

Exosome therapy for osteoarthritis prevention in a novel turkey post-traumatic osteoarthritis model

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Introduction: as a bipedal, human will not redistribute the weight to upper limb. In this point, turkey is closely to human and superior to the rabbit, pig, dog, mice, goat, and other quadruped models. More recently our works have already verified after arthroscopic anterior cruciate ligament (ACL)/posterior cruciate ligament (PCL) / medial meniscus (MM) transections in turkey's knee, which can lead to significant joint instability and post-traumatic osteoarthritis (PTOA), it showed more clinically relevant (**Fig.1**). Our recent research utilized exosomes extracellular vesicles to treat OA in a rat model. Preliminary data indicates that the purified exosome product (PEP), produced under FDA-compliant conditions at the Mayo Clinic's Advanced Products Incubator (API), significantly mitigated OA development by modulating chondrocyte autophagy and apoptosis in a PTOA rat model. As an ideally larger PTOA model, turkey offers an excellent opportunity to explore OA therapeutics. Therefore, we propose to investigate whether PEP can effectively prevent or retard OA progression in this novel turkey PTOA model.

Methods: We hypothesized that PEP could effectively attenuate PTOA development. In this proposal, a total of 30 white turkeys will be used and divided into three groups including saline control, HA, HA+PEP treatments following PTOA creation (n=6). A randomly selected either right or left knee will undergo ACL/PCL/medial meniscus transection (APMMT) to initiate PTOA. One week after APMMT, 500 μ L of 20% PEP delivered via HA will be injected into the index knees at the 1,2,3,4 week after surgery. The turkeys will be euthanized at 12 weeks following APMMT, and the OA and healthy knees from each turkey will be harvested for analyses including gross morphological examination and OARSI scores, CT scan analysis for subchondral bone, histology (bone/cartilage morphology) and immunohistochemistry (IHC) for inflammation, apoptosis, and chondrogenesis mentioned above. The knee function will be also evaluated with gait analysis before APMMT and every two weeks after APMMT and injection until sacrificed. Before sacrificed second look with arthroscopy for gross of intra-articular.

Results: Gait analysis revealed significant functional changes in the operated limb, with reduced stance ratio and peak vertical force throughout the 12 weeks period ($p < 0.001$). Gross examination confirmed obvious cartilage damage with surface irregularities. Histological analysis using modified Safranin O staining showed disrupted cartilage surface, decreased proteoglycan content (**Fig. 2**). CT scan examination demonstrated decreased cartilage thickness and signal intensity in the operated knee, particularly over the medial femoral condyle and tibial plateau (**Fig. 3**). Second-look arthroscopic assessment at 12 weeks revealed significant cartilage degeneration in the medial and lateral compartment.

Discussion: The APMMT turkey model successfully replicates key PTOA features and offers advantages of bipedal gait, arthroscopic intervention, and rapid disease development. This provides a valuable platform for investigating PTOA pathogenesis and testing potential therapies. Exosomes extracellular vesicles PEP injections in early stage can prevent and retard OA progression, next step of the following research of PEP injections at the late stage of APMMT turkey model (6,7,8,9 week after surgery) would figure out if PEP also have positive effects as treatment for OA.

Key Words: Knee/tibial-fibula, Ligament and Tendon, Musculoskeletal Modeling, Osteoarthritis

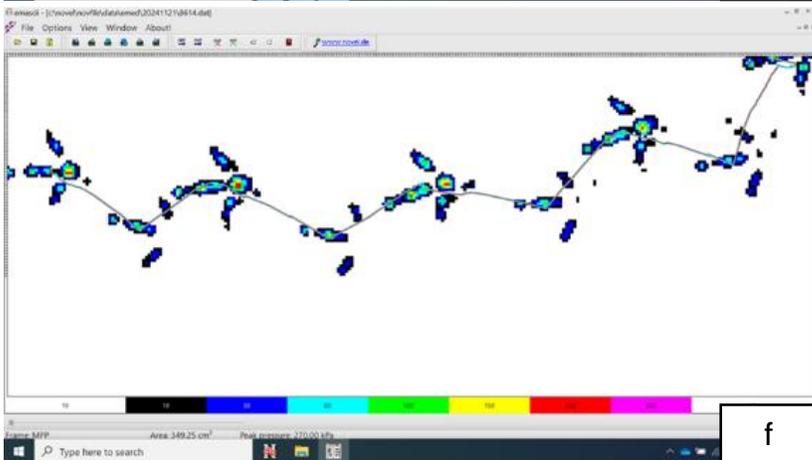
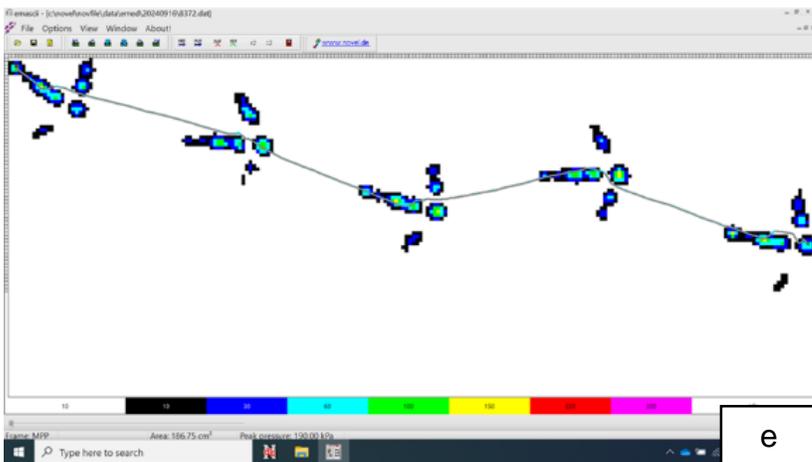


Fig.1 Typically subluxation after APMMT (lateral view X ray) and OA limp gait: (a) before APMMT. (b) after APMMT: anterior subluxation.
(c) anterior drawer test. (d) posterior drawer test. (e) before APMMT. (f) after APMMT: surgery on the left knee

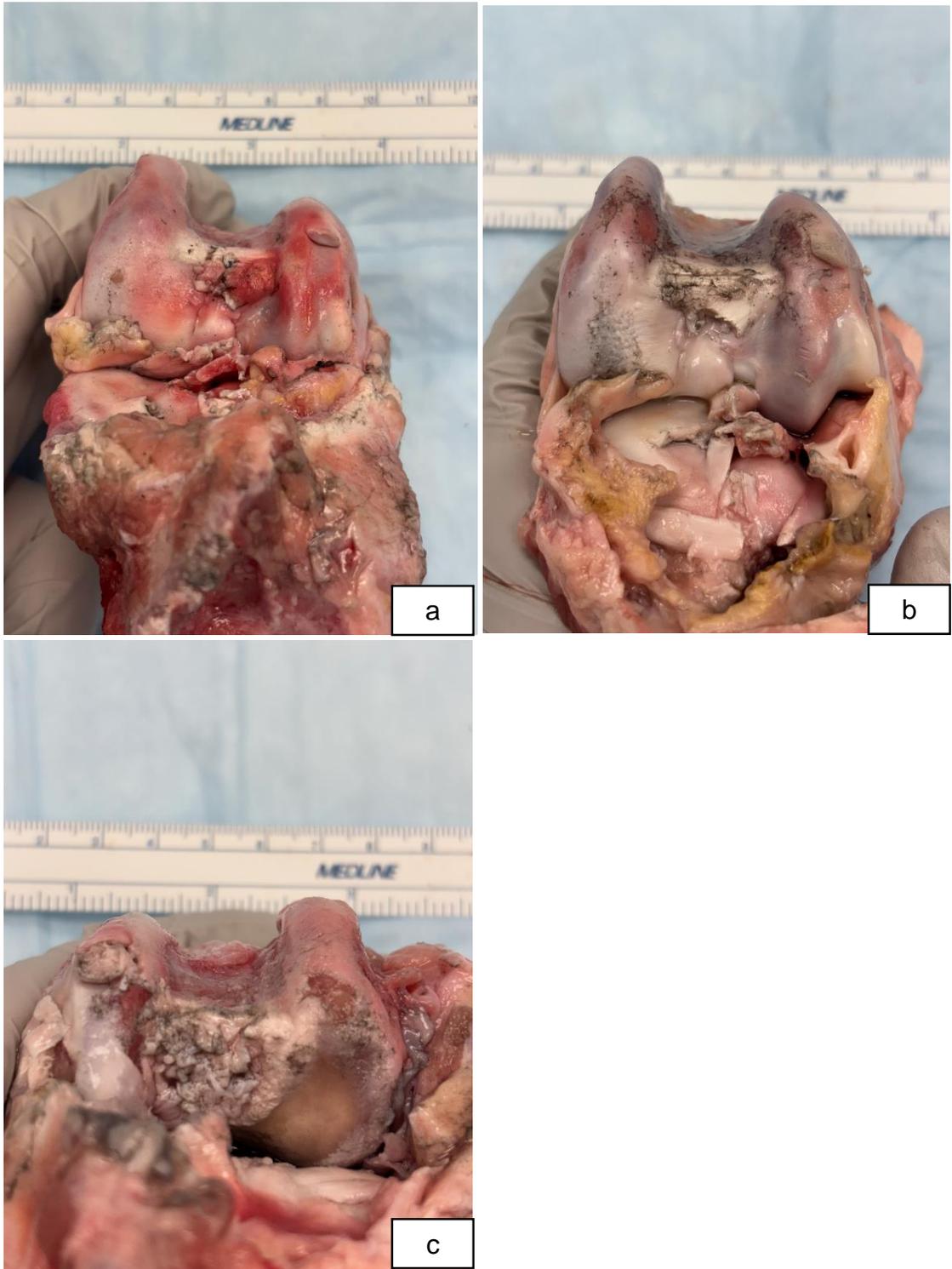


Fig.2 Gross view of femur side: (a) PEP+HA group. (b) HA group. (c) Saline group

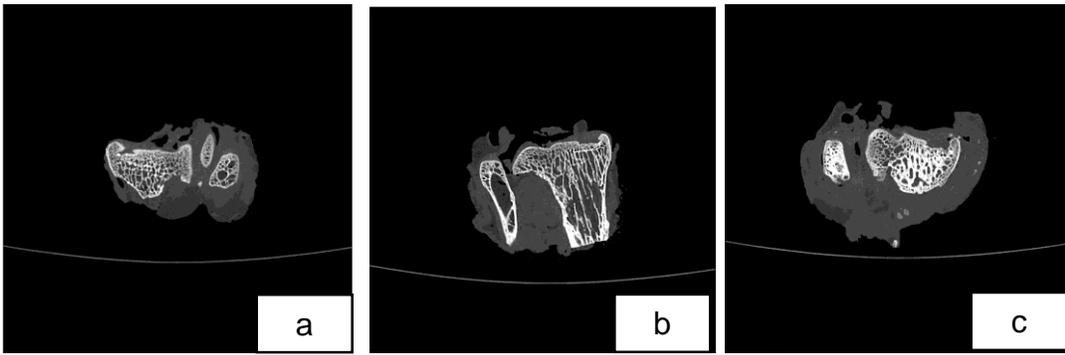


Fig.3 CT of the tibial plateau coronal scan: (a) PEP+HA group. (b) HA group. (c) Saline group