Minimally Invasive Polarization Sensitive Optical Coherence Tomography (PS-OCT) for assessing Pre-OA, a pilot study on technical feasibility

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ABSTRACT

Objective: Efforts to develop chondroprotective approaches to halt osteoarthritis (OA) progression have recently increased. Current imaging techniques are critical in managing advanced OA, but greater resolution is needed to identify reversible stages (pre-OA). Optical coherence tomography (OCT) is a micron scale imaging technology widely used in ophthalmology, cardiology, and neurology. We previously demonstrated that polarization sensitive OCT (PS-OCT) can identify pre-OA in vitro, in animals, and in open surgical fields. This feasibility study examines performing intraarticular PS-OCT using a flexible endocatheter introduced through a stiff 18-gauge spinal needle. Results are critical for designing larger clinical trials examining minimally invasive PS-OCT's ability to identify pre-OA.

Design: Fifteen patients undergoing arthroscopic partial medial meniscectomy were selected to confirm their risk for rapid progression to OA. Magnetic resonance imaging (MRI) was obtained at time 0 and at 2.5 years to determine if significant OA developed over this short period and for correlation with time zero PS-OCT results.

Results: Over half of the patients developed frank OA by $2.65 \pm 0.28$ years. All cartilage surfaces were successfully imaged by PS-OCT, but endocatheter redesign is needed. Normal to severely abnormal areas by PS-OCT (all normal by MRI) were successfully identified. PS-OCT assessments were promising for predicting OA progression ($p < 0.008$). However, the study's low power prevented definite conclusions regarding predictive value.

Conclusions: This pilot study produced at least two outcomes critical for future larger trial designs: medial meniscectomy patients are well-suited for studying PS-OCT's ability to predict future OA and substantial endocatheter redesign is needed.

1. Introduction

Current osteoarthritis (OA) imaging modalities, though critical in managing advanced disease, are not viable for identifying reversible pre-OA [1,2]. Late-stage detection by these imaging modalities limits OA treatment options commonly to pain control and arthroplasty. With the recent increase in efforts to develop chondroprotective agents and approaches to combat OA, a need exists for an imaging technology that can both identify and serially monitor pre-OA [1]. This technology would be a powerful asset aiding in chondroprotection agent development as well as clinically monitoring treatment. In addition, the high resolution serial imaging would provide insights into the pathophysiology of OA. Interest in developing chondroprotective agents has only been a mainstream concept in recent years [1,3]. Example potential chondroprotective agents are Sprifermin to stimulate chondrogenesis through Fibroblast Growth Factor (FGF) receptors and TissueGene-C where allogeneic human chondrocytes are modified to express Transforming Growth Factor -β1 (TGF-β1) [4,5]. This is in addition to approaches to alter mechanical stresses, such as gait correction or physical therapy [6,7]. The number of potential chondroprotective targets is large and the topic is reviewed in detail elsewhere [1,3].

We have previously demonstrated the technology optical coherence tomography (OCT), a micron scale imaging modality, can identify cartilage changes prior to cartilage thinning, fissuring, or alterations in
In addition to OCT adjuvant approaches, for clinical applications [16,17,19,20]. In the late 1990’s, we demonstrated structural (conventional) procedures or pharmaceutical trials, this study used patients undergoing vascular OCT radially imaging catheter was used. Its strengths and limitations rather than conventional OCT or dual channel PS-OCT. A commercial, radially imaging OCT catheter (Lightlab Imaging, Westford, MA, USA) was used in this study. But to understand the principles of PS-OCT, in this figure, we will show intraarticular imaging perpendicular to the cartilage surface. In Fig. 2, we will show radial imaging from the current study. These tibial cartilage images in Fig. 1 were from an earlier study where imaging was performed during total knee replacement (TKR) with an open surgical field [12]. We used a large forward imaging hand-held probe (1.5 cm diameter) analogous to an ultrasound transducer. The left side of the top image shows normal cartilage which has a smooth banding pattern where the bands are approximately evenly spaced and there are no significant gaps. The highly organized collagen of healthy cartilage makes it birefringent, sensitive to the polarization state of incident light. Most tissue of the body is not highly organized, so no banding patterns are seen. When cartilage collagen becomes disorganized, as in early OA, the banding pattern is disrupted or lost [9]. In the left of the lower image, mildly diseased cartilage is seen where bands are still present, but the pattern is distorted. The right side of both images A and B demonstrate severely diseased cartilage with banding being completely lost. Image courtesy of Li et al. [12] More detailed discussions of PS-OCT physics can be found elsewhere [26].

OCT is analogous to ultrasound, measuring the back reflection of infrared light rather than sound [16–18]. It is used routinely in ophthalmology, cardiology, and neurology. The resolution of OCT is 2–10 μm, approximately at the magnification of histopathology. Image acquisition rates reach 120 frames/second. OCT utilizes fiber optic technology, allowing for endocatheters as small as the 0.43 mm, the diameter used in this study. Current OCT engines are conveniently sized, similar to that of a defibrillator.

Since the early 1990s, we have studied, developed, and applied OCT, in addition to OCT adjuvant approaches, for clinical applications [16,17,19,20]. In the late 1990’s, we demonstrated structural (conventional) OCT identified cartilage OA changes on a micron scale [8,12,21]. This included cartilage thinning, loss of the bone cartilage interface, microfissures, and the presence of fibrocartilage. These findings have subsequently been confirmed by multiple groups [22–25]. While structural OCT is a powerful technology for assessing musculoskeletal tissue, we have found the adjuvant OCT technique, single channel PS-OCT, more effective for assessing early cartilage changes [9,12,15,21]. It allows detection of early OA changes (collagen disorganization) before cartilage thinning or surface fissuring. Most tissue in the body is not birefringent or sensitive to the polarization state of incident light. For tissue with highly organized microstructure (such as cartilage with organized collagen), the back reflection intensity varies with the polarization state of the incident light [26]. This is seen by an organized banding pattern as shown in Figs. 1 and 2A [12]. Loss of collagen organization is one of the first pathophysiological changes of early OA [27–29]. We have demonstrated the reduction or disappearance of tissue birefringence assessed by single channel PS-OCT correlates with collagen disorganization [9–11]. We initially demonstrated this with in vitro human cartilage correlating polarization sensitive picrosirius stained histopathology with PS-OCT banding [9]. In addition, in four rat studies, we demonstrated PS-OCT changes preceded changes in the cartilage surface or subchondral bone, again confirmed with picrosirius [10,11,14]. In 2005, in patients undergoing open knee surgery (total knee replacement, TKR) using a 1.5 mm diameter OCT hand held probe (compared to the 0.43 mm endocatheter used here), we confirmed our results [12]. In this study, because the cartilage was removed during TKR (but after imaging), we were able to correlate PS-OCT imaging in vivo with histopathology (once the cartilage was excised). Two additional technical studies from our group support single channel PS-OCT over dual channel PS-OCT for this application as single channel was only minimally susceptible to artifacts (ex: angle, catheter bending, and pressure) [26,30]. The difference between single and dual channel we have reviewed elsewhere in detail but briefly single channel measures relative birefringence (banding) while dual channel produces absolute polarization values (numerical value) [30]. Therefore, for this study, we focused exclusively on single channel PS-OCT assessments rather than conventional OCT or dual channel PS-OCT.

This small technical feasibility study is critical in developing a protocol for a larger trial. First it seeks to demonstrate the feasibility of effectively performing PS-OCT via an endocatheter introduced through an 18-gauge spinal needle. Second, as no endocatheter exists specifically designed for intraarticular imaging, a commercially available cardiovascular OCT radially imaging catheter was used. Its strengths and limitations for this application will be evaluated. It will be determined if a dedicated intraarticular endocatheter needs to be designed and built, or whether the commercial cardiovascular catheter is sufficient. Third, though it is not envisioned that PS-OCT will be limited to orthopedic procedures or pharmaceutical trials, this study used patients undergoing arthroscopic partial medial meniscectomy. This patient population has two advantages for studying the ability of PS-OCT to predict future OA. One advantage is the high percentage of this patient population that have rapid OA progression [31–33]. This is likely because changes in mechanics lead to high energies being delivered, in particular, to the medial tibial plateau [6]. Therefore, Magnetic Resonance Imaging (MRI) was obtained at time 0 and in 2.5 years to look for the development of new OA. Another advantage of using the meniscal surgery patients is the camera (CCD, charged carrier device) of the arthroscope confirmed endocatheter position estimated externally. This pilot study was needed to design a larger clinical trial, identifying the current protocol feasibility and modifications which need to be made in the protocol and current technology.

2. Methods

This prospective study was approved by the institutional review

![Fig. 1. Principles of Polarization Sensitive Optical Coherence Tomography (PS-OCT) Imaging](image-url)
Fig. 2. Intraarticular Polarization Sensitive Optical Coherence Tomography (PS-OCT) Imaging of Normal, Mildly Diseased, and Severely Diseased Cartilage with a Radially Imaging Endocatheter. The radially imaging, commercially available cardiovascular PS-OCT endocatheter (Lightlab Imaging, Westford, MA, USA) was introduced into the joint through an 18 gauge spinal needle. Fig. 2A shows normal banding indicating organized collagen of healthy joint cartilage (yellow arrow). But as it is radially imaging rather than imaging parallel to the cartilage surface, only a small area of cartilage can be assessed at a time (where the light is perpendicular to the surface). The advantages and disadvantages of using this commercially available, radial imaging catheter are examined in the manuscript. Compared to Fig. 1, with radial imaging, pixels are lost imaging the joint space (orange arrow) and also because the A-scans are not parallel (green arrow). Analogous to ultrasound, the two-dimensional image is a B-scan which is composed of the all the one-dimensional back reflections of light (A-scans). In Fig. 1, the A-scans are approximately parallel to each other (perpendicular to the tissue) even deep into the sample. With Fig. 2A, where the A-scan is perpendicular to the surface (yellow arrow), imaging is optimal and sufficient for this study. But when a radial endocatheter is used to image a planar surface, A-scans are diverging from each other with distance from the catheter (green arrow). This reduces lateral resolution with depth as the A-scans become farther apart. In addition, this catheter has a focal length of 1.2 mm but the distance between endocatheter and cartilage surface is much shorter. The true lateral resolution is much worse than the 25 μm at the focus because the focal point is deep in the sample. As discussed in the text, we will design our next endocatheter to avoid these issues. Fig. 2B shows abnormal banding representing mild-moderately disorganized collagen with disrupted but not lost banding (yellow arrow). Fig. 2C shows no banding as the collagen organization is lost. Fig. 2D is an image generated along the length of the catheter (sagittal), reconstructed from one A-scan from each radial image, as the optics are pulled back in the non-moving outer sheath. The yellow arrow shows areas of birefringent cartilage while the white arrow shows cartilage with no birefringence. The green arrow represents the catheter on the cartilage. Future embodiments for intraarticular imaging should image in a sagittal plane. However, the optics (ex: focal length) and pull back rate, as well as the catheter stiffness, are among the parameters that need to be optimized to design an arthroscope for sagittal intraarticular imaging. The PS-OCT scores for images A through D are 0, 2, 4, and 4, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
Table 1
Magnetic Resonance Imaging (MRI) cartilage Grading Protocol. This table outlines the grading scale used for knee MRI images. Based on morphology the approximate correlation between the OARSI histopathology grading systems would be MRI 0 and 1 equals OARSI 1, MRI 2 equals OARSI 2, MRI 3 equals OARSI score 3, MRI 4 equals OARSI score 4, MRI 5 equals OARSI score 4.5, and MRI 6 include OARSI scores of 4.5 and 5.34.

| Grade | Cartilage description |
|-------|-----------------------|
| 0     | Normal                |
| 1     | Signal heterogeneity with intact cartilage surface |
| 2     | Superficial fraying or fissuring |
| 3     | Deep fissuring         |
| 4     | Thinning <50%         |
| 5     | Thinning >50%         |
| 6     | Full-thickness cartilage loss |

Table 2
Polarization Sensitive Optical Coherence Tomography (PS-OCT) cartilage grading protocol. Table 2 outlines the grading scale used to analyze knee cartilage in PS-OCT images for each sagittal plane. PS-OCT scores of subjects included all corresponded to OARSI histopathology scores of zero at time 0. Even a patient with a PS-OCT score of 6 would correspond to an OARSI histopathology score of zero, as all only had birefringence changes as surface changes are excluded. There were no PS-OCT scores measured at 2.8 years34.

| Grade | Cartilage Description |
|-------|-----------------------|
| 0     | Normal/mild- predominantly healthy, disorganization <10% |
| 1     | Mild- predominately healthy, extent of disorganization >10% but less than 50% |
| 2     | Mild/moderate- approximately 50% of surface disorganized |
| 3     | Moderate- birefringence disorganized in majority of surface |
| 4     | Moderate/severe- Less than 50% of surface birefringence completely lost |
| 5     | Severely diseased tissue – More than 50% of surface birefringence completely lost |

as outlined in Table 1. Approximate comparison’s with Osteoarthritis Research Society International (OARSI) histopathology scores are provided in the table legends using prior MRI/histopathology comparisons [34]. In all included patients, by MRI, the cartilage at time zero had an intact surface and at most showed some heterogeneity (corresponding to an OARSI score of 0). For this small pilot study, it was sufficient to assign a single grade to each of these four cartilage surfaces based on the most significant OA identified (highest score). Any patient receiving a grade greater than 1 in any region (at time zero) was considered beyond pre-OA (pre-study criterion) and excluded from the PS-OCT imaging portion of the study. The 2.5 year MRIs were performed more precisely at 2.65 ± 0.28 years because of variations in patients’ availability. A Signa, 3.0 T General Electric MRI system (General Electric Healthcare, Waukesha, WI) was used. MRIs employed standard 7 pulse sequences and imaging planes including the following: localizer images, sagittal proton density, coronal T1 weighted fast spin echo (FSE), and three planes of T2 fat saturated FSE images. Pixel resolution was 512 × 256, except at stages 1, 6, and 7 where they have been reduced. Slice thickness was 3.5 mm. The gaps were 0.5 mm. The field of view varied from 14 to 24 cm.

A PS-OCT scoring system is specifically used in this study for assessing collagen organization. The grading system specifics are described in Table 2. The PS-OCT scoring system incorporates both the degree of birefringence (normal, disorganized, and absent), see Fig. 2A–C, and extent of cartilage surface involved (see Fig. 2D). The time zero PS-OCT scores of these included all corresponded to OARSI histopathology scores of 0. Each cartilage surface was assigned the highest score of the 6 sagittal sections.

2.1. Statistical analysis

Only patients with time zero MRI scores of 1 or less were included in assessing PS-OCT’s ability to identify those patients who will progress to frank OA. For statistical analysis, patients were divided into two groups based on their time zero PS-OCT scores, normal (scores 1 or less) and abnormal (scores over 1). An unpaired t-test was performed to examine statistical differences between 2.5 year MRI scores for the normal and abnormal PS-OCT groups (at time zero). Statistical analysis was performed with Prism 7 (GraphPad Software Inc. La Jolla, CA, USA).

3. Results

In all fifteen patients, PS-OCT images were successfully obtained in all cartilage sections. Specifically, each condyle/plateau was completely imaged along six adjacent sagittal planes spaced approximately 1.0 mm apart. However, several challenges arose that need to be addressed in the design of future larger trials. First, four of these soft cardiovascular endocatheters broke (stopped functioning) with the first three patients when the tip struck a solid surface. No catheters were lost after the third patient. Second, PS-OCT imaging initially added over 15–20 min to the procedure in the first five patients. Getting into each sagittal plane, with the pliable catheter, generally required numerous attempts. After the fifth patient, PS-OCT imaging did not extend beyond 10 min as the operator became skilled in handling the catheter even though it was pliable. The final issue associated with the endocatheter was the limitations of radial imaging. These radial imaging endocatheters did allow both the condyle and plateau to be assessed simultaneously, so these commercial catheters remain an option for future studies. But over 50% of the pixels were wasted imaging the joint space (Fig. 2A orange arrow) or when cartilage areas lateral to the catheter were imaged obliquely (Fig. 2, green arrow). When imaging a relatively flat surface like cartilage radially, light entering obliquely has A-scans that separate with depth, leading to deterioration of lateral resolution with depth (Fig. 2A, green arrow). Imaging exclusively perpendicular to cartilage surfaces (Figs. 1 and 2A yellow arrow, and 2D) would be superior as A-scans do not diverge from each other with depth [12].

Again, fifteen patients were included whose MRIs were clinically read as having no OA. However, in the blinded MRI reads during data analysis after 2.5 years, five of the time zero MRIs were later determined to have mild structural damage beyond pre-OA using the pre-study defined criteria. They had fraying or the presence of a small fissure(s) (MRI score of 2.3 ± 0.4). They were excluded from the section of the study designed to evaluate pre-OA (PS-OCT predicting OA development), as changes beyond collagen disorganization are not the focus of the study. They were included in all other sections of the study. This included demonstrating the ability to generate PS-OCT images of all cartilage surfaces, as well as showing evidence of progression at 2.5 years (as a separate group). These excluded patients all had absent birefringence in the areas with MRI abnormalities, consistent with loss of collagen organization as pre-OA [29]. In next larger clinical trial, inclusion MRIs will need to be graded based on the study scoring system and not based on the clinical reading.

Four patients did not follow up for their second MRIs. Eleven patients were therefore available to verify the OA progression rate was high in this patient population. In the six patients with normal time zero MRIs, they progressed from 0.3 ± 0.3 to 1.6 ± 1.6 in MRI scores. But as discussed below, of these six patients 50% progressed to severe OA by MRI (3.0 ± 1.0) while the remainder did not change (0.3 ± 0.3). Example results from patients from each group are shown in Figs. 4 and 5. In the second group of five excluded, they progressed from 2.3 ± 0.4 (fraying to small fissuring) to 3.0 ± 0.7 (fissuring and cartilage thinning) in 2.5 years. In a future larger trial, these patients with MRI grade 2 (fraying or microfissures), with no birefringence, should be studied but as a separate group from grades 0 and 1 as the amount of OA at 2.5 years was similar in this small cohort.

We used this small cohort of patients with no frank structural damage at time zero by the MRI to evaluate trends between PS-OCT patterns and the development of frank OA. Presented here is representative PS-OCT data from the medial tibial plateau of these patients. The patient

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numbers are too small to draw diagnostic conclusions, but it does demonstrate trends consistent with the hypothesis. The medial tibial plateau is the section of the knee that has been shown most likely to develop OA after medial meniscectomy [31–33]. For this technical feasibility study, the scoring system grades the entire medial tibial plateau using the highest score of the six sagittal planes. No attempt was made to correlate regions of the plateau/condyle by PS-OCT and MRI due to the small patient numbers. The extremes of collagen organization/disorganization were observed ranging from normal by PS-OCT to complete loss of birefringence, successfully meeting an objective of the study. In a sub-analysis, patients were divided by PS-OCT score into those which had a value either above or below 1.0 (normal). The two groups MRIs were compared at 2.5 years. Three patients received time zero PS-OCT scores placing them into the normal group (0.3±0.3), and the other three received time zero PS-OCT scores qualifying for the abnormal group (4.3±0.3). Neither group had evidence of OA by MRI or arthroscopy at time zero. Interestingly, the mean MRI scores at 2.5 years for the normal group was 0.3±0.6, unchanged from time zero, and for the abnormal group it was 3.0±1.0, severe disease (extensive progression). The data was significant (p < 0.008) because of the large difference between the two groups, so was suggestive PS-OCT predicts progression. However, the power is insufficient to make diagnostic conclusions. The median ages at arthroscopy were not statistically different (P > 0.22) with means of 47±1.4 (progression) and 52±4.5 (no progression).

Fig. 3. Demonstrating Polarization Sensitive Optical Coherence Tomography (PS-OCT) Catheter Placement for a Sagittal Assessment. As stated in the text, each condyle/plateau was completely imaged along 6 adjacent sagittal planes spaced approximately 1.0 mm apart. This image shows the PS-OCT endocatheter in one sagittal plane photographed by an arthroscope introduced separately. The white arrow demonstrates the nonmoving outer sheath, the yellow arrow shows the internal optics (lens, light directing prism, and optical fiber), and C is the cartilage. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 4. An Example Image of Normal Time Zero Polarization Sensitive Optical Coherence Tomography (PS-OCT) Cartilage Imaging: No Development of OA by Magnetic Resonance Imaging (MRI) at 2.5 Years. Image A shows the time zero MRI for a 59 year old male. Knee MRIs were performed with a 1.5 T magnet (General Electric Healthcare, Waukesha, WI) employing standard 7 pulse sequences and imaging planes including the following: localizer images, sagittal proton density, coronal T1 weighted fast spin echo (FSE), and three planes of T2 fat saturated FSE images. Image B shows an MRI from the same patient, using the same MRI parameters, approximately 2.5 years later. No significant OA is noted at either time point. The regular (normal) banding pattern is identified by the white arrows and the endocatheter in the lumen is shown by the yellow arrow. The time zero PS-OCT score was 0 for this cartilage surface. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
4. Discussion

A need exists to identify OA at potentially reversible stages, particularly as investigations into disease modifying agents and approaches are expanding [1–3]. Both radiographs and MRIs are critical in the management of established OA. But radiographs lack the sensitivity to detect pre-OA, as does conventional MRI. More advanced MRI techniques are under investigation for diagnosing earlier OA. In this regard, multi-echo T2-mapping has been employed to assess the concentration, orientation, and integrity of collagen and water in cartilage and has been suggested as a sensitive technique for early detection of cartilage degeneration [35–37]. Compared to T2-mapping, quantitative T2*-mapping has demonstrated a number of benefits including shorter scan times and higher resolution. But while these techniques have been successful in assessing myocardium, they have not found a clinical role for cartilage assessment, particularly because of the low resolution. There is no current clinical MRI technique which can measure pre-OA in vivo. PS-OCT has shown consider promise for diagnosing pre-OA as discussed and prospective clinical trials are now needed. This pilot study produced at least two outcomes critical for future, larger clinical trials: 1. Medial meniscectomy patients are well-suited for assessing the predictive value of PS-OCT due to the rapid onset of OA and 2. Substantial endocatheter redesign is needed.

As discussed in the introduction, our in vitro and animal work, in addition to work imaging during total knee replacement (TKR), strongly support the ability of PS-OCT to diagnose pre-OA [8,9,11,12,21]. The most critical next step is to determine if abnormal PS-OCT regions predict progression to frank OA, an observation we have seen in animals [10]. A larger study, designed using the results from this feasibility study, is needed. In addition, the demonstration PS-OCT can be performed minimally invasively suggests its potential as a broadly applicable diagnostic. This feasibility study provides critical information in designing a randomized clinical trial to achieve these objectives, which includes insight into an optimal OCT endocatheter design for minimally invasive intra-articular imaging.

This feasibility study also supports using patients undergoing medial meniscectomy in the next larger trial. This is not to suggest that PS-OCT would only be used during orthopedic interventions or therapeutic research, which would make it of only limited value. Our group is pursuing a minimally invasive approach in parallel with arthroscopic imaging. The minimally invasive procedure may or may not ultimately benefit from external ultrasound guidance. This will be addressed once the diagnostic value of PS-OCT has been confirmed. It is also possible with advances in quantum second order correlations (SOC) in the future, PS-OCT can be performed without needing to enter the joint at all [38]. But in studying if abnormal PS-OCT measurements predict progression to OA, this patient population has advantages. First, our data is consistent with previous reports that a significant percentage of these patients progressed to frank OA (over a short time period) in the medial tibial plateau [31–33]. Second, using this patient population will allow evaluation, by the arthroscope, of the new stiffer endocatheter’s maneuverability as was done in this feasibility study.

This feasibility study also provided information needed for optimizing the endocatheter design for the double blind clinical trial. In the

Fig. 5. An Example Image of Abnormal Time Zero Polarization Sensitive Optical Coherence Tomography (PS-OCT) Imaging: Development of Substantial OA by Magnetic Resonance Imaging (MRI) at 2.5 Years. Image A shows the time zero MRI of a 44 year old male with no significant knee OA. Knee MRIs were performed with a 1.5 T magnet (General Electric Healthcare, Waukesha, WI) employing standard 7 pulse sequences and imaging planes including the following: localizer images, sagittal proton density, coronal T1 weighted fast spin echo (FSE), and three planes of T2 fat saturated FSE images. The MRI in Image B shows that the patient, using the same MRI parameters, developed OA 2.5 years later. Image C is the time zero PS-OCT image from the same patient which shows severely disorganized banding (white arrows). The time zero PS-OCT score was 4 for this cartilage surface.
future trial, we will likely need to build our own endocatheters specific for the joint, which is not a trivial task. The commercial catheters used in this study were thoroughly tested in patients, are sterile, and have been engineered to a small cross sectional diameter. But they image radially, which is needed for imaging atherosclerosis in approximately circular coronary arteries. The endocatheter had several limitations for joint imaging which need to be addressed for the larger clinical trial. First, the biggest challenge was the endocatheter was too pliable. It made maneuvering in the joint space more difficult and led to a high catheter damage rate in the first few patients. While the operator eventually became skilled at handling the catheter, no longer breaking the catheters, a stiffer catheter will reduce the risk of breakage and improve maneuverability. This will also likely reduce OCT imaging time. Second, while radial imaging allowed both the condyle and plateau to be assessed simultaneously, over 50% of the pixels were lost because imaging the joint space (rather than cartilage) occurs Fig. 2A (orange arrow) and also a large number of A-scans are oblique and therefore diverging as described in Fig. 2A (green arrow) and results section. It is optimal the beam is perpendicular to the cartilage surfaces or when angular imaging is performed, the A-scans are parallel. So lateral resolution deteriorates with depth (except when the beam is perpendicular, Fig. 2A yellow arrow) with the diverging A-scans (radial catheter imaging a planar surface). Though likely forward imaging at the end of a catheter would provide superior visualization to radial imaging, it would be difficult to image all the cartilage surface if the tip needs to point perpendicular to the surface. In addition, the direction of the tip would likely need to be mechanically controlled, substantially increasing the diameter and imaging time. We feel imaging in the plane of the endocatheter (sagittal plane) is the optimal design, similar to that seen in Fig. 2D. Therefore, the light beam will be directed into the cartilage along the whole length of the pull back and no off-angle imaging (or imaging of the joint space) will be obtained. This avoids the pixel loss described in Fig. 2A. The optics again will be able to move within a transparent outer sheath, but the outer sheath has to be stiffer as described. The pull-back rate will be reduced, improving performance, as the high pull back rate of this catheter is needed to obtain a complete image during one saline flush in the coronary artery. Third, the focal length will be reduced to less than 0.5 mm as the endocatheter is closer to the cartilage than the 1.2 mm needed for intravascular imaging (Fig. 3). In this study, the theoretical lateral resolution of 25 μm is at the focus 1.2 mm deep, being substantially worse at the surface. In addition, the pixel size needs to match the axial and lateral resolution (of the pull back), which would be 30 μm or less. It is likely our group will need to build this endocatheter. We have successfully built probes, including catheters and endoscopes, for other clinical applications [39–41]. However, none of these match the specifications needed for intraarticular imaging.

With the recent increase in efforts to develop methods to halt the progression of OA, a need exists for imaging technologies which identify it at early, reversible stages (pre-OA). We have developed, and will continue to develop, single channel PS-OCT to achieve this objective. The long-term goal is to use PS-OCT minimally invasively or non-invasively to identify pre-OA. If PS-OCT could only be used during orthopedic procedures or pharmaceutical research, it would only be of limited value. However, to invest in the development of a clinically viable PS-OCT systems for OA, it must first be demonstrated PS-OCT predicts future development of OA. This paper, with small patient numbers, was not intended to test this hypothesis. Surprisingly, the data in this study correlating time zero PS-OCT results with 2.5 year MRIs was still promising (p < 0.008), but lacked the power to draw definitive conclusions. This pilot study examined the strengths and limitations of a minimally invasive design for future larger clinical trials. Among the observations, we confirm OA progresses relatively rapidly in the majority of this patient population and a redesign of the endocatheter is essential. This pilot study provides critical information for the design of a large clinical trial to assess the ability of PS-OCT to identify pre-OA and progression to frank OA.

Authors contributions

All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data. All authors contributed to drafting the article or revising it critically for important intellectual content. All authors gave their final approval of the manuscript to be submitted.

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Plain language summary

Osteoarthritis (OA) needs to be diagnosed at earlier, reversible stages. Current imaging techniques, such as X-ray and MRI, are critical in managing more advanced disease. Here we continue to advance the technology optical coherence tomography (OCT) for diagnosing OA at reversible stages.

Patient consent

All patients were consented. The consent and protocol were approved by the Institutional Review Board (IRB) of Brigham and Women's Hospital, Boston, Massachusetts USA.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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