INTRODUCTION: Development and assessment of disease modifying treatments for osteoarthritis has been hampered by difficulty identifying cartilage degeneration prior to the development of irreversible changes. Optical coherence tomography (OCT) is a new imaging technology that can be incorporated into arthroscopes to image human articular cartilage with structural clarity comparable to histology\(^1,2\). OCT demonstrates cartilage degeneration prior to the development of irreversible changes. Assessment of changes to OCT form birefringence may be predictive of reversible changes implicated in the pathogenesis of osteoarthritis such as insensitivity to the anabolic effects of Insulin Growth Factor-1 (IGF-1)\(^3\). The aim of this study is to test the hypothesis that OCT can be used to diagnose human cartilage degeneration early enough for restoration of the ability to increase proteoglycan synthesis in response to IGF-1.

METHODS: Ninety-three residual cartilage specimens were harvested in compliance with IRB approved protocols from cartilage with grossly intact articular surfaces and assessed using a conventional arthroscope and probe. Twelve scans per core were obtained using polarized OCT (Zeiss) to determine the presence or absence of OCT cartilage form birefringence (fBrf) (Figure 1), and processed for histology (Safranin O, H&E, picrosirius red). Specimens were graded as normal or abnormal by arthroscopy, OCT and histology using the criteria of Table 1. Agreement between histology and arthroscopy and between histology and OCT for diagnosis of early degeneration were calculated using unweighted kappa statistics. Sensitivity/specificity was determined using histology as the standard. For metabolic studies, specimens were segregated into two groups based on whether OCT fBrf was retained or not. Tissue from each group were harvested and cultured in 10% FBS for 24 hours. Nitric Oxide Synthase restored the ability of cartilage that had lost OCT form birefringence to increase proteoglycan synthesis in response to IGF-1.

RESULTS: Diagnosis. OCT diagnosis of cartilage abnormality had better agreement with histopathological diagnosis of early cartilage degeneration than arthroscopic probe diagnosis. Loss of OCT form birefringence had good agreement (κ=0.76) with histopathology while assessment of “softening” using an arthroscopic probe had only fair agreement (κ=0.48). Using histopathology as the standard, OCT assessment of cartilage form birefringence improved the sensitivity of early diagnosis of cartilage abnormality from 50% (arthroscopic probe) to 80% (OCT), with a specificity of 86% (OCT).

Metabolism. While basal proteoglycan synthetic levels were similar, specimens without OCT form birefringence exhibited insensitivity to the anabolic effects of IGF-1. In specimens retaining cartilage OCT form birefringence, IGF-1 increased proteoglycan synthesis by 93% (p=0.036). This anabolic response was not observed in specimens without OCT form birefringence. Nitric Oxide (NO) has been implicated in chondrocyte insensitivity to IGF-1\(^3\) and measured NO levels were 50% higher in cartilage without OCT form birefringence (p=0.047).

Treatment. Given the elevated NO, cartilage without OCT form birefringence was incubated for 24 hours in 1 mM N\(^\text{\textsuperscript{-}}\)monomethyl-L-arginine (L-NMA) to inhibit NO Synthase, and then switched to DMEM with or without 50 ng/ml of IGF-1 for 48 hours. Incubation of specimens with L-NMA lowered NO released into the medium from 51 pM/mg tissue to 22 pM/mg tissue (p=0.021). In L-NMA treated tissue that had lost OCT form birefringence, IGF-1 stimulated PG synthesis by 137% (p=0.037) demonstrating restoration of IGF-1 responsiveness (Figure 2).

DISCUSSION: These results demonstrate the potential of OCT to identify human cartilage degeneration prior to the development of irreversible changes. Assessment of changes to OCT form birefringence was more sensitive than tactile probing for diagnosis of early cartilage degeneration in human cartilage with intact articular surfaces. The data further show that changes to OCT form birefringence may be predictive of reversible cartilage insensitivity to the anabolic effects of IGF-1. Because OCT is nondestructive and can be used arthroscopically\(^1\), this enhanced diagnostic potential may have research and clinical implications for early treatment of human cartilage degeneration as a strategy to delay or prevent the onset of disabling osteoarthritis.


AFFILIATED INSTITUTIONS FOR CO-AUTHORS: *VAMC Pittsburgh; †UPMC Eye Center, Department of Ophthalmology, University of Pittsburgh (NIH R01-EY013178-6; P30-EY008098)