Analysis of subchondral insufficiency fracture of the knee associated with meniscal tear using a mouse osteoporotic model

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INTRODUCTION: Subchondral insufficiency fracture of the knee (SIFK) is a subtle fracture beneath the articular cartilage, thought to represent an early stage of spontaneous osteonecrosis of the knee. Although osteoporosis has been considered a predisposing factor, its direct role in SIFK pathogenesis remains unclear [1]. The purpose of this study was to investigate whether SIFK is associated with osteoporosis using an osteoporotic mouse model. We hypothesized that osteoporosis contributes to the development of SIFK.
METHODS: Senescence-accelerated mouse prone 6 (SAMP6), a strain that spontaneously develops osteoporosis, was used as the osteoporotic model, and wild-type (Wt) (C57BL/6J) mice served as controls. Sixteen-week-old both strain female mice underwent destabilization of the medial meniscus (DMM) surgery. Mice were sacrificed at 3, 7, and 14 days postoperatively. Histological morphology was assessed using Safranin O–fast green staining, and bone volume/tissue volume (BV/TV) and subchondral bone plate thickness (Subcho. BP. Th) in the medial tibial plateau were evaluated according to a subchondral bone scoring system [2]. TRAP staining was used to quantify the number of TRAP-positive osteoclasts in the region. Comparisons were made using two-way analysis of variance followed by the Tukey–Kramer post hoc test.
RESULTS: Figure-based analysis showed that in Wt mice, progressive subchondral sclerosis was observed over time, whereas no sclerosis was seen in SAMP6 mice, which instead exhibited SIFK-like changes at Day 14 (Fig. 1). TRAP staining showed that SAMP6 mice demonstrated a broader distribution and greater number of TRAP-positive cells over time compared with Wt mice (Fig. 2). Quantitative analysis showed that in Wt mice, BV/TV increased significantly by Day 14 after DMM compared with Day 3 ($p = 0.04$), whereas no significant time-dependent change was detected in SAMP6 mice. At the same time points, BV/TV was significantly higher in Wt than in SAMP6 mice following DMM at every time point (Wt vs SAMP6 Day3: 55.6 ± 9.0% vs 42.0 ± 7.3, $p=0.04$; Day7: 65.2 ± 5.5 vs 46.4 ± 10.0, $p=0.01$; Day14: 71.5 ± 8.4 vs 44.7 ± 6.2, $p< 0.001$). Subchondral bone plate thickness also increased significantly in Wt mice by day 7 (60.9 ± 10.7μm) and 14 (67.1 ± 5.8μm) compared with day 3 (41.9 ± 5.9μm) ($p=0.01$, $p < 0.001$, respectively), and was significantly greater at Day 14 in Wt than in SAMP6 mice (47.1 ± 12.7μm, $p < 0.01$). Regarding TRAP staining, osteoclast counts increased from Day 3 to Day 14 after DMM in both Wt (Day3: 0.4 ± 0.5, Day14: 3.8 ± 0.8, $p < 0.001$) and SAMP6 (Day3: 5.0 ± 0.8, Day14: 8.0 ± 1.6, $p < 0.0001$) mice, with SAMP6 showing significantly higher numbers of TRAP-positive cells than Wt at days 7 (Wt: 1.8 ± 0.8, SAMP6: 5.8 ± 1.6, $p < 0.001$) and 14 (Wt: 3.8 ± 0.8, SAMP6: 8.0 ± 1.6, $p < 0.0001$) (Fig. 3).
Discussion: Osteoporotic mice developed SIFK-like lesions rather than OA-like subchondral sclerosis after meniscal destabilization, suggesting distinct pathological mechanisms. In Wt mice, meniscal overload triggered a reparative sclerotic response. In contrast, osteoporotic mice exhibited changes characterized by the absence of subchondral sclerosis or thickening of the subchondral bone plate. These findings indicate that decreased bone quality alters the mechanical response of subchondral bone to injury, predisposing it to insufficiency fractures instead of adaptive hardening. Previous reports have shown that osteoporotic OA models demonstrate minimal subchondral sclerosis during the early postoperative period, consistent with our results [3]. This study was limited by the short observation period and the use of SAMP6 mice as a senile-type osteoporosis model. In conclusion, this study suggests histologically that osteoporosis may contribute to the onset of SIFK.
SIGNIFICANCE/CLINICAL RELEVANCE: This study may help clarify the role of osteoporosis in SIFK, supporting earlier diagnosis and prevention.
REFERENCES: 1. Yokota S, et al. Biomedicines 2024; 2. Nagira, et al. Sci Rep 2020; 3. Xu X, et al. Med Sci Monit 2019.

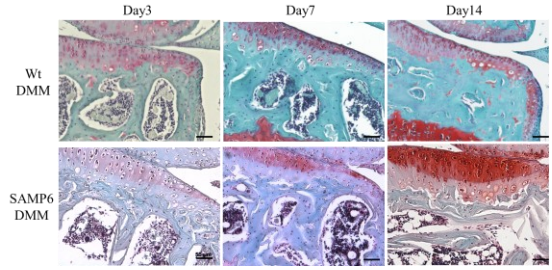

Figure 1. Histological analysis using Safranin O-fast green staining.

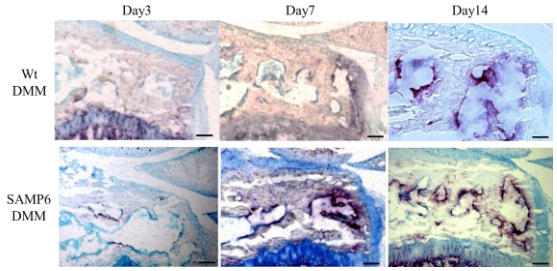

Figure 2. Immunohistochemical analysis using TRAP staining.

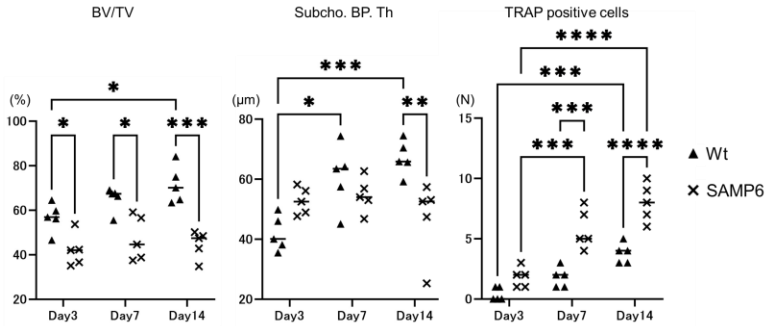

Figure 3.
BV/TV, Subcho. BP. Th and TRAP positive cells of the medial tibial plateau (All data were presented as the mean ± standard deviation. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001). BV bone volume, TV tissue volume Subcho. BP. Th subchondral bone plate thickness.