The Impact of Rehabilitation on Bone Healing Depends on Injury Severity

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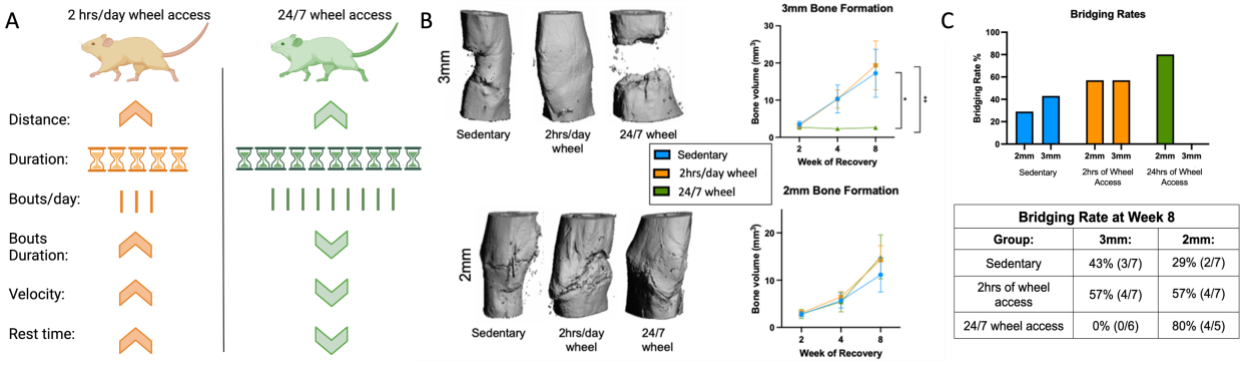
INTRODUCTION: Complex bone injuries exhibit high complication rates and poor functional recovery, partially due to insufficient understanding of how rehabilitative loading impacts bone healing. The emerging field of regenerative rehabilitation aims to uncover the relationship between regenerative medicine and rehabilitation strategies by exploring how mechanical stimuli impact the ability for tissues to regenerate. Within this field, our lab investigates rehabilitation regimens that may aid in functional regeneration of bone healing in our rodent segmental defect model. Though it is well established that loading can increase bone formation, several studies have documented that excessive strains across bone defects were detrimental to healing and others have observed that low strains repressed callus formation and subsequent bone healing. These findings highlight the lack of knowledge regarding the optimal regimes of loading and subsequent translation into rehabilitation decisions. To help address this need, we investigated how distinct rehabilitation profiles impact functional bone healing after different injury sizes. Further, our study gave rats voluntary access to exercise wheels for either unlimited duration (24hrs/day) or restricted duration (2 hrs/day) to investigate how exercise duration impacts bone healing after bilateral surgically induced femoral injuries. We expected the group with 2 hrs/day of wheel access to run significantly less distance and duration than the group with 24/7 wheel access. We hypothesized that restricted rehabilitation (2 hrs/day of wheel access) would increase bone formation in an injury size dependent manner.

METHODS: To investigate the effects of rehabilitation parameters on bone healing of different injury sizes, we assessed longitudinal activity and bone healing in bilateral 2 and 3mm femoral defects that were stabilized with compliant fixation plates. Rehabilitation regimens were facilitated by providing access to a rodent exercise wheel (Exotic Nutrition Store). A total of 20 rats were included across sedentary (n = 7), restricted access (2 hrs/day of wheel access, n = 7), and unlimited access (24 hrs/day of wheel access, n = 6). Rats in the sedentary group were housed in standard cages with no wheel, while the restricted access subjects were housed in standard cages and manually transferred to wheel cages from 8-10pm daily. Subjects in the unlimited access group were housed in wheel cages. In-vivo radiography and microCT scans were performed at two, four, and eight-week time points to monitor bone healing. Continuous activity data were collected using revolution counters. Lafayette Scurry software and Python codes were used to calculate activity parameters (running distance, duration, number of daily running bouts, bout duration, rest time, and velocity). The two-tailed Mann Whitney U-test was used to analyze the impact of rehabilitation conditions on activity parameters. Two-way ANOVA with Tukey's multiple comparisons test was used to analyze the impact of rehabilitation conditions and time on bone formation. All work was approved by University of Oregon's IACUC.

RESULTS SECTION: Unexpectedly, both rehabilitation groups ran the same daily distance ($p = 0.7104$) independent of hours of wheel access (Figure 1A). The group with unlimited access ran for a significantly longer duration and more running bouts per day compared to the restricted access group ($p = 0.0006$, Figure 1A). We also found that the unlimited access group ran at a significantly slower velocity, shorter bout duration, and rested less hours than the group with 2 hours of daily wheel access ($p = 0.0006$, Figure 1A). MicroCT 3D reconstructions of 3mm explanted femurs revealed consistent nonunion in the unlimited access group, while the restricted access group exhibited more uniform bridging than femurs from sedentary subjects (Figure 1B). Further, microCT quantification revealed that unlimited access, which resulted in subjects training more often and resting for fewer hours each day, exhibited significantly less bone formation than the group with restricted wheel access ($p = 0.0063$) and sedentary counterparts ($p = 0.0192$, Figures 1B). In contrast, for the 2mm injuries, we found that there was no difference in the bone volume or bridging integrity across rehabilitation conditions (Figure 1B). We also found that bridging rates of the unlimited access group changed with injury severity as 3mm bone injuries had a 0% bridging rate while 2mm bone injuries had an 80% bridging rate (Figure 1C).

DISCUSSION: Our unexpected finding that both rehabilitation groups ran roughly the same daily distance (m/day) may be due to several factors including (1) the 2 hrs/day of wheel access group was well rested, allowing them to run more and faster during their restricted running window and (2) this group was behaviorally more motivated to run after habituation to the restricted window of wheel access. Unlimited wheel access resulted in subjects training more often with a shorter daily rest time, which ultimately led to significantly less endpoint bone volume than sedentary and restricted wheel access subjects for 3mm defects. In fact, all 3mm defects from the unlimited wheel access group resulted in non-union (Fig. 1C). However, 2mm defects exhibited similar bone formation independent of rehabilitation conditions. This finding suggests that optimized rehabilitation protocols depend on patient-specific factors such as injury severity. For more severe injuries, limiting exercise and ensuring adequate rest is critical to avoid negative effects on bone healing. In contrast, for less severe injuries, rehabilitation exercise improved bridging rates compared to sedentary conditions.

SIGNIFICANCE/CLINICAL RELEVANCE: Despite recent advancements in understanding of mechanobiology principles, there remains a clinical need for data-informed rehabilitation and an improved understanding of how mechanobiology principles translate to clinical rehab decisions. The objective of this study was to investigate how distinct rehabilitation profiles impact functional bone regeneration in an injury-specific manner. Our healing results reveal that optimal rehabilitation conditions depend on injury severity, highlighting the clinical importance for patient-specific factors when formulating rehabilitation regimens.



Bridging Rate at Week 8		
Group:	3mm:	2mm:
Sedentary	43% (3/7)	29% (2/7)
2hrs of wheel access	57% (4/7)	57% (4/7)
24/7 wheel access	0% (0/6)	80% (4/5)

Fig. 1. Running more bouts/day with shorter rest time inhibited bone formation for large bone defects but did not influence healing of smaller bone defects. (A) Diagram summarizing rehabilitation profiles. (B) microCT reconstructions and bone volume quantifications within centered region of 3mm and 2mm defects. (C) bridging rates after 8 weeks of recovery.