論　文　内　容　要　旨

High-fat diet-induced obesity accelerates the progression of spontaneous osteoarthritis in Senescence-Accelerated Mouse Prone 8 (SAMP8)

（高脂肪食による肥満誘導は早期に変形性関節症（OA）を示す老化促進マウス（SAMP8）の OA 重症度を促進する）

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Objectives: Osteoarthritis (OA), the most prevalent joint disease, is characterized by cartilage loss and bone remodeling, primarily affecting weight-bearing joints like hips and knees. OA is a multifactorial disorder, which risk increases with aging and obesity due to years of joint wear and tear, with obesity also contributing to chronic low-grade inflammation. Aging and obesity often jointly contribute to OA progression, significantly impacting healthcare systems, especially considering the growing elderly population. The Senescence-accelerated mouse (SAM) strain, including senescence-prone (SAMP) and senescence-resistant (SAMR) lines, has been used in aging studies. Among SAMP, SAMP8 has been used as a mouse model to investigate aging-related neurological and cognitive deficits, such as Alzheimer's disease. According to our previous findings, SAMP8 was noted to spontaneously exhibit significant joint degeneration at an early age, as much early as 14 weeks of age. Despite numerous studies on the obesity-OA relationship, the influence of obesity on accelerated aging-related primary OA and its mechanisms remains unclear. This study aims to determine the impact of obesity induced by a high-fat diet (HFD) on OA development in a spontaneous OA mouse model, SAMP8.

Methods: SAMP8 at five weeks were fed either a normal chow diet or an HFD for ten weeks to induce obesity. Parameters related to obesity, liver function, and lipid and glucose metabolism were analyzed. At 14 weeks of age, mouse knee joints were fixed, decalcified, and embedded in paraffin, then sectioned and Safranin O stained for histological assessments. Damage to the articular cartilage, meniscus, subchondral bone sclerosis, and synovitis was evaluated using the previously described histopathological scoring systems. Besides, bone mineral density and muscle strength were analyzed for determining osteoporosis and sarcopenia. Histological immunohistochemistry and TUNEL staining were performed to evaluate markers for cartilage degeneration and chondrocyte apoptosis.

Results: At 14 weeks of age, HFD group significantly increased in body weight, liver tissue weight, and fat accumulation. Markers for fatty liver, liver and adipose tissue inflammation as well as liver damage were aggravated in HFD group. However, while an impaired clearance of blood glucose and signs of hyperglycemia were already present in some mice, the HFD did not further exacerbate these diabetes mellitus indicators.

Knee histopathological analysis revealed that HFD-fed mice displayed reduced Safranin-O staining, indicative of increased cartilage loss, along with a significant increase in OARSI scores. The severity of OA was higher in the medial compartment compared to the lateral, and the deterioration of medial menisci was more pronounced in the HFD group. Synovitis, commonly associated with OA, was significantly worsened in the HFD group. Both groups displayed sclerotic changes at the medial tibial subchondral bone, with subchondral bone scores peaking at 14 weeks.

Despite already having significantly lower bone mineral density (BMD) compared to SAMR1 mice, HFD-fed SAMP8 did not show further bone density decline or early-onset muscle strength decrease at 14 weeks.

Mechanistically, HFD feeding led to increased chondrocyte apoptosis in knee articular cartilage and upregulation of C/EBP homologous protein (CHOP), a mediator of endoplasmic reticulum (ER)-stress-induced apoptosis. However, there are no changes in the expression of cellular senescence marker $p16^{INK4a}$ or cartilage degradation markers MMP13 and ADAMTS5 following HFD feeding.

Conclusions: Ten weeks of HFD feeding promotes spontaneous OA progression in 14-week-old SAMP8, potentially via liver damage subsequent chondrocyte apoptosis. This aging-obese mouse model may prove valuable for further exploration of spontaneous OA pathophysiology.