

# HIGH RESOLUTION IMAGING OF MUSCULOSKELETAL DISEASE, PARTICULARLY CARTILAGE PATHOLOGY, WITH A NEW IMAGING TECHNOLOGY

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## INTRODUCTION

Over the years orthopedic surgeons have used modalities such as plain radiography, magnetic resonance imaging (MRI), and ultrasound to assess joints and other musculoskeletal structures. Each of these imaging modalities has its own advantages; however, there are still instances when these technologies do not possess adequate resolution to effectively assess the relevant pathology. An example is the current inability to assess cartilage during treatment for osteoarthritis.

We have developed a new technology, optical coherence tomography (OCT), for the assessment of articular cartilage, tendons, and ligaments. OCT is analogous to ultrasound, but measures the intensity of backreflected infrared light rather than sound.[1-3] These efforts in orthopedic imaging have received several awards, including the Presidential Award in Science and Engineering from President Clinton in 1998.

OCT has several advantages for the assessment of musculoskeletal pathology. First, OCT has a resolution of 10 – 25 times that found in other clinical imaging technologies. Laboratory-based state-of-the-art OCT systems have attained resolutions as high as 4  $\mu\text{m}$ .[4] Second, OCT has a faster speed of acquisition.[5] OCT can image with an acquisition rate of up to 16 frames per second, which could allow this technology to image surgical procedures in near real time. Third, since OCT is based on fiber optics, imaging instruments utilizing OCT technology can be built with cross-sectional diameters as small as 0.014 inches.[6] This opens the potential of designing OCT catheters to be incorporated into arthroscopic instruments or bedside needle-based devices. Fourth, the entire unit is compact, similar in size to an ultrasound unit, and can be readily transported into a surgical ward or clinic. Finally, since OCT is

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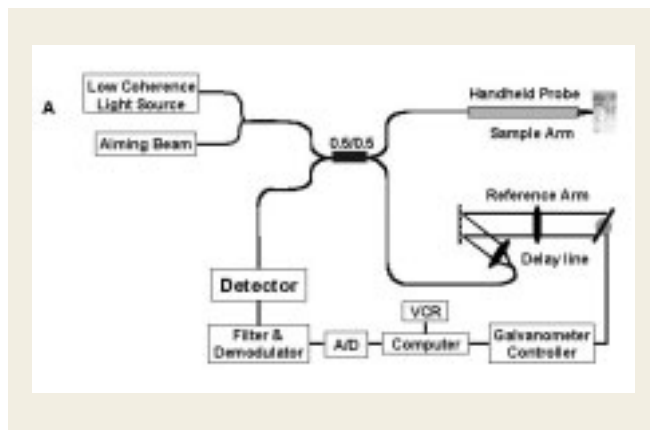
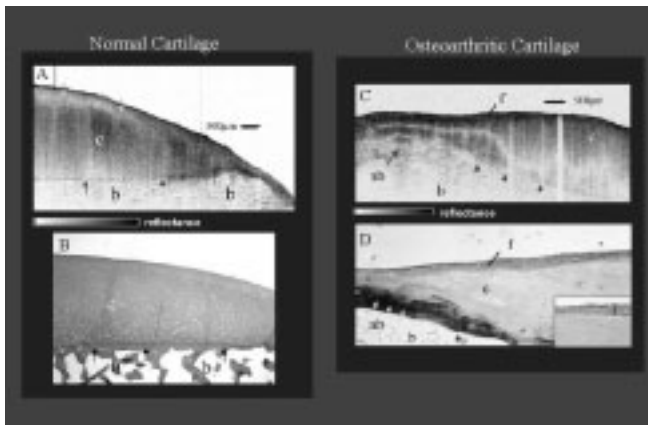


Figure 1: Schematic of an optical coherence tomography device.

based on optics, it can be combined with other spectroscopic techniques to assess the optical and biochemical aspects of the tissue being imaged.

## TECHNICAL ASPECTS OF OCT

The details of OCT have been previously described.[1-3] As stated, OCT is analogous to B-mode ultrasound, measuring the backreflection of near-infrared light rather than sound waves. Due to the high speed of light, the echo delay time cannot be measured electronically (as it is with ultrasound) and therefore OCT relies on a technique known as low coherence interferometry. Figure 1 depicts a schematic of a general OCT system and illustrates the principle of low coherence interferometry. The broad bandwidth light, which can be thought of as a series of pulses, is split into two separate arms, referred to the reference and sample arms. Light that passes down the reference arm is reflected back from a movable mirror. The sample arm directs the light toward the tissue being imaged. Once the light reaches the tissue it can be absorbed or scattered. Light back-reflected from the tissue will ultimately be recombined with the light from the reference arm at the beam splitter. If the light has traveled the same path length in both arms, to within the coherence length (or in the context of our analogy, the pulse length), interference will occur when the light is recombined at the beam splitter. Therefore, OCT measures the intensity of this interference and uses it to represent backreflection within tissue. The beam in the sample arm scans the tissue to generate two- and three-dimensional images.



**Figure 2:** Comparison of normal and osteoarthritic cartilage. The arrows in the OCT images (A and C) indicate the bone cartilage interface. The corresponding histology is seen in B and D. Reproduced from Herrmann *et al*, 1999, with permission.

The resolution of OCT is dependent upon the bandwidth of the source (range of wavelengths within the beam). The wider the bandwidth, the greater the resolution. OCT is essentially an “optical biopsy” technique, allowing resolutions close to 2-10X that of microscopy, with a penetration depth slightly greater than a mechanical biopsy of approximately 3mm.

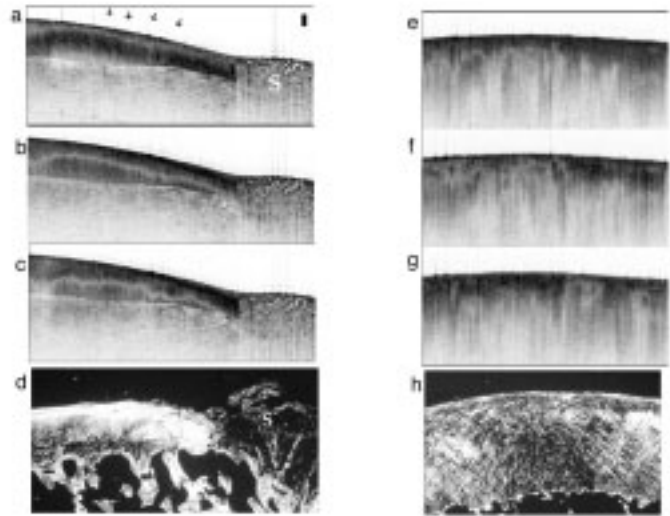
### IMAGING OSTEOARTHROTIC CARTILAGE

Recent research has indicated that the progression of osteoarthritis (OA) may be delayed or halted if treatment is initiated early in the course of the disease. In order to facilitate the treatment of OA, it will be necessary to image the articular cartilage at higher resolutions than are currently available. Unfortunately, the limited resolution of current imaging technologies does not allow the accurate monitoring of early cartilaginous changes. While MRI is effective for the macroscopic assessment of the joint, resolutions of current clinical devices are between 250 – 300  $\mu\text{m}$ . With this limited resolution, it is difficult to detect fine changes in the articular cartilage. Furthermore, the high cost of MRI would be a limiting factor in its successful implementation as a screening tool. Specifically, it would be impractical to use this technology at many time points, particularly if multiple joints are involved.

Another powerful technique is arthroscopy. In addition to its ability to facilitate joint repair, arthroscopy allows for direct inspection of the surface of the cartilage and ligaments. However, both the inability to image below the cartilage surface and the expense prevent its use as a routine screening procedure.

### OCT IMAGING OF CARTILAGE

Our group has investigated the capability of OCT to image the musculoskeletal system, with an emphasis on articular cartilage.[2] In Figure 2, an OCT image of normal cartilage appears on the upper left. On the lower left, an image of the corresponding normal histology is shown, where “c” is cartilage and the arrow indicates the bone-cartilage interface. Due to the high resolution of OCT, the cartilage thickness in this image can be measured to within 10 $\mu\text{m}$ . On the upper right in Figure 2, an OCT image of the diseased cartilage of an osteoarthritic



**Figure 3:** Polarization sensitive changes in normal and osteoarthritic cartilage of the knee. The OCT images on the left (a-c) are of normal cartilage taken at different polarization stages. The picrosirius red staining indicates a high degree of birefringence present. “S” represents the supporting tissue connected to the cartilage. The OCT images on the right (e-g) are of osteoarthritic cartilage. Histology (h) indicates diminished birefringence. Reproduced from Drexler *et al*, 2001, with permission.

femoral head is shown. In this image, cartilage thinning is seen on the left side. In addition, a fibrous band (f) has developed on the surface, and disruption of the bone-cartilage interface has occurred (nb). On the lower right is the corresponding histology. This study has also revealed that OCT is capable of detecting articular cartilage defects such as microfibrillations and fibrosis.[2]

Among the earliest changes in OA is the breakdown of collagen. We have developed OCT with polarization sensitivity (PS-OCT) to identify organized collagen.[7] In normal cartilage, the image changes with alterations in the polarization state of the incident light. Figure 3 compares images obtained from normal and OA cartilage with respect to polarization sensitivity.[7] On the upper left of the figure, OCT images (a,b,c) of normal cartilage are seen. In these images a smooth banding pattern is present that changes with the polarization state. It is important to note that these bands do not correspond to any specific structure, but rather arise from the birefringent (polarization) properties within cartilage. This birefringence is due to the highly organized nature of collagen within healthy articular cartilage, which behaves like a polarization filter. The fourth image (d) is the corresponding histologic section stained with picrosirius, a specialized staining technique where increased brightness demonstrates highly organized collagen. In the three images to the right of the figure, the cartilage is thick but with evidence of disease (e,f,g). It can be seen that there are essentially no changes with the polarization state of the incident light in the OCT images. In the picrosirius stained histology (h), there is a dramatic attenuation in the brightness, representing a reduction in the organization of the collagen network. These results indicate that OCT can detect early degenerative changes in articular cartilage, before cartilage thinning and fibrillations occur.

*In vivo* studies using a hand-held probe during open knee surgery have also been completed.[8] Results similar to previous *in vitro* studies were obtained, indicating that OCT can be used during surgical procedures to assess the extent of articular cartilage damage. Currently we are designing a probe that could be used during arthroscopic procedures.

#### ANIMAL MODELS OF OSTEOARTHRITIS

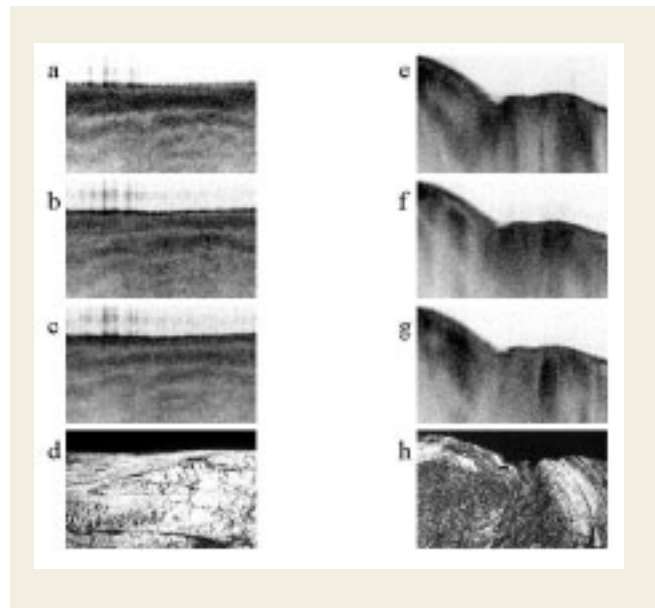
The development of new therapeutics will require the use of animal models to assess the progression of osteoarthritis. Currently, most studies utilizing animals require a large number of animals, since animals need to be sacrificed at different time points. By incorporating OCT as a means of assessing cartilage, we have developed rat and rabbit models for sequentially following joint cartilage properties without the need for animal sacrifice.[9] These studies have been performed in both chemically and mechanically induced models of arthritis. We believe that the rat model may be the model of choice for ultimately assessing many therapeutic approaches by the research community. The benefits of this model include a reduction in costs, avoidance of difficulties in data analysis due to differences in the heterogeneity present within a population, and the use of smaller amounts of novel therapeutics (often available only in small quantities).

#### ASSESSING THE MICROSTRUCTURE OF TENDONS AND LIGAMENTS

Abnormalities of tendons and ligaments can lead to significant morbidity. Examples include injuries of the Achilles tendon, anterior cruciate ligament (ACL), or patellar tendon. While there are many technologies capable of assessing tendons and ligaments with above 200  $\mu\text{m}$  resolution, there are instances where a higher resolution would be of value. Since these tissues are composed of highly organized networks of collagen fibers, they also display birefringence, which allows for assessment by OCT. Any alteration in the normal organized arrangement of collagen fibers should result in an attenuation of the birefringent properties of the tissue. We have imaged both normal and diseased tendons and ligaments to determine if OCT can monitor changes in these properties. Figures 4a-4c depict an area of an ACL with no evidence of injury or disease imaged at different polarization states.[10] Due to the birefringence of the tissue, a banding pattern is present similar to that seen within normal cartilage. As the polarization state is altered, the position of the bands is shifted. This is consistent with the picrosirius image in figure 4d, demonstrating organized collagen. In contrast, OCT images from a section of disrupted ACL (Figures 4f-h) do not show the birefringence or clear banding pattern. Future work is needed to determine if polarization-sensitive changes detected by OCT can indicate areas susceptible to injury or if these techniques can help to determine the etiology of patient discomfort, such as in Achilles tendinosis.

#### OTHER WORK

In addition to the projects described above, our group also has several other ongoing projects. One clinically important



**Figure 4:** Comparison of normal and ruptured ACL. The OCT images on the left (a-c) are of normal tissue taken at different polarization stages. The picrosirius red stained sample (d) indicates a high degree of birefringence. The OCT images on the right (e-g) are taken at a ruptured site of the tendon. Histology (h) indicates a loss of birefringence. Reproduced from Martin *et al*, In press, with permission.

focus is on developing OCT to assist in guiding small nerve and vessel repair in trauma and microsurgical flap reconstruction.[11] In particular, these applications may allow one to distinguish between sensory and motor fibers in peripheral nerves. We also are investigating the utilization of OCT in the guidance of laser cartilage repair. Other basic work focuses on such technical issues as analysis of dispersion,[12] reduction of system noise levels, absorption spectroscopy, improving our understanding of birefringence of collagen with SEM, and automated high speed quantification of cartilage thickness.[13,14]

#### CONCLUSION

OCT represents a promising new technology for the assessment of the musculoskeletal system. In particular, the most important application will likely be the assessment of cartilage and the monitoring of its changes during therapeutic intervention.

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Sang-gil Lee, Steve Kronlage and his wife, Neil Harness, Rajiv Sethi, and Phani Dantuluri enjoy a night out as the Hand Service



Steve Kronlage, Sang-gil Lee, Rajiv Sethi, and Phani Dantuluri celebrate the end of a rotation on the hand service.