Review article

Photoacoustic tomography for human musculoskeletal imaging and inflammatory arthritis detection

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\textbf{A B S T R A C T}

With the capability of assessing high resolution optical contrast in soft tissues, photoacoustic imaging (PAI) can offer valuable structural and functional information of human joints, and hold potential for diagnosis and treatment monitoring of inflammatory arthritis. Recent studies have demonstrated that PAI can map 2D and 3D morphology of the cartilage, synovium, vascularity, and bone tissue in human peripheral joints. Initial trials with patients affected by inflammatory arthritis have also suggested that PAI can detect the hemodynamic properties in articular tissues as well as their changes due to active inflammation. This review focuses on the recent progress in technical development of PAI for human musculoskeletal imaging and inflammation detection. PAI can provide non-invasive and non-ionizing serial measurements for monitoring of therapeutic interventions with the potential for higher sensitivity than existing imaging modalities such as ultrasound. However, further investigation is needed to validate the value of PAI in rheumatology clinical settings.

1. Introduction

Joint disorders caused by disease and injury are among the leading cause of activity impairment, work disability, reduced quality of life, and high health-care costs. Among joint diseases, arthritis occurs in 23% of the adult population (approximately 54 million people) in the United States [1–3] and has been the most common cause of disability for the past 15 years [4]. The major clinical manifestations of rheumatoid arthritis (RA) and osteoarthritis, which are the representative arthritis diseases, are abnormal and damaged cartilage, synovial, and bone tissues, resulting in severe mobility impairment of joints. Currently, the best established method of assessing joint damage in RA and osteoarthritis has been medical imaging [5], such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US) imaging [6,7]. Imaging studies of the joint are helpful in preclinical applications and clinical diagnosis with the choice of imaging modality depending on the clinical manifestations, diagnostic considerations, and the capabilities of specific imaging modalities. Advanced functional imaging for early diagnosis and highly sensitive assessment of the treatment outcome are invaluable in clinical applications.

Inflammatory arthritis, such as RA, are associated with proliferation of synovial tissue and destruction of articular cartilage. Synovial angiogenesis is an important early symptom in the development and perpetuation of inflammatory arthritis [8,9]. Angiogenesis from a combination of hypoxia and high metabolic demand increases the number of synovial vessels [10], which drives synovial infiltration and hyperplasia. The presence of hyper vascularized synovial tissue is directly associated with disease activity. MRI and US are the established advanced imaging modalities which help with the diagnosis of arthritis by providing visualization of joint vascularity, synovitis and joint erosions. MRI, because of supreme image contrast, is great in assessing soft tissue changes related inflammation in and around the joints, cartilage damage, and bone marrow edema underlying active erosion. However, use of MRI is limited by its high cost, which is especially a concern for frequent monitoring studies. In addition, MRI may not work for patients with implanted devices. US imaging offers dynamic assessment, high resolution for anatomical imaging, and high sensitivity in identifying blood flow. It is also easily available and affordable, hence, widely

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accepted in clinical evaluation of inflammatory arthritis [11,12]. However, since it relies on measuring the speed of the blood flow relative to the probe, Doppler US is intrinsically more sensitive to the faster blood flow in relatively large vessels, while angiographic micro vessels with slow flow speeds, which are more relevant to inflammation, are often missed. Moreover, US imaging is not available for evaluating hypoxia, another important physiological biomarker of inflammatory arthritis [13].

Photoacoustic imaging (PAI) has evolved as a non-ionizing, non-invasive, powerful and low cost imaging modality with the unique capability of presenting high sensitivity optical contrast in deep biological tissue with excellent detail [14–17]. This emerging optical imaging technology, which has temporal and spatial resolution comparable to US imaging, has been developed and trialed in various preclinical and clinical applications [18–23]. The optical absorption contrast in the visible to near-infrared (NIR) region presented by PAI is intrinsically sensitive to the contents of oxygenated and deoxygenated hemoglobin [24,25]. Therefore, PAI offers great potential in identifying and characterizing soft-tissue inflammation based on the detection of hemodynamic changes. For inflammatory arthritis, both hyper-vascularization and hypoxia, two physiological hallmarks reflecting the increased metabolic demand and relatively inadequate oxygen delivery of the inflammatory synovial tissue, can potentially be assessed by this functional imaging modality. In this paper, we review the studies and applications that have been focused on musculoskeletal imaging and inflammation detection. Earlier studies on animal models have demonstrated the feasibility of PAI in describing joint tissue structures, as well as morphological and functional changes in the joints affected by chronic or acute inflammation [26,27]. Other former studies have focused on the development of PAI enhanced by various optical contrast agents toward the goal of molecular level imaging of arthritis [28,29]. Although the results from these studies on animal models are encouraging, the research on human subjects is crucial to understand the potential values and limitations of this new technique for clinical applications. This review, therefore, focuses on the recent progress in technical development for imaging of human joints and the initial studies on patients affected by inflammatory arthritis.

2. Imaging of joints using home-built system with single transducer(s)

In one of the earliest studies, Wang et al. developed a tomographic PAI system for cross-sectional imaging of human finger joints, and initially tested the performance of this system on human fingers harvested from an unembalmed cadaver [30]. The target imaging planes in the proximal interphalangeal (PIP) and the distal interphalangeal (DIP) joints of the digits were scanned circumferentially with an unfocused single transducer (XMS-310, Panametrics) working at a center frequency of 10 MHz. The circular scan of photoacoustic (PA) signal over 240 steps covered the entire 2π range of the digit plus the axial scan along the digit, as shown in Fig. 2(a). PA signals were scanned by two transducers (V320-SU, Olympus) with a diameter of 19 mm, focal length of 25.1 mm, and central frequency of 7.5 MHz, with the concept of virtual detector also being utilized. The 720-nm laser light delivered through four optical fiber bundles illuminated the surface of the finger with an estimated light fluence of 2.8 mJ/cm². Fig. 2(c) shows the PA images at three different cross-sections in a human DIP joint in vivo. With an estimated lateral and axial resolution of 70 μm and 240 μm, respectively, phalanx and tendons in the human finger joint can be recognized, which was confirmed through the comparison with the MRI image from the same joint, as shown in Fig. 2(d).

Aiming to visualize the vascularity across the interphalangeal joints, van Es et al. developed a home-built PAI system utilizing 32 transducers (Imasonic), as shown in Fig. 3(a) and (b) [33]. These transducers working at 6.25 MHz central frequency with bandwidth over 80% were driven by a 32-channel pulser/receiver (Lecoeur-Electronique) sampling at 80 MS/s. These 32 transducers covered 85° of a circle with a radius of curvature of 40 mm, enabling in-plane resolution of 100 μm. Delivered by six optical fiber bundles, the average light fluence on the finger surface was 6.8 mJ/cm². To acquire a cross-sectional image, the transducers and optical fibers were fixed to the water tank which was rotated around the finger. Multiple slices along a healthy human finger were acquired by stepping the imager through various heights while the finger remains stationary in the water. PA images of eight cross-sections in the PIP and the DIP joints of the finger are shown in Fig. 3(c)–(j); while (c#), (e#), (g#), and (i#) are enlarged images showing more details in the areas marked by the dashed squares. These PA images at 805 nm laser wavelength show rich blood vessels with diameters between 100 μm and 1.5 mm. In Fig. 3(k) and (l), two B-scan US images along an axial section and a sagittal section, respectively, show the tissue structures in the finger, as well as the locations where the eight cross-sectional PA images were acquired. This study on a normal volunteer indicates the capability of PAI in mapping spatially distributed blood vessels in human fingers.

3. Imaging of normal joints using linear array probe

Although PAI of human finger joints using home-built systems based on single transducers has been validated successfully by several groups, a common problem is the limited imaging speed due to the need for a mechanical scan of the detector(s) around the target joint. Moreover, these home-built systems, despite providing satisfactory PA image quality, usually cannot enable concurrent US imaging. Clearly, realizing PAI function through a linear array driven by a commercial US unit would provide many advantages and could accelerate the clinical acceptance of this novel imaging modality. With the dual-modality arrangement, US and PA images of the same joint can be obtained simultaneously, using the same system and resulting in naturally coregistered images. Since US is an established tool for musculoskeletal imaging, images from US could be used to guide the PAI procedure and help to interpret PA images. More importantly, by using a linear array driven by a commercial grade medical US system, the development of PAI can be accelerated by taking advantage of the state-of-the-art US technologies, e.g., large number of parallel channels facilitating real-time image acquisition and display.

In a study by Xu et al., PA imaging was achieved on a commercial US unit (z.one, Zonare Inc.) and used for imaging of human finger joint in vivo [34]. Unlike most of the previous studies in which human fingers were imaged via cross sections, the imaging of finger joints in this study was performed along either the coronal middle planes or the sagittal middle planes. This is the common way followed by clinical US imaging of human peripheral joints for diagnosis of inflammatory arthritis. As
Fig. 1. (a) Schematic of a home-fabricated tomographic PAI system for imaging of human joints ex vivo. (b) A cross-sectional image along a PIP joint. (c) A cross-sectional image along a DIP joint. (d)-(e) Corresponding anatomical photographs from the same joints confirming the imaging results in (b) and (c), respectively. AP: aponeurosis, PH: phalanx, SK: skin, SU: subcutaneous tissue, TE: tendon, VP: volar plate. Adapted with permission from Ref. [30].

Fig. 2. (a) Schematic of a PAI system for joint imaging utilizing virtual detector concept in image reconstruction and the cylindrical scanning in data collection. (b) Photograph showing the PAI-joint interface for DIP joint imaging. (c) Cross-sectional PA images along three slices in a DIP joint of a female middle finger. (d) Comparison between the PA image and the corresponding MRI image. Adapted with permission from Ref. [32].

Fig. 3. (a) Schematic of a home-built PAI setup involving 32 transducers and 6 optical fibers. (b) Photograph of the system. (c)-(j) PA cross-sectional images along different slices in a healthy index finger of a volunteer. The images are taken at the positions shown in the longitudinal US image (l) and are concentrated at the PIP joint and the DIP joint. (c#), (e#), (g#), and (i#) Enlarged images from the boxes in (c), (e), (g), and (i), respectively. (k) Cross-sectional and (l) longitudinal US images of the finger. Adapted with permission from Ref. [33].
shown in Fig. 4, the PA signals from the illuminated joint were acquired using a linear array (L10-5, Zonare Inc.) with 128 elements, working in the frequency range of 5–10 MHz. The laser at 740-nm wavelength was coupled into a bundle of optical fibers and delivered to the human finger with an estimated light fluence on the skin surface of 4 mJ/cm². Both PA and US images of normal PIP joints of volunteers were scanned and compared, as seen in some example results shown in Fig. 4(d)–(g). Based on different contrast, the PA and US images from the same joints showed similar structures, as both could delineate the contours of the tendons and bones with comparable spatial resolution.

Although the results from this initial work involving a linear array driven by a clinical US unit are encouraging, the capability of this commercial grade US unit was not fully utilized in the imaging experiment due to limited access to the functions of the US unit. First, the PA signals were acquired at a high speed using the linear array, the PA image reconstruction and display were completed offline on a standalone PC connected to the US unit. Second, to achieve sufficient signal-to-noise ratio (SNR) for PA, PA signals from the target joints had to be averaged over 90 laser pulses, further reduced the imaging speed.

In another study performed by the same research group [35], real-time PA and US dual modality imaging of human fingers was achieved using a linear array probe (CL15-7, ATL) driven by a research US platform (V1, Verasonics). The array probe with 128 elements, 11.25 MHz center frequency, and 75% -6 dB bandwidth scanned the finger joints along the sagittal sections. Powered by a GPU card (Ge-Force GTX690 GPU card, 3072 CUDA cores, NVidia) in the controlling PC, the US platform was able to perform signal scanning, image reconstruction and display for both PA and US imaging all in a truly real-time manner. To facilitate accelerated parallel computation, the back-projection algorithm for PA image reconstruction was optimized, which not only reduced the computational cost but also made the program executable on the GPU card. This imaging system, with the PA and US functions fully integrated, was tested for its performance in imaging normal human finger joints in vivo, as the example results shown in Fig. 5. Using the same laser which delivered light fluence on the skin surface of 4 mJ/cm² at the wavelength of 720 nm, this system achieved an imaging frame rate of 10 Hz which was limited by the pulse repetition rate of the laser.

4. Imaging of joints affected by arthritis

As one of the earliest attempts for in vivo detection of arthritis in human finger joints by using PAI, Xiao et al. developed a system involving spherical scanning with eight 1-MHz transducers (Valpey Fisher) [36]. As shown in Fig. 6(a), the transducers were equally spaced along a 210° arc arm, and could be rotated around the target joint for either 2D or 3D imaging. Pulsed light at 805 nm wavelength with a repetition rate of 10 Hz and a pulse width of < 10 ns was guided via an optical fiber, and illuminates the target joint with light fluence on the skin surface around 10 mJ/cm². In the initial trial, 6 subjects including two osteoarthritis (OA) patients and 4 healthy controls were enrolled. All participants were white females with mean age of 61 (ranging from 45 to 71). The left second DIP joint from each subject was imaged and clinically examined by a rheumatologist prior to the experimental scanning. Fig. 6(b)–(g) presents the 2D images along the coronal sections of the DIP joints for the 6 subjects examined. In each image, the bones with highest absorption could be delineated from the adjacent tissues. The joint space could also be identified (marked by the arrow). It was noticed in these images that, compared with the healthy joints, the OA joints had an elevated absorption coefficient in the joint cavities and narrowed joint space. The average absorption coefficient of cartilage (red) and fluid (blue) from the OA joints, as quantified from the PA images, were also compared to those from the normal joint, as presented in Fig. 6(h). This initial trial on OA patients, although involving only single laser wavelength and limited number of human subjects, led to some encouraging findings.

Using the system shown in Fig. 3, van Es et al. also performed an initial study on a 42-year old female patient affected by early rheumatoid arthritis [37]. This home-built system equipped with 32 transducers distributed along an arc and driven by 32-independent channels as well as 6 optical fiber bundles for light delivery was designed specifically for cross-sectional imaging of human finger joint in vivo. The patient had an inflamed right third PIP joint with signs of synovitis on Color-Doppler US. Fig. 7 shows the PA image from the inflamed PIP joint. Laser light at wavelength of 800 nm illuminated the finger with light fluence less than 5.6 mJ/cm². To obtain the result in Fig. 7, twelve views around the finger were taken with 20 averages per view. The acquisition of each 2D PA cross-sectional image required 1 min. In the PA image, a collection of small blood vessels could be distinguished at the dorsal side. This region, marked with a circle, was situated 4–6 mm distance from the surface and lies between the skin and bone, and was believed to be at the location of the synovial membrane dorsal to the joint space. This group of small thread shaped and point shaped blood vessels were thought to be associated with arthritis; however, this was not validated in this initial study on the arthritis patient.

Based the imaging system described in Fig. 5, Jo et al. has recently performed an initial clinical trial on patients affected by inflammatory arthritis [38]. The dual modality system allowed simultaneous 2D PA and US imaging of human finger joints. Two functional biomarkers including hyperemia (increased blood content) and hypoxia (decreased blood oxygen saturation) in joint tissues were explored as measurements to differentiate arthritic and normal joints.

By performing PAI at a single wavelength (S800 nm), the spatially distributed hemoglobin content reflecting the hyperemia in synovial
tissue in the metacarpophalangeal (MCP) joints of 16 patients were imaged and compared to the results from 16 healthy controls, with example results shown in Fig. 8. For each joint, the PA image in pseudo-color was super-imposed on the US image scanned using the same system. Taking advantage of the excellent sensitivity of PAI to blood hyperemia and the superior performance of US in delineating joint structures, hyperemia and its relative position in the joint can be visualized. In the PA images from joints affected by arthritis, strong signals in the areas next to the phalanges were apparent alongside the strong expected signals in the skin and phalanges. These signals were expected from hyperemia, and were confirmed by the Doppler US images from the same joints acquired using a commercial US unit (Z.ONE PRO, ZONARE). The hyperemia detected by PAI were further quantified, and student t-tests were conducted to validate whether PA measurements of hyperemia could differentiate the arthritic joints from the normal ones. The statistical analyses demonstrated significant differences between the arthritic joints and the normal joints.

In addition, by conducting PAI of each joint using two laser wavelengths (576 nm and 584 nm), decreased hemoglobin oxygenation (i.e., hypoxia) in synovium as another physiological biomarker of synovitis was assessed. Marked differences in blood oxygen saturation levels between the arthritic and the normal joints were detected. The result from this initial trial on human subjects is encouraging, suggesting that PAI, as a complement to musculoskeletal US, may enable the assessment of additional physiology biomarkers of inflammatory arthritis in vivo.

5. Conclusion and discussion

Although inflammatory arthritis is a prevalent, and often disabling disorder, development of effective therapy is hindered by the lack of objective outcome measures. While patient-reported quality of life measures and markers of inflammation are still used in diagnosis and treatment decisions, there is a significant need for robust joint imaging technology. Early initiation and timely escalation of anti-inflammatory therapies prevent disease progression, limit mobility, and preserve function and maintain quality of life. This targeted approach requires diagnostic technologies sensitive enough to detect pathological and functional change in response to treatment. Specifically, the imaging should enable early detection and accurate grading of subtle inflammation in intra-articular and juxta-articular soft tissues at the early stage of arthritis, well before irreversible bone destruction and remodeling occur; the imaging should also help with early identification of non-responders, so that treatment modification can be implemented earlier, minimizing unnecessary exposure to the potent side effects of drugs and reducing the cost by limiting ineffective treatment. Novel soft-tissue imaging technologies, such as PAI, which feature sensitivity comparable to MRI [39–41] but with significantly reduced costs and

Fig. 5. (a) Schematic of PA and US dual modality real-time imaging system for human peripheral joints built on a research US platform and a linear array probe. (b)–(e) PA and US imaging of a human proximal interphalangeal joint. (b) PA image using traditional back-projection method. (c) PA image using optimized back-projection method. (d) PA image after envelop detection of the image in (c). (e) Grey-scale US image. TE: tendon, JO: joint, PE: periosteum, BO: bone, and IN: inner structure of tendon. Adapted with permission from Ref. [35].

Fig. 6. (a) Photograph of a PAI system applied to the imaging of finger joints from normal volunteers and OA patients. (b)–(e) Recovered absorption coefficient images for four normal joints. (f)–(g) Recovered absorption coefficient images for two OA joints. (h) Average absorption coefficient of cartilage (red) and fluid (blue) for the healthy (H1-H4) and the OA (OA1-OA2) joints. Adapted with permission from Ref. [36].
more practical point of care applications are strongly desirable for efficient clinical management of arthritis.

Recent preliminary trials of PAI on human subjects, including those affected by inflammatory arthritis, have presented some encouraging results, suggesting that the diagnostic information from the emerging PAI technology could be similar or better when compared to the current imaging technologies, such as MRI and US, that are widely used in the clinical management of inflammatory arthritis and other musculoskeletal disorders. Besides its non-invasive and non-ionizing features, the advantages of PAI in inflammatory arthritis includes excellent soft tissue contrast and intrinsically high sensitivity to characterize both blood volume and blood oxygen saturation. PAI, either stand-alone or combined with the state-of-the-art US imaging techniques, could provide clinicians with a powerful and easy-to-use tool for screening, diagnosis, and treatment monitoring of arthritis. Both the applications of technology and the clinical trials of PAI can largely benefit from combining this technology to the clinically approved advanced diagnostic US imaging modality, which is currently the gold standard equivalent in clinical diagnosis. By combining PA to US, a set of important and unique functional information, such as hypoxia and increased blood volume/hemoglobin (even in the absence of any appreciable flow), can be added to pathological information already present, such as synovial thickening, erosions and subtle increase in neovascularity. Combining the identification of underlying pathological findings with associated functional changes in a single scan will facilitate more definitive early diagnosis with comprehensive disease assessment than by using conventional musculoskeletal US alone. Recent studies of PAI of human joints have been focused on the small joints of human fingers. Besides the fact that these joints are smaller in size and, therefore, can be scanned in their entirety with the high-frequency US probes, these peripheral joints of human hands and feet are usually among the earliest to be affected by some inflammatory arthritis and are widely accepted to be best markers of overall joint damage [42]. The imaging depth of PAI, however, should be sufficient for the study of larger human joints, such as knee, ankle, and wrist joints, especially when working in the optical spectral window of 700–950 nm. To explore the feasibility, future trials should involve these larger joints that can be scanned by US imaging currently.

Given the lack of bedside availability and high cost of MRI, there is a clinical need for a reliable point-of-care clinical tool to assess disease activity and response to therapy in patients with inflammatory arthritis. This requires the documented outcome measures to be robust, precise, practical, reliably reproducible, and sensitive to early inflammatory change. PAI has a great potential to be this clinical tool. To promote the acceptance of PAI in clinical settings, future development should focus on collecting convincing clinical data documenting the accuracy of core outcomes (e.g., assessment of blood volume, hypoxia) of PAI in management of arthritis. Another hypothesis is that PA in combination with
US should be able to confidently detect the treatment response earlier (when compared to US alone) by quantifying both functional and pathological hemodynamic changes in soft articular tissues. To examine these hypotheses, blind tests on large numbers of patients, both pre- and post-treatment, to objectively compare the performance of PAI and US with US alone could be conducted using clinical scores of disease activity and/or MRI findings as the gold standard. PAI image quality and resolution could be improved by using detectors working at higher frequencies. The value of volumetric information for diagnosis and treatment assessment of arthritis is very promising and should also be explored by comparing 3D and 2D PAI findings. We also expect that the sensitivity of PAI based on the endogenous tissue contrast may be comparable to contrast-enhanced MRI, so that PAI could be developed as a label-free, low-cost, surrogate of MRI for arthritis imaging. To the best of our knowledge, there has been no studies comparing the diagnostic accuracy between PAI and MRI modalities. A future study comparing the two modalities might be critical for establishing PAI as a standard diagnostic tool for arthritis.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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