BETA$_2$-ADRENERGIC AGONIST INDUCED HYPERTROPHY OF THE QUADRICEPS SKELETAL MUSCLE DOES NOT MODULATE DISEASE PROGRESSION IN THE RODENT MENISCOTOMY MODEL OF OSTEOARTHRITIS

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Purpose: It is well established that patients with knee osteoarthritis (OA) exhibit marked muscle weakness, commonly associated with the quadriceps muscle group. Conversely, there is evidence that a strong quadriceps muscle may protect both against further joint damage in established OA and be a protective factor in the initiation of OA. Numerous studies have shown that exercises aimed at improving the quadriceps muscle have beneficial effects in OA patients, which include reduced knee pain and increased physical ability. However, improving skeletal muscle strength and functional performance through intensive exercise regimes is often inappropriate or contra-indicated for the majority of OA patients.

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Conclusions: Our data reveal that clenbuterol induced skeletal muscle hypertrophy is unable to mimic the previously reported beneficical effects of increased musculature derived through targeted strength training, in a rodent model of meniscectomy induced OA.

RELATIONSHIP OF WEIGHT-BEARING AND NON-WEIGHT-BEARING PAIN IN KNEE OA WITH (CENTRAL) FEMOROTIBIAL DENUDED AREAS - DATA FROM THE OA INITIATIVE

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Purpose: The relationship of structural changes in OA and clinical outcomes, such as pain, is of high interest for imaging biomarker validation. A wide range of MRI-based features, such as bone marrow lesions, have been investigated. One recent study showed a significant relationship of denuded bone areas (dABs), measured with MRI, with the existence and the incidence of knee pain in OA. In the absence of a friction-less cartilage surface, peak pressures and shear forces occurring during weight-bearing may generate pain in the richly innervated bone tissue. This may be most relevant in central femorotibial subregions, where the meniscus is not involved in pressure distribution. We therefore investigated whether dABs are more closely related to weight-bearing (WB) than non-weight-bearing (NWB) pain, and whether dABs in central locations of the femorotibial cartilages are more strongly related to pain than “any” dAB, including peripheral locations.

Methods: A subsample of the OAI (public-use data sets 0.2.1 [clinical] and 0.1.1 [image data]) (n=537; 211 male; 326 female; age 62.1±9.7 y; 41 KLG 0/1 [calculated from osteophyte and JSN scores]; 239 KLG2; 235 KLG3; 22 KLG4; BMI 29.7±4.6 kg/m$^2$; public data releases O.E.1 and E.1.E.) was studied. Manual segmentation of the femorotibial cartilages (MT, LT, cMF, cLF) was performed on baseline MRI acquisitions, including dABs. These were defined as subchondral bone areas not covered by cartilage, delineated in more than one 1.5mm slice. dABs in “any” region or in central subregions of the medial and lateral tibia and femur were analyzed. Self-reported pain frequency was assessed based on item P1 of the Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscore. As previously suggested, WB pain intensity was assessed based on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) LK 3.1 pain subscale questions #1 (walking) & #2 (stairs). NWB pain intensity was based on questions #3 (night) & #4 (sitting). The relationship between dABs and pain was analyzed using univariate (Mann-Whitney) and multivariate tests (general linear models), comparing “any” dAB with no dAB, and “central” dAB with no dAB.

Results: 214 of the 537 knees displayed “any” dAB and 63 of those “central” dABs; 118 knees were never painful, but 419 had pain at least monthly (KOOS item P1). Knee pain frequency was significantly related to “any” femorotibial dAB (p=0.02 for univariate analysis and p=0.01 (r=6.5%) after correcting for sex, age and BMI) and to “central” dAB (p=0.04 and 0.001/r=8.2%), respectively). WB pain intensity showed borderline significance with “any” dAB (p=0.06 and 0.04; r=9.6%) and a significant relationship with “central” dABs (p=0.03 and 0.002; r=10.9%). NWB pain was not significantly related to “any” dAB (p=0.20 and 0.28; r=6.6%) or “central” dAB (p=0.051 and 0.09; r=6.5%). The r2 values for WB pain and central dABs were, however, not
significantly higher than for NWB pain and “any” dAB, respectively (Fisher Z).

Conclusions: In this cross-sectional study we demonstrated a significant relationship between dAB and pain frequency. The relationship of dABs with WB pain intensity appeared to be somewhat (but not significantly) stronger than for NWB pain, and the relationship for “central” femorotibial dABs somewhat (but not significantly) stronger than of “any” dAB.

062

BONE-MARROW STIMULATION BY DRILLING VERSUS MICROFRACTURE LEADS TO BETTER CARTILAGE REPAIR IN RABBITS

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Purpose: Microfracture (MFX) and drilling (DRL) are widely practiced surgical procedures for bone marrow stimulation cartilage repair, but they have inherent mechanical differences and have not been systematically compared for a desired cartilage repair outcome. This study compared subchondral characteristics and cartilage repair outcomes following MFX versus DRL, and examined the effect of hole depth in a rabbit model.

Methods: Trochlear cartilage defects were prepared bilaterally in 24 skeletally mature rabbits. Perforations were made into subchondral bone using MFX or DRL techniques. MFX holes were made to a depth of 2 mm (MFX2) and drill holes made to either 2 mm or 6 mm depth under cooled irrigation (referred to as DRL2 and DRL6, respectively). Animals were sacrificed 1, 14, 21 and 90 days postoperatively, and defects assessed by micro-CT, histology, immunohistochemistry and histomorphometry.

Results: MFX induced acute crushing and compaction of bone, leaving dense bone around MFX2 holes (Fig. 1A, C) which essentially blocked connection with bone marrow. DRL, however, removed bone and debris from holes to provide access channels to marrow stroma (Fig. 1A–D). In contrast to generally accepted dogma, significantly more empty osteocyte lacunae (bone necrosis) were detected in bone lining the MFX holes, compared to the DRL holes generated under cooled irrigation where no apparent heat necrosis was seen (Fig. 1E). Deeper DRL holes at 6 mm penetrated the epiphysial scar (the closed growth plate) in rabbits and produced greater subchondral hematoma with increased access to deep marrow cavity (Fig. 1B, D).

At Day 14 and Day 21, greater bone repair and a more robust angiogenic and chondrogenic response were seen in DRL vs. MFX holes. Bone repair attained similar heights in DRL6 and DRL2 despite initial greater bone removal in deep holes (Fig. 2A, C) which were essentially blocked connection with bone marrow. DRL, however, removed bone and debris from holes to provide access channels to marrow stroma (Fig. 1A–D). In contrast to generally accepted dogma, significantly more empty osteocyte lacunae (bone necrosis) were detected in bone lining the MFX holes, compared to the DRL holes generated under cooled irrigation where no apparent heat necrosis was seen (Fig. 1E). Deeper DRL holes at 6 mm penetrated the epiphysial scar (the closed growth plate) in rabbits and produced greater subchondral hematoma with increased access to deep marrow cavity (Fig. 1B, D).

At Day 14 and Day 21, greater bone repair and a more robust angiogenic and chondrogenic response were seen in DRL vs. MFX holes. Bone repair attained similar heights in DRL6 and DRL2 despite initial greater bone removal in deep holes (Fig. 2). Results at 90 days revealed that DRL produced more tissue repair than MFX (1.6±0.84 mm² vs. 1.0±0.67 mm², P=0.007), and had a statistically significant increase in the hyaline character vs. MFX as indicated by percent of tissue repair positive for Safranin-O (43.3±25.85% vs. 26.7±26.85%, P=0.015) and collagen type II staining (91.0±8.28% vs. 81.2±18.24%, P=0.009). Compared to shallow perforation, deep DRL stimulated more effective cartilage repair with significantly greater tissue volume, defect fill and resurfacing (P<0.01 for all). The repair in DRL6 was also more hyaline than in DRL2 as judged by significantly more proteoglycan, more.