Introduction:
In anterior cruciate ligament (ACL) reconstruction using tendon grafts, the tendon to bone healing is one of the important key factors to success. To enhance tendon-bone healing in the bone tunnel, tissue-engineering approaches, including the use of growth factors and mesenchymal stem cells have been tested on animal models and reported their effectiveness. However, there are some disadvantages such as complicated synthesis, expensiveness, and biological safety. Simvastatin, an inhibitor of the competitive 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, is a convenient and economical drug which has been widely used to treat hyperlipidemic. In recent years, it has been reported that statins possess pleiotropic effects, such as the improvement of endothelial effect, anti-inflammatory effect, bone anabolic effect, and stimulation of angiogenesis. Although several reports have shown a certain therapeutic effect of Simvastatin on bone formation with neovascularization (1-3), systemic administration of Simvastatin made the effect minimum because of the clearance in liver, and high dose administration therefore may cause systemic adverse side effects(4). In order to overcome the problem of low efficacy/frequent side effects by high dose of Statin treatment, we utilized biodegradable gelatin hydrogels as a tool for drug delivery system (5) for tendon-bone healing in ACL reconstruction. We therefore aimed to prove the hypothesis that enhanced angiogenesis and osteogenesis by local administration of low dose Simvastatin-conjugated gelatin hydrogel promote the tendon-bone healing after ACL reconstruction.

Materials and Methods:
Animal model of ACL reconstruction
Thirty-five skeletally mature White Rabbits (weighting 3.0-3.5kg) were used to evaluate the effect of simvastatin on the healing of tendon graft in a bone tunnel using established model of ACL reconstruction. All animals underwent bilateral ACL reconstruction. The bone tunnels were drilled 2.5mm in diameter in the femur and tibia referred to the foot print. An ipsilateral semitendinosus tendon was used as a graft and sutured to the soft tissue at the tunnel exits. The gelatin hydrogel incorporating simvastatin 250ug were implanted into the bone tunnels in the right knees and the gelatin hydrogel alone were implanted into the bone tunnels in the left knees as the control.

Results:
Histological evidence of tendon-bone healing
Histological evaluation was performed with hematoxylin-eosin and Russell-Movat pentachrome staining to assess the tendon-bone healing at week 2, 4 and 8. In the simvastatin group, more newly formed bone and less inflammatory cells were seen in the interface at week 2. More chondroid cells (stained blue) and the perpendicular fibers connecting tendon to bone existed in the simvastatin group at week 4 and 8 (Fig.1).

Biomechanical testing
The femur-ACL graft-tibia complex (n = 5 at each group at each time point) was used for biomechanical testing using a tensile sensor. Ultimate failure load was significantly larger in the simvastatin group than in the control group at week 2. (Fig.3)

Discussions:
The results suggested that the local administration of low dose simvastatin-conjugated gelatin hydrogel promote the tendon-bone healing in early stage via angiogenesis and osteogenesis. This convenient and economical method will be possible to be a new strategy to promote recovery after ACL reconstruction.

References