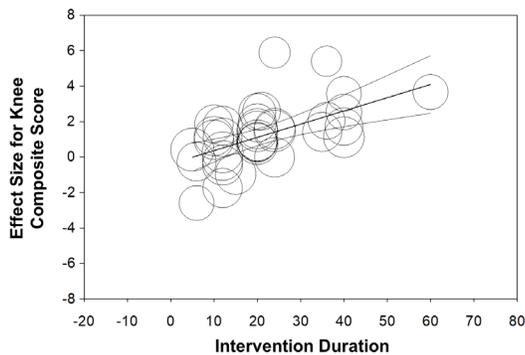


Figure 2. Longer exercise intervention durations (X-axis) was significantly ($p<0.001$) associated with greater ES for knee composite scores for knee OA severity (Y-axis).

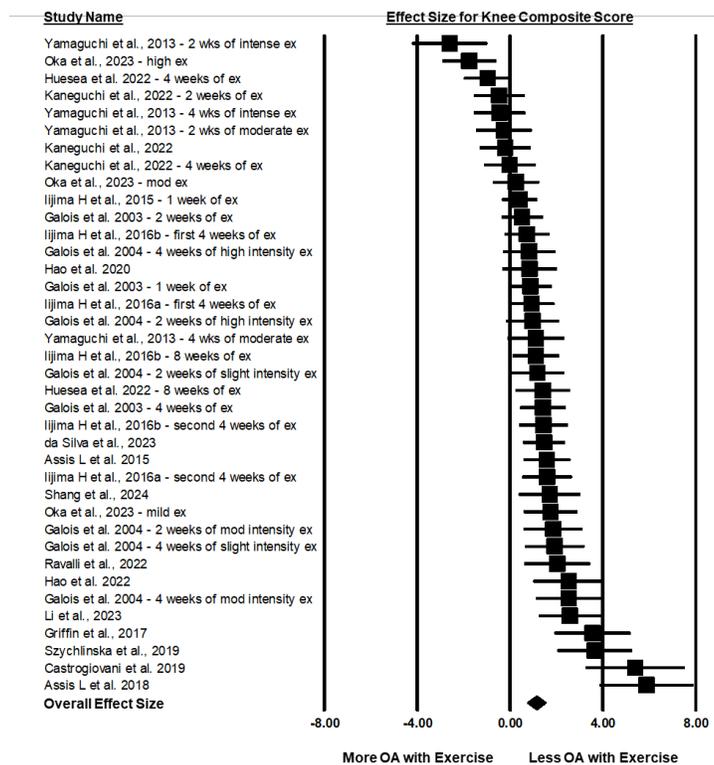


Figure 1. Knee OA severity (OARSI or Mankin composite score) forest plot indicating significantly less PTOA in the WB locomotive exercise groups ($p<0.001$).