Comparison of the regenerative potential of autologous adipose-derived stromal cells (ASC) and bone marrow stromal cells (BMSC) for osteochondral repair in a porcine osteochondral defect model

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Introduction

Tissue engineering offers promising advancements in the treatment of chondral defects by employing cell-scaffold systems to regenerate cartilage. Biphasic and 3D scaffolds, designed to enhance cell migration and extracellular matrix alignment, demonstrate superior clinical outcomes, though challenges remain in achieving durable hyaline cartilage. In this regard a composite of 3D scaffolds and pre-differentiated Mesenchymal stromal cells (MSCs) has proven to be advantageous. MSCs are promising due to their autologous applicability, multipotency, and hypoimmunogenic properties. While bone marrow derived stromal cells (BMSCs) already proved their strong chondrogenic potential, adipose-derived stromal cells (ASCs) are a competitive alternative for their higher availability, ease of harvest, and lower donor-site morbidity. This study compares the chondrogenic regenerative potential of donor matched autologous ASCs and BMSCs combined with a 3D biphasic collagen scaffold in a porcine full-thickness cartilage defect model

Methods

This study was designed as a prospective, comparative and randomized preclinical study. This study was approved by the regional authority (LANUV NRW, Germany; approval no. 81-02.04.2020.A198). The study included 16 Goettingen Mini Pigs (32 knee specimens). Chondral defects with a diameter of 6 mm were surgically induced on the medial femoral condyle of both hind limbs, respecting the subchondral plate (2- 3mm depth). Among the 32 knee specimens, eight were treated with Optimaix 3D® (Fa. Matricel; scaffold of 3D porcine collagen matrix) that had been seeded with ASCs, eight with Optimaix 3D® and BMSCs, eight were administered with Optimaix 3D® only and eight were administered with a blank defect. ASCs were isolated from the pig's fat of the hip region. BMSCs were isolated from the bone marrow of the pig's iliac crest. After 6 months, specimens were euthanized for obtaining macroscopic sections (Fig. 1) for MRI and later histological sections to analyze chondral tissue of the defect region with O' Driscoll score, histomorphometry and immunohistochemistry.

Results

Compositional MRI revealed that the gold-standard dGEMRIC sequence and non-contrast T_2 mapping both detected superior cartilage regeneration in autologous versus untreated controls. We demonstrated that the O'Driscoll score (Fig. 2) was significantly lower in blank defects (6.52 ± 5.14) and Optimaix 3D® (9.14 ± 4.68) compared to ASCs (11.71 ± 6.84) and BMSCs (17 ± 2.89) treatments ($p< 0.03$). Histomorphometric analysis of toluidine blue staining intensity was conducted to assess differences in proteoglycan content between native cartilage and repaired tissue (Fig. 3). Scaffold with ASCs (56.5% ± 28.87) and BMSCs (74.61% ± 18.64) treatments achieved a significantly higher proteoglycan content in the repaired tissue compared to blank defects (18.22% ± 8.25) and Optimaix 3D® (28.86% ± 23.7) ($p<0.02$). For immunohistochemical analysis, Collagen VI, Collagen II, and Collagen I were assessed. The BMSC + Optimaix 3D® and ASC + Optimaix 3D® groups exhibited higher levels of pericellular Collagen VI distribution with moderate interstitial presence (index BMSC: mean 1.8 ± 0.5; ASC: 1.3 ± 0.43), which is indicative of a physiological organization characteristic of hyaline cartilage. In the quantitative image analysis of the immunohistochemical stainings, the BMSC + Optimaix 3D® group exhibited a Col II/Col I ratio of 3.8 ± 0.5 within the defect area, while the ASC + Optimaix 3D® group showed a ratio of 2.8 ± 0.8, indicating a hyaline cartilage-like phenotype of the regenerated tissue.

Discussion

The present study demonstrates that the combination of a biphasic 3D collagen scaffold with mesenchymal stromal cells (MSCs) significantly enhances hyaline cartilage regeneration and integration in a porcine full-thickness chondral defect model. Both ASCs and BSMCs improved histological and histomorphometric outcomes compared to scaffold- only and untreated controls. Our findings are consistent with previous preclinical studies showing that BMSCs in scaffold-based cartilage repair result in superior histological scores. Although BMSCs outperform ASCs in terms of hyaline-chondrogenic tissue formation, the magnitude of improvement in proteoglycan restoration of ASCs underlines their clinical value, given their ease of harvest, higher yield, and reduced donor-site morbidity. The superior performance of BMSCs may be attributed to their higher intrinsic chondrogenic lineage commitment and osteoarticular predetermination compared to ASCs. Strengths of the present study include the use of a large animal model with joint size and biomechanics similar to humans, randomized group allocation, and blinded histological assessment. The use of a standardized defect model allowed for direct comparison between cell types under controlled conditions. Limitations include the absence of long-term follow-up to assess tissue durability, the lack of biomechanical testing, and the fact that the sample size was powered for histological but not for all secondary outcomes. The significant differences observed between the scaffold-only and MSC-treated groups further support the concept that cell-seeding is essential to maximize the regenerative potential of advanced biomaterial scaffolds.

Significance/ Clinical Relevance

According to NIH significance criteria, this work addresses an important unmet clinical need of durable hyaline cartilage restoration regardless of defect size, patient age, sex, or subchondral bone structure. By directly comparing two autologous, clinically accessible cell sources in a translational large- animal model, the demonstrated efficacy of ASCs supports their potential to broaden access to effective, autologous cartilage repair strategies and reduce morbidity associated with bone marrow harvest. Important parameters such as cell count, application method, pretreatment of ASCs and biofunctionalization of scaffolds (secretion of growth factors like TGF-ß, inhibitors etc.) for establishing an optimal cell-scaffold composite can be optimally clarified in such large animal studies.

Figure 1 Macroscopy

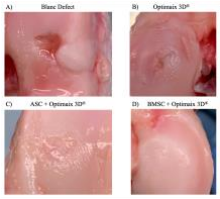
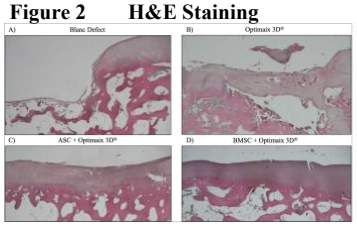


Figure 2 H&E Staining



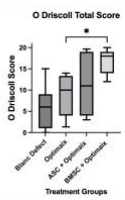


Figure 3 Toluidin staining