Image-guided optical spectroscopy in diagnosis of osteoarthritis: a clinical study

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Abstract: This goal of this study was to clinically evaluate the potential of a novel hybrid imaging techniques, called x-ray guided multispectral diffuse optical tomography, for identifying physiological parameters of joint tissues that can be used to distinguish between osteoarthritic and healthy joints in the hand. Between 2006 and 2009, the distal interphalangeal (DIP) finger joints from 40 subjects including 22 osteoarthritis patients and 18 healthy controls were examined clinically and scanned by the hybrid imaging platform that integrated a C-arm based x-ray tomosynthetic system with a mutlispectral diffuse optical imaging system. Based on the reconstructed results from the 40 subjects, it was observed that oxygen saturation and water content were two statistically most significant physiological discriminators for differentiation of the healthy joints from the osteoarthritic ones.

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1. Introduction

Osteoarthritis (OA) is the most common arthritic condition worldwide and is estimated to affect nearly 60 million Americans. It is a degenerative disease, a consequence of age-related changes, genetic predisposition, and abnormal biomechanical forces that combined, lead to joint failure [1,2]. The prime features of OA include the progressive degeneration of articular cartilage, subchondral bone remodeling, osteophyte formation, a variable degree of synovial membrane and increased volume of synovial fluid [2,3]. In particular, there is increasing evidence that OA is a disease involving a metabolic dysfunction of bones [4–6]. It is likely that this metabolic dysfunction of bone, often associated with high metabolism of subchondral bone and connected joint soft tissues, will cause changes in tissue oxygen saturation ($S_{T}O_2$), deoxy-hemoglobin (Hb), oxy-hemoglobin (HbO_2) and water content (H_2O). While there is currently no cure for this disease, numerous studies have shown that the progression of articular damage may be modified by medical or surgical intervention if the disease is detected early [7]. These studies, combined with recent developments in gene therapy, have generated substantial demand for noninvasive techniques for detecting early changes in the joints, when intervention is likely to have its greatest effect. Several conventional techniques

have been applied to detect OA, including x-ray radiography, computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI) [8–10]. Among these conventional techniques, MRI represents the most powerful tool for evaluating joint abnormalities, particularly when using a surface coil or contrast agent [10]. However, MRI is expensive, and may not be suitable for long term, routine monitoring of OA. In particular, MRI as well as other conventional techniques provides only anatomical structure of the joints, which is difficult to detect early metabolic changes involved in an OA joint. As such, highly sensitive and specific imaging methods are urgently needed to detect the physiological change of early-stage OA.

Due to the numerous advantages of low cost, portability, and non-ionizing radiation, near-infrared (NIR) diffuse optical spectroscopy (DOS) and tomography (DOT) have been employed to characterize biological tissues quantitatively and qualitatively [11]. DOS and DOT have shown the promise for therapeutic monitoring of breast cancer and stroke, functional brain and breast cancer as well as finger joints imaging [12–16]. DOS and DOT have more than 30 year history of being used to access tissues total hemoglobin concentration, hemoglobin oxygen saturation, water and lipid concentration and tissue scattering. Early work in the field of tomographic DOS focused on reconstruction of optical properties of tissues at several selected wavelength. Then least-square fitting algorithm was utilized to estimate the chromophore concentrations based on the recovered optical properties and Beer's Law [17,18]. Now several methods are proposed to directly image the chromophore concentrations without first estimating the optical properties in either continue-wave (CW) or in the frequency domain system [19,20]. An interesting study has shown that oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb), water and scattering amplitude heterogeneity could be successfully recovered using CW measurements at four optimized wavelengths in the 650–930nm range [21]. However the downside of tomographic diffuse NIR spectroscopy (NIRS) is its low resolution due to the multi-scattering events that occur along each photon path. One key way for optical imaging to readily be integrated into medicine is as an “add-on” to larger and currently accepted high-resolution clinical imaging systems, such as mammography, ultrasound, x-ray computed tomography or tomosynthesis, and magnetic resonance [11]. For example, the use of prior spatial and spectroscopic prior information has been reported to achieve high-resolution DOT imaging with NIRS [20,22]. According to the integration of NIRS and multi-modality imaging setups, chromophore concentrations are able to be reconstructed with high imaging accuracy using spatial guidance from high-resolution imaging methods and spectral *a-priori* information provided by NIRS [20].

We have recently reported the use of DOT to detect OA in the finger joints of five subjects [16]. In this case study, we have shown that there exist significant contrasts in both absorption and scattering coefficients between OA and normal joints. We have also shown that the resolution of DOT can be dramatically improved when high resolution anatomical structure of the joints from x-ray is incorporated into the optical image reconstruction as *a priori* [23,24]. In the present study, we aim to use x-ray guided multispectral DOT to obtain quantitative parameters of joint tissues in the hand from 40 human subjects, in an attempt to capture the typical physiological/metabolic classifiers that can be used to distinguish between OA and healthy joints.

2. Methods and materials

2.1 Study design and patients

Forty new subjects (five previous subjects are excluded for this study since their imaging results have been reported [23]) were enrolled in the study between July 2006 and June 2009: 22 patients with OA and 18 healthy volunteers. All subjects (female; mean age 51 years; age range 32–80) signed informed consent forms before participating in the study. Subjects were contacted either directly at the rheumatology outpatient clinics or via leaflets and posters

about the study that were distributed in the clinics and were invited to participate. The clinical study was approved by the Institutional Review Board of the University of Florida (UF).

Clinical examination of each patient was performed by a single experienced rheumatologist (E.S.S) at UF. Patients with OA were identified by the clinical features of bony thickening of the distal interphalangeal (DIP) finger joint and the absence of other arthropathies, including rheumatoid arthritis, psoriatic arthritis and gout, as well as any traumatic injury to the joint that was selected for imaging. The control group consisted of 18 healthy volunteers who had no known OA or other joint diseases. Patients were randomly sent to us for optical scanning after examined by the physician in his clinic room. No diagnostic information was provided before optical imaging. Only one DIP joint of the index or middle finger from each subject was optically scanned in this study.

Fig. 1. (a) Photograph of the integrated hybrid x-ray/DOT system. The insert is a close-view photograph of the finger/fiber optics/x-ray interface. (b) Schematic of the interface. Note that both the plexiglass container and finger tip holder can be translated horizontally for separate DOT and x-ray data acquisition.

2.2 Imaging systems

The hybrid x-ray/DOS imaging system that has been described in detail previously [16,23] integrates a modified mini C-arm x-ray system (MiniView 6800, GE-OEC, UT) with a homemade 64x64-channel photodiodes-based DOT system [see Fig. 1(a)]. The tomosynthetic imaging is realized through the modified C-arm x-ray system. Tomographic x-ray images are reconstructed from 2D projections using an improved shift-and-add algorithm we developed previously [23]. In this algorithm, we first segment or normalize the projection images and then apply the shift-and-add algorithm on the segmented projection images at multiple angles, which results in accurate reconstruction of the three dimensional (3D) structures of joints. The CW-based DOS system consists of laser modules, a hybrid light delivery subsystem, a fiber optics/tissue interface, a data acquisition module, and light detection modules [23]. The system has eight diode lasers (B&W TEK Inc., DE and Power Technology Inc., AR) with wavelengths from 634nm to 974nm working as light sources. The cylindrical fiber optics/tissue interface is composed of 64 source and 64 detector fiber bundles that are positioned in 4 layers along the surface of a plexiglass container and cover a volume of 15x30mm. In each layer 16 source and 16 detector fiber bundles are alternatively arranged. The space between the finger and the wall of the plexiglass container is filled with tissue-like phantom materials as coupling media consisting of distilled water, agar powder, Indian Ink

and Intralipid, giving an absorption coefficient of 0.014mm^{-1} and a reduced scattering coefficient of 1.0mm^{-1} [23].

In the hybrid imaging of joint tissues, the x-ray imaging is performed immediately after the DOS data acquisition. To eliminate the artifacts in the x-ray projections possibly caused by the optical interface, we have used a co-axial post to support the optical interface such that the interface can be translated along the post [see the insert in Fig. 1(a) and the schematic of the interface shown in Fig. 1(b)]. During an exam, the subject first places the finger into the plexiglass container through a plastic ring while the distal end of the finger rests against a finger tip holder installed at the end of the co-axial post. Then the optical interface is slid forth to be in contact with the plastic ring structure that is used to lock the position of the optical interface. Immediately after the DOS scanning, the optical interface is slid back for x-ray exposure while the finger stays at the same position. Four small metal spheres (1mm in diameter) are embedded along the surface of the plastic ring as fiducial markers for accurate co-registration of the x-ray and optical imaging.

2.3 X-ray guided tomographic DOS reconstruction algorithm

When the clinical data acquisition is finished, the following step is to generate the x-ray aided spectroscopic images based on a robust 3D reconstruction algorithm. We have developed a hybrid regularization based scheme for x-ray guided DOT image reconstruction, which is able to handle the cases where x-ray tomography is insensitive to the target tissues or lesions [23]. For example, in the area of joint imaging x-ray is not able to detect the cartilage and fluids as well as other soft tissue changes inside the finger joints, although the changes associated with the soft tissues can be easily captured by low resolution DOT alone. For the hybrid regularization-based nonlinear reconstruction algorithm, the objective function is written [23]:

$$\text{Min: } \Omega = \|\Phi^c(\lambda) - \Phi^o(\lambda)\|^2 + \beta[\|\Phi^c(\lambda) - \Phi^o(\lambda)\|^2 + \lambda' \|\mathbf{L}(\chi - \chi^0)\|^2] \quad (1)$$

where χ is the chromophore concentrations, β is the hybrid regularization parameter, λ' is the regularization parameter determined by combined Marquardt and Tikhonov regularization schemes. $\Phi^o(\lambda) = (\Phi_1^o, \Phi_2^o, \dots, \Phi_M^o)^T$ and $\Phi^c(\lambda) = (\Phi_1^c, \Phi_2^c, \dots, \Phi_M^c)^T$, where $\Phi_i^o(\lambda)$ and $\Phi_i^c(\lambda)$ are observed and computed photon density for $i = 1, 2, \dots, M$ boundary measurement locations with wavelength λ . The x-ray structural *a priori* information is incorporated into the iterative process by using the spatially variant filter matrix $\mathbf{L}$. The Laplacian-type filter matrix was used and its elements, L_{ij} were constructed according to the visible region or tissue type it was associated with x-ray derived priors as follows [20,23]:

$$L_{ij} = \begin{cases} 1 & \text{when } i = j \\ -1/nn & \text{when } i, j \in \text{one region} \\ 0 & \text{when } i, j \in \text{different region} \end{cases} \quad (2)$$

where nn is the finite element node number within a tissue type. The photon density $\Phi_i^c(\lambda)$ can be calculated from the photon diffuse model using the finite element method,

$$\nabla \cdot D(r, \lambda) \nabla \Phi(r, \lambda) - \mu_a(r, \lambda) \Phi(r, \lambda) = -S(r, \lambda) \quad (3)$$

In addition, according to Beer's law, the wavelength-dependent tissue absorption is

$$\mu_a(\lambda) = \sum_{i=1} \epsilon_i(\lambda) c_i \quad (4)$$

in which c_i is the concentration, $\varepsilon_i(\lambda)$ is the extinction coefficient of the i th chromophore (HbO₂, Hb or H₂O) at wavelength λ [18]. Thus the forward model is further written,

$$\nabla \cdot D(r, \lambda) \nabla \Phi(r, \lambda) - \sum_{i=1} \varepsilon_i(\lambda) c_i \Phi(r, \lambda) = -S(r, \lambda) \quad (5)$$

For the inverse problem, the following updating equation for the hybrid regularization is deduced when $\beta = 1$,

$$\Delta \chi = (J^T J + J^T J + \lambda' I + L^T L)^{-1} [J^T (\Phi^o(\lambda) - \Phi^c(\lambda))] \quad (6)$$

where J is the Jacobian matrix formed by $\partial \Phi(\lambda) / \partial \chi$ at the boundary measurement sites; D is the diffusion coefficient which can be written as $D = 1 / (3(\mu_a + \mu'_s))$ where μ'_s is the reduced scattering coefficient and assumed as constant here; $\Delta \chi = (\Delta c_{1,2}, \dots, \Delta c_{1,n}, \Delta c_{2,1}, \Delta c_{2,2}, \dots, \Delta c_{2,n}, \Delta c_{3,1}, \Delta c_{3,2}, \dots, \Delta c_{3,n})^T$ is the updating vectors for the 3 absorbers and n is the total finite element node number; $S(r, \lambda)$ the laser source strength. The Jacobian matrix J is denoted: $J = [\tilde{J}_{Hb, \lambda}, \tilde{J}_{HbO_2, \lambda}, \tilde{J}_{H_2O, \lambda}]$, where $\tilde{J}_{c_i, \lambda}$ represent the Jacobian submatrices for different chromophores and written,

$$\tilde{J}_{c_i, \lambda} = \frac{\partial \Phi^o(\lambda)}{\partial \mu_a} \frac{\partial \mu_a}{\partial c_i} \quad (7)$$

Thus the image formation task here is to update initial chromophore concentration distributions via iterative solution of Eqs. (5) and (6) so that a weighted sum of the squared difference between computed and measured photon density in Eq. (1) can be minimized.

2.4 Image analysis methods

Image reconstruction of the DIP finger joint with the optical coupling phantom/media (30x20mm in volume) was performed with a finite element mesh of 2,705 nodes and 13,440 tetrahedral elements for each of the 40 subjects. The 3D x-ray images allowed us to segment the imaging domain into three types of tissue volumes: bones, approximated soft tissues surrounding the joint cavity and background phantom media. The initial guesses of different absorbers were optimized for the joint tissues and bones using x-ray guided forward fitting algorithm. It should be noted that optical measurements from 6 wavelengths (633, 670, 723, 805, 853, 896nm) are used to ensure the reconstruction accuracy and minimize the parameter crosstalk between different absorbers [21]. The optical scattering coefficient used is a homogeneous constant which is optimized via the forward fitting algorithm. We would like to perform the investigation of scattering amplitude heterogeneity later due to the unknown molecular mechanism of OA joint tissues.

The known anatomy from x-ray made it possible to accurately reconstruct images of S_TO₂, Hb, HbO₂ and H₂O concentrations in the finger joints. The values of these metabolic parameters were also provided for each tissue type of the finger joints, which were calculated based on the mean values for each segmented region. The ability of different metabolic parameters captured by x-ray guided DOT to discriminate between OA and normal DIP joints were tested using the Receiver Operating Characteristic (ROC) Curve. For artificial statistical and classification method, sensitivity was directly calculated as TP/(TP + FN), specificity as TN/(TN + FP), positive predictive value as TP/(TP + FP), and negative predictive value as TN/(TN + FN), where TP represents the number of true-positive findings, TN represents the number of true negative findings, FP represents the number of false-positive findings, and FN represents the number of false-negative findings. In addition, several paired sample student *t*-tests for each classifier were performed to assess the differences between two-group subjects (i.e., OA-Healthy groups).

3. Results

Fig. 2. Reconstructed Hb (a) and HbO₂ (b) concentration (μM) images at selected dorsal/coronal planes for an OA joint with apparent abnormal radiographs.

Fig. 3. Reconstructed Hb (a) and HbO₂ (b) concentration (μM) images at selected dorsal/coronal planes for a healthy subject.

Reconstructed 3D physiological images (multiple dorsal and coronal slices) from the representative OA and normal joints are presented in Figs. 2 and 3. We find that bones can be clearly delineated for both OA and normal joints. While there is no clear boundary between the cartilage and fluid, the joint soft tissues can be identified. For the OA joint shown in Fig. 2, we observe smaller Hb and HbO₂ concentrations of soft tissues compared those from the bones. And it seems the drop of HbO₂ concentration relative to the bones is bigger than that from Hb concentration. Likewise, for the healthy joint displayed in Fig. 3, smaller Hb and HbO₂ concentrations of soft tissues were also observed. However, it seems that the drop of HbO₂ concentration relative to the bones is smaller than that from Hb concentration. Since for different subjects, the Hb and HbO₂ concentrations of joints are quite different, the $S_T\text{O}_2$ was computed and provided as the effective classifier.

Figure 4 shows the recovered $S_T\text{O}_2$ and H₂O content images for the OA patient in Fig. 2 with significant radiologic signs including joint space narrowing, while Fig. 5 displays the reconstructed images for another OA joint with less-apparent joint space narrowing compared to the healthy one plotted in Fig. 6. We note that the $S_T\text{O}_2$ and H₂O content of joint soft tissues from the OA patients [Figs. 4(a)–4(d) and 5(a)–5(d)] are significantly different with those from the healthy subjects (Figs. 6a–6d), suggesting the potential of these physiological parameters as classifiers for OA detection.

As such we provide in Figs. 7(a)–7(c) the analysis results based on the recovered metabolic findings from all the subjects examined in this study. As shown in Fig. 7, there exist clear differences between OA and healthy joints based on the physiological parameters obtained. In addition, a combined image feature parameter is used to achieve better separation between healthy and diseased joints, which is defined as the ratio of $S_T O_2$ between the joint soft tissues and peri-articular bone divided by the H_2O content of the joint soft tissues.

Table 1. Statistical analysis showing the difference between OA and healthy joints

Classifiers	Tissues	Cases	Mean	S.D.	<i>p</i>	<i>t</i>
$S_T O_2$	Joint	OA	59.11 (%)	4.1691	1.2780×10^{-12}	10.143
		Healthy	69.64 (%)	1.6045		
	Bones	OA	70.09 (%)	1.6370	0.8090	1.7907
		Healthy	71.25 (%)	2.3958		
H_2O	Joint	OA	62.87 (%)	5.9220	2.996×10^{-12}	9.8470
		Healthy	43.72 (%)	6.6440		
	Bones	OA	30.33 (%)	6.1338	1.0515×10^{-8}	7.1809
		Healthy	18.44 (%)	3.9291		
Combined image feature	OA		0.0135(x100)	0.0016	9.322×10^{-18}	14.737
	Healthy		0.0233(x100)	0.0027		
Ratio of $S_T O_2$ between joint and bones	OA		0.8437	0.0618	1.3886×10^{-10}	8.5625
	Healthy		3.9787	0.0293		

According to the statistical analysis, we can further evaluate whether the $S_T O_2$, combined image feature parameter and H_2O content are appropriate to serve as distinguishers between OA and healthy joints. As such, the *t*-tests are completed for all these statistically significant classifiers and the testing results are provided in Table 1. We immediately find they reveal statistically significant differences between healthy and OA joints.

According to ROC curves analysis, we find the recovered physiological parameters can effectively differentiate between healthy and OA joints, with an optimal sensitivity of 0.73 and specificity of 1.0 for H_2O , while the sensitivity and specificity are 0.86 and 1.0, respectively for $S_T O_2$. The best sensitivity-specificity pair is reached when the combined image feature is used, where a sensitivity of 0.91 and a specificity of 1.0 are obtained. Our imaging results are independently provided to the hospital and compared with the diagnosis results from the rheumatologist, which should give a reasonable evaluation of our imaging modality.

Fig. 4. Reconstructed images at selected dorsal/coronal planes for the OA patient in Fig. 2: (a) the SrO_2 (%) slices along coronal planes; (b) the SrO_2 slices along dorsal planes; (c) the H_2O content(%) slices along coronal planes; (d) the H_2O content slices along dorsal planes; (e) the tomographic x-ray image from an arbitrary view.

Fig. 5. Reconstructed images at selected dorsal/coronal planes for another OA joint having essentially normal plain radiographs: (a) the SrO_2 slices along coronal planes; (b) the SrO_2 slices along dorsal planes; (c) the H_2O content slices along coronal planes; (d) the H_2O content slices along dorsal planes; (e) the tomographic x-ray image from an arbitrary view.

Fig. 6. Reconstructed images at selected dorsal/coronal planes for the healthy joint in Fig. 3: (a) the $S_T O_2$ slices along coronal planes; (b) the $S_T O_2$ slices along dorsal planes; (c) the H_2O content slices along coronal planes; (d) the H_2O content slices along dorsal planes; (e) the tomographic x-ray image from an arbitrary view.

4. Discussion

Fig. 7. Differentiation of OA and healthy joints based on (a) the $S_T O_2$ of joint and bone tissues, (b) the H_2O content of joint and bone tissues, and (c) the combined image feature.

We found from Table 1 that both $S_T O_2$ and H_2O of joint soft tissues are able to distinguish well between OA and normal joints in the majority of the subjects, which also agree well with our findings in Figs. 7(a) and 7(b). Interestingly, the differences in mean $S_T O_2$ for periarticular bone between healthy and OA joints do not appear to be so significant [Fig. 7(a) and Table 1]. We noted that in most OA cases the mean $S_T O_2$ values of joint soft tissues are smaller than those for bones. Further, compared with the $S_T O_2$ values of bones, we observed a significant drop in the magnitude of $S_T O_2$ value of soft tissues for the OA joints, while we saw only a small drop for this parameter of soft tissues for the healthy ones. In some healthy cases, the $S_T O_2$ values of soft tissues are comparable to those of the bones. Interesting observation can also be made from Fig. 7(b) and Table 1 where we can see that H_2O content value of soft tissues for the OA joints is overall significantly higher than that for the healthy ones. This finding of significantly elevated water content for OA joints is supported by the literature in OA pathology [25]. Surprisingly, a striking separation of osteoarthritic from normal joints was found when the combined image feature is used as classifier for each joint examined, as shown in Fig. 7(c) and Table 1. Combining these measurements into a single parameter increased the sensitivity and specificity of the detection to the point where the two indexes for x-ray guided multispectral DOT are comparable to other imaging modalities, such as ultrasound [26]. Noted it is possible that the imperfect spatial information from x-ray scanning was incorporated into the DOT reconstruction. However, even if we consider the effect of the imperfect spatial information in image reconstruction, the imaging quality from the hybrid scanning method is still enhanced compared that from DOT only [27].

Changes in cartilage, underlying subchondral bone, and synovial fluid are the tissues most affected by OA. Bone is frequently remodeled in OA, with new bone formed either as osteophytes at the margins of the articular cartilage or as a change in subchondral bone density. These changes in bone structure can allow blood flow to more easily penetrate the subchondral bone plate and the calcified cartilage that lies between subchondral bone and cartilage. There is now accumulative scientific evidence suggesting that the trigger for many of these changes is the low oxygen levels in the diseased tissues including the cartilage of an OA joint [28]. These low oxygen levels will cause the formation of new blood vessels, allowing the diseased synovium to invade the surrounding tissues [28]. It seems these changes correlate well with the decreased $S_T O_2$ seen in the soft tissues of OA joints in our study. The mild inflammatory changes frequently seen in the synovial fluid of patients with OA would

also produce high water content in joint soft tissues, a feature that is often seen in our measurements. In addition, normal cartilage is tough, elastic, very durable and comprised mainly of collagen (20-30%) and water molecules (67-80%). Finally the changes in OA cartilage also include proteoglycan loss, with a resultant increase in hydration of the articular cartilage. These changes likely contribute to the increase in water content and decrease in oxygen saturation seen in the soft tissues of OA joints [28].

In summary, we have developed an imaging platform that integrates x-ray tomosynthesis with multispectral DOT for the metabolic assessment of OA in the finger joints. Currently the diagnosis of OA is primarily based on clinical examinations and the absence of abnormal laboratory tests, making it impossible to differentiate between OA and healthy joints at an early stage. Although the diagnostic and prognostic value of classifying patients by imaging findings has not been fully determined and there is no single, well-accepted quantitative classification system for the early diagnosis of OA by imaging techniques, initial attempts have produced interesting insights. Due to its low sensitivity and specificity, conventional radiographs may be normal in patients with OA, especially early in the disease process. We have demonstrated here that the anatomical information from x-ray imaging can be combined with multispectral DOT so that high resolution metabolic/functional images of joint tissues are achievable, which may shed light on the early detection OA in the finger joints. A further clinical investigation should be conducted to differentiate OA at different stages for the large weight-bearing joints of the lower extremities. It is also definitely necessary to validate if this technique can distinguish well between OA, rheumatoid arthritis and psoriatic arthritis in the joints using the simple optical imaging systems [29,30].

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