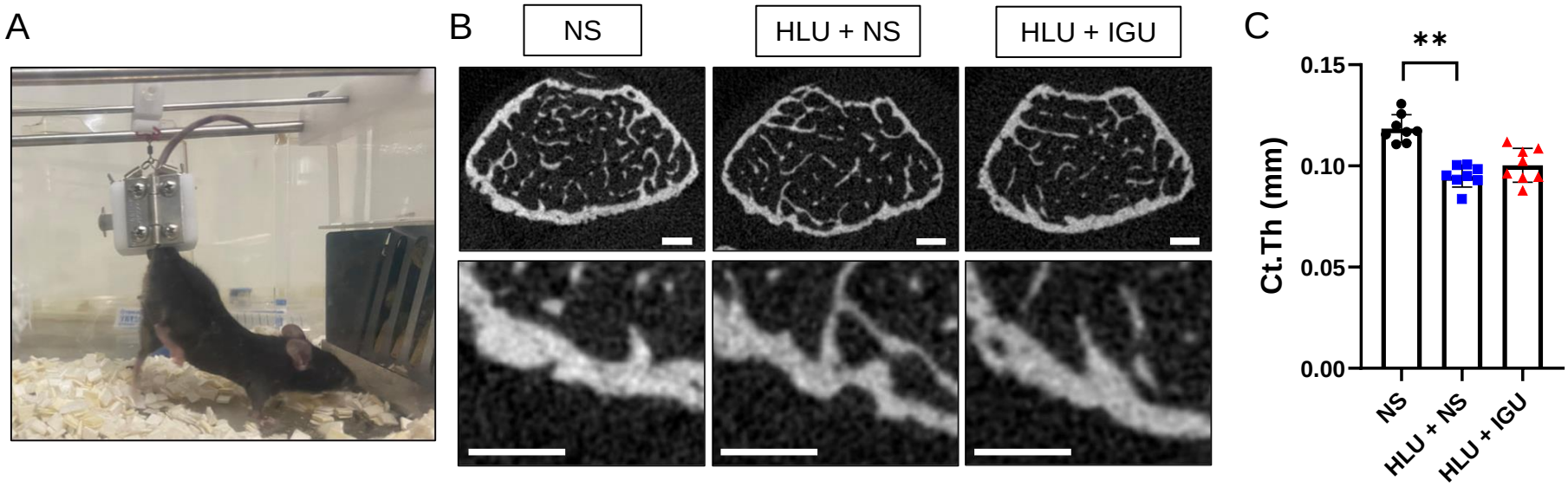
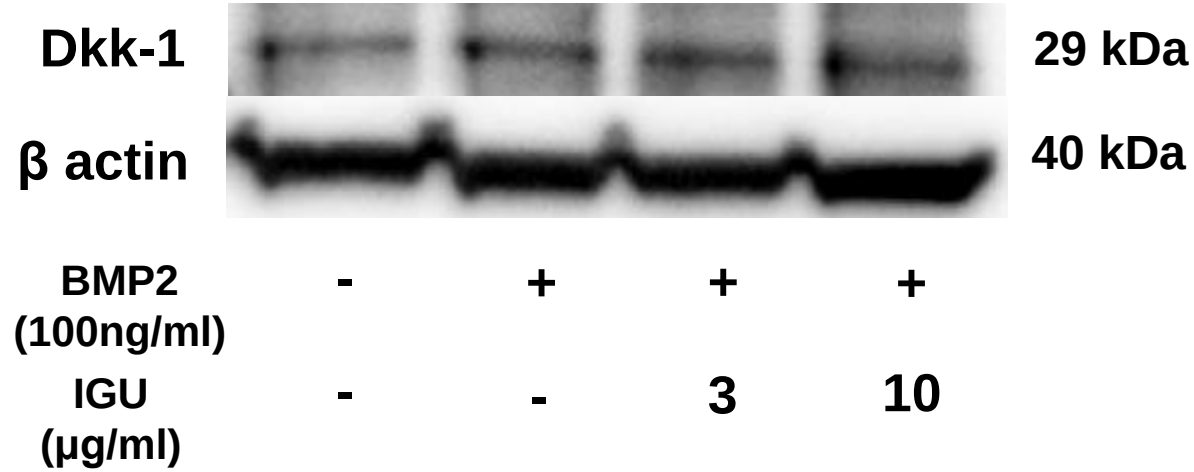
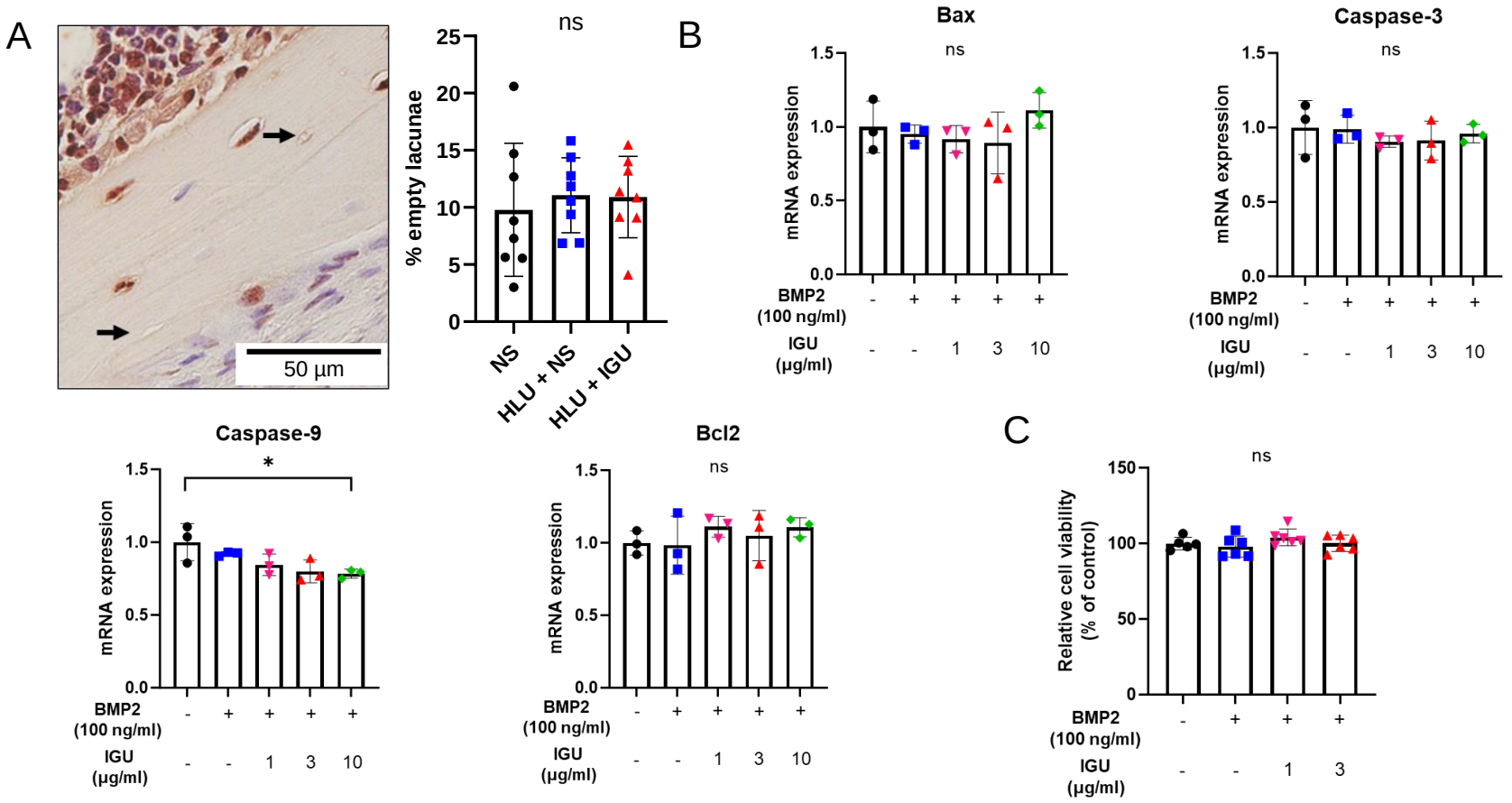


Supplemental Figure 1. Effects of normal saline (NS) or iguratimod (IGU) on cortical bone loss in hindlimb-unloaded (HLU) mice. (**A**) Tail-suspended hindlimb-unloaded mice confined in the cage, demonstrating the suspension system. (**B**) Representative microcomputed tomography images of the distal femur in the three groups after the intervention. Scale bars: 500 μm. (**C**) Quantification of the cortical bone parameter: cortical thickness (Ct.Th). One-way ANOVA followed by Tukey's post-hoc analysis, **$p < 0.01$. All data were expressed as mean ± standard deviation for eight mice in each group.



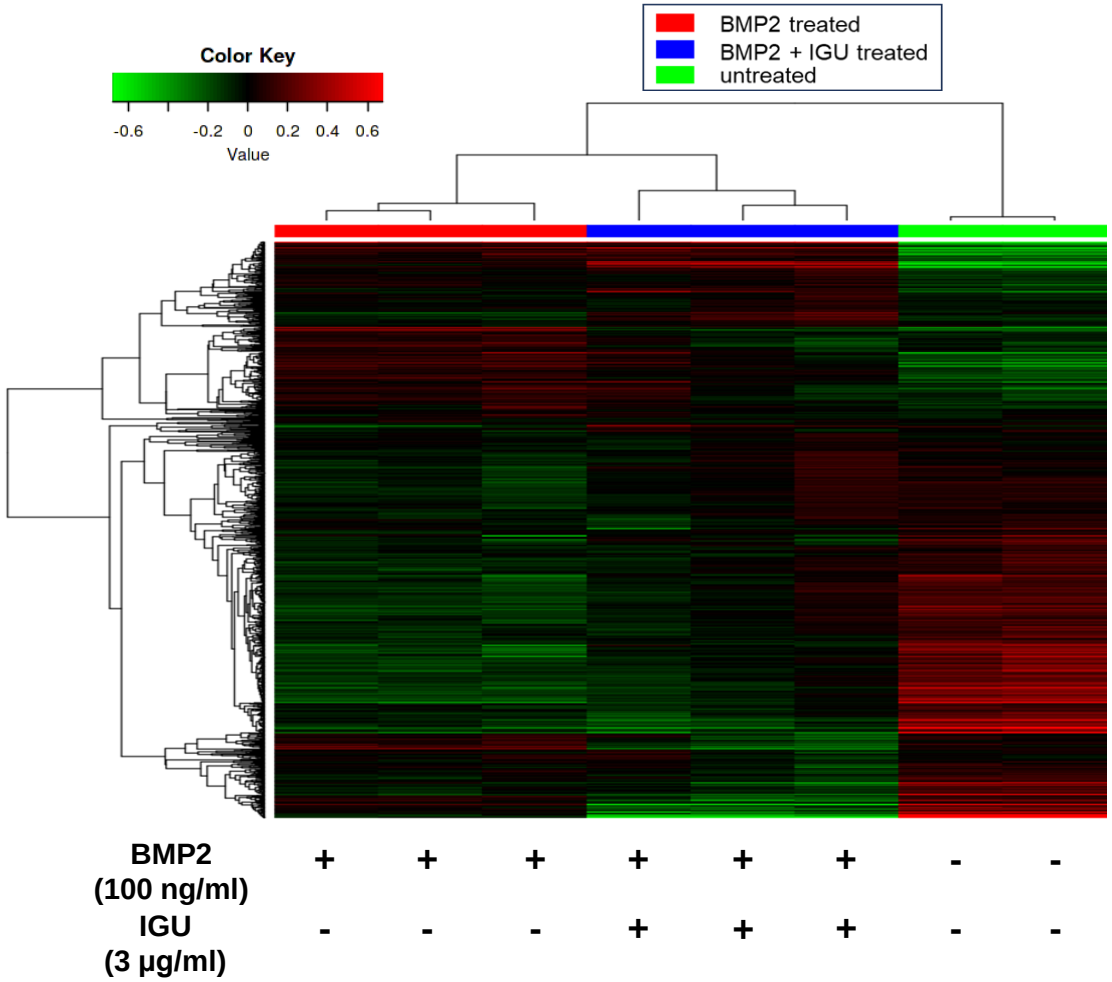
Supplemental Figure 2. Effects of iguratimod (IGU) on osteocyte-related gene, Dkk-1 expression.

Western blotting analysis of Dkk-1 using Saos-2 cells treated with bone morphogenetic protein-2 (BMP2) with or without IGU.

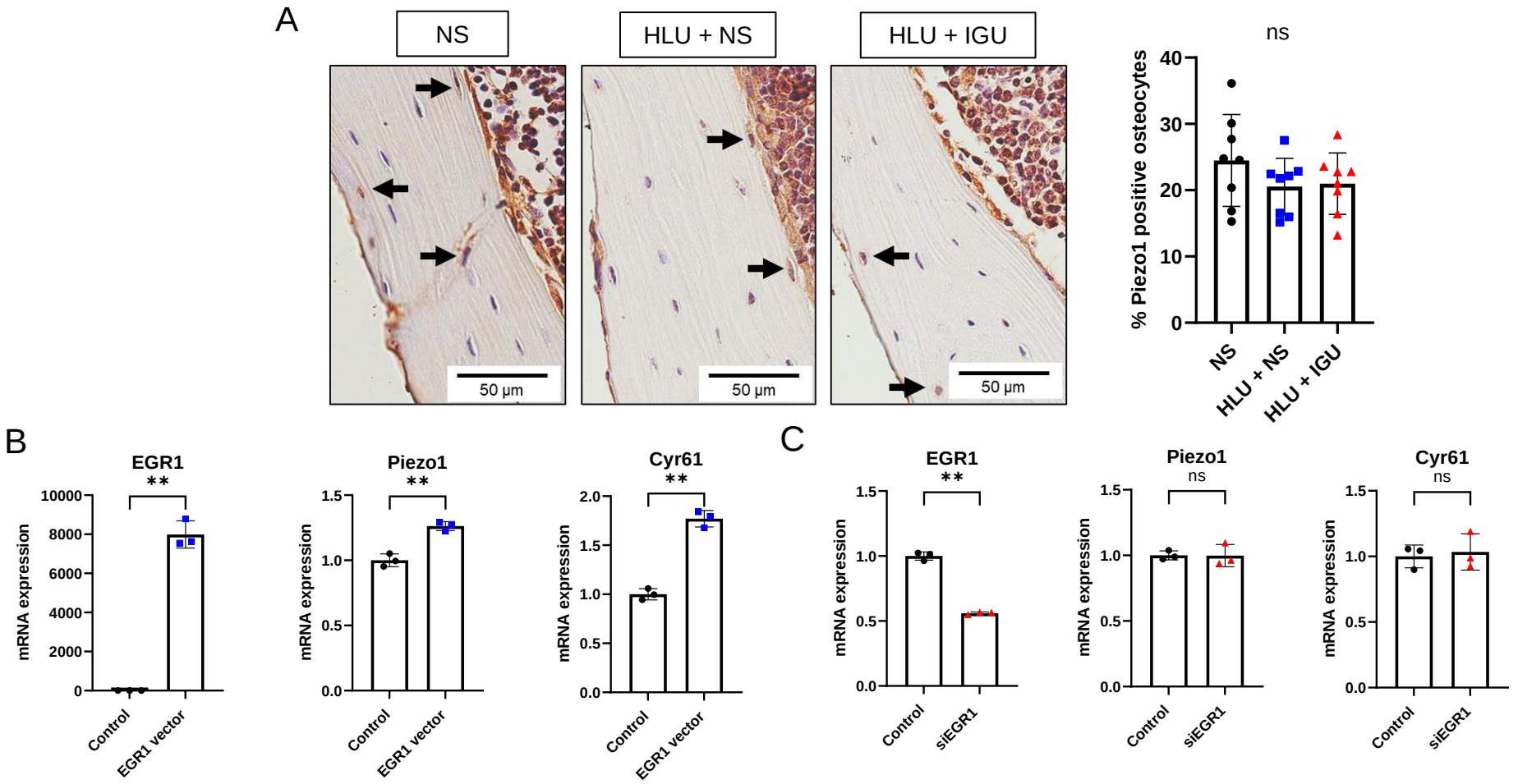


Supplemental Figure 3. Effects of iguratimod (IGU) on osteocyte apoptosis.

(**A**) Quantification of the relative number of empty lacunae in the cortical bone of the distal femur obtained from each group (normal saline (NS), hindlimb-unloaded (HLU) + NS, and HLU + IGU). The black arrows indicate the empty lacunae. (**B**) Reverse transcription quantitative polymerase chain reaction analysis of apoptosis-related gene expression in Saos-2 cells treated with bone morphogenetic protein-2 (BMP2) with or without IGU (data from three independent experiment data for each group). (**C**) Evaluation of cell proliferation in Saos-2 cells treated with different concentrations of IGU in the presence of BMP2 (data from five to six independent experiments for each group). Statistical significance was determined using one-way ANOVA followed by Tukey's post-hoc test (*$p < 0.05$). All data are presented as mean ± standard deviation. ns = not significant.



Supplemental Figure 4. The heatmap of differentially expressed genes, which were detected by RNA sequencing analysis on Saos-2 cells from untreated, bone morphogenetic protein-2 (BMP2)-treated, and BMP2 + iguratimod (IGU)-treated groups. Hierarchical clustering analysis was performed to generate a gene expression profile map of Saos-2 cells under untreated conditions, as well as conditions treated with BMP2 or BMP2 + IGU. The gene expression levels are represented by different colors: red points indicate up-regulated genes, green points indicate down-regulated genes and black points represent genes with no change in expression.



Supplemental Figure 5. Effects of iguratimod (IGU) on Piezo1-related genes.

(**A**) Immunohistochemical staining of Piezo1 in the distal femur cortical bone of each group (normal saline (NS), hindlimb-unloaded (HLU) + NS, and HLU + IGU) (data eight independent experiments for each group). The black arrows indicate Piezo1-positive osteocytes. (**B and C**) Saos-2 cells were transiently transfected with the early growth response protein 1 (EGR1) overexpression vector (**B**) or the EGR1-specific siRNA (**C**). Reverse transcription quantitative polymerase chain reaction analysis was conducted to examine the expression of EGR1 and Piezo1-related genes (data from three independent experiment data for each group). Statistical significance was assessed using one-way ANOVA followed by Tukey's post-hoc test (**$p < 0.01$). All data are expressed as the mean ± standard deviation. ns = not significant.