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Is There a Role of Photoacoustic Imaging in Sports Medicine: Evidence Today

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ABSTRACT

Diagnostic imaging in sports medicine includes traditional imaging modalities such as x-ray, computed tomography (CT), and magnetic resonance imaging (MRI). Despite having certain advantages, these imaging techniques often have lower sensitivity and specificity, making it difficult to detect soft tissue injuries and early-stage cartilage damage. They also lack the ability to assess the biomechanical properties and functional states of tissues. Photoacoustic imaging (PAI) offers a powerful, non-ionizing, and cost-effective alternative to traditional imaging techniques in the diagnosis and therapeutic monitoring of sports injuries. PAI combines the benefits of optical imaging and ultrasound to provide high-resolution images of deep tissues, including tendons and ligaments. This technology uses pulsed lasers to irradiate tissues, causing thermal expansion and generating ultrasound waves, which are then captured and converted into images. PAI is particularly adept at depicting blood vessels and soft tissues with high resolution and sensitivity to the optical absorption contrasts of oxy- and deoxyhemoglobin. It can assess tissue oxygenation and metabolic activities, which are crucial for evaluating the healing process in sports injuries. Herein, the role of PAI in sports medicine is assessed and particularly its advantages over traditional imaging methods such as x-rays, CT scans, and MRI scans in diagnosing musculoskeletal injuries.

1 | Introduction

The human musculoskeletal system is composed of a multitude of structures, including bones, cartilage, ligaments, tendons, menisci, and muscles [1, 2]. These structures work in concert to support body movement and maintain postural stability. However, they are susceptible to injury during physical activities. Musculoskeletal health is crucial for people's mobility and ability to live independently [3]. The discipline of sports medicine is comprehensive in its scope, encompassing the prevention, diagnosis, treatment, and rehabilitation of sports-and exercise-related injuries. A significant objective of sports medicine is to

Abbreviations: ACL, anterior cruciate ligament; ADC, apparent diffusion coefficients; DMD, duchenne muscular dystrophy; DMM, destabilization of medial meniscus; FLS, fibroblast-like synoviocytes; GAG, glycosaminoglycans; HA, hyaluronic acid; ICRS, International Cartilage Repair Society; IO MP, iron oxide microparticles; LIPA, laser induced photoacoustic; MSOT, multispectral optoacoustic tomography; OA, Osteoarthritis; PAE, photoacoustic elastography; PAI, photoacoustic imaging; PLGA, polylactic acid-hydroxyacetic acid copolymers; PLL-MNPs, poly-l-lysine and melanin; RA, rheumatoid arthritis; SO2, synovial oxygen saturation; TSC, tendon stem cells.

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utilize advanced medical imaging technologies to accurately diagnose early injuries to musculoskeletal tissues, thereby guiding subsequent treatment and rehabilitation plans. Currently, x-rays, computed tomography (CT), and magnetic resonance imaging (MRI) are the most commonly employed imaging techniques in clinical practice.

x-ray imaging, one of the earliest medical imaging techniques, is primarily utilized for the examination of fractures and joint abnormalities [4–6]. However, it lacks the capacity to diagnose soft tissue injuries, such as ligament tears or muscle damage. Computed tomography (CT) scans provide more detailed images than x-rays and can more clearly demonstrate bone injuries. Nevertheless, they have limitations in soft tissue imaging and expose patients to higher doses of radiation. MRI is the preferred method for identifying soft tissue injuries (such as muscle, ligament and cartilage damage), offering high-resolution images, but at a higher cost and with longer scanning times [7, 8]. Although these imaging techniques play a crucial role in diagnosing musculoskeletal injuries, they each have their own limitations. For example, early cartilage damage and certain types of meniscal injuries may be difficult to detect with sufficient sensitivity and specificity using the above imaging techniques. Furthermore, these techniques frequently fail to fully display the biomechanical properties and functional states of tissues, which are essential for the creation of personalized treatment and rehabilitation plans. In response to these challenges, the field of sports medicine is exploring more advanced imaging techniques, such as photoacoustic imaging (PAI), functional MRI (fMRI), diffusion tensor imaging (DTI), and ultrasound elastography [9, 10].

PAI is an emerging medical imaging technique that has evolved into a non-ionizing, non-invasive, powerful, and cost-effective imaging method with a unique ability to provide high sensitivity optical contrast in deep biological tissues, offering exceptional detail [11–14]. The principle of this technology involves using pulsed lasers to irradiate tissues, causing a slight temperature rise, which leads to thermal expansion and the generation of ultrasound waves. These ultrasound waves are then received by detectors and converted into images(Figure S1) [15–18].

The aim of this narrative review is to examine the role of PAI in sports medicine and particularly to assess its advantages over traditional imaging methods such as x-rays, computed tomography (CT) scans, and magnetic resonance imaging (MRI) scans in diagnosing musculoskeletal injuries.

2 | Method

For this review, we searched PubMed, Web of Science, and Google Scholar with a time range from inception until June 2024. The search strategy consisted of both Medical Subject Headings and text words including ("photoacoustic imaging" [Title/Abstract] OR "optoacoustic imaging" [Title/Abstract] OR "photoacoustic tomography" [Title/Abstract]) AND ("sports medicine" [Mesh] OR "bone" [Mesh] OR "cartilage" [synovium] OR "tendon" [Mesh] OR "muscle" [Mesh]), without limiting the publication date. The inclusion criteria for the literature are as follows: the study must involve PAI, photoacoustic tomography, or optoacoustic imaging technologies, and focus on musculoskeletal injuries related to bones, cartilage, tendons, ligaments, muscles, and synovium in sports medicine. The study population may include both preclinical (animal models) and clinical (human) applications, with research addressing sports-related injuries or disorders such as fracture healing, osteoarthritis, cartilage damage, tendon injuries, muscle ischemia, and rheumatoid arthritis. Additionally, the research should evaluate the effectiveness of PAI in diagnosing, monitoring, or providing functional information about musculoskeletal tissues, such as blood flow, oxygenation, and tissue microstructure, and should compare PAI with traditional imaging methods (e.g., MRI, CT, x-ray, or ultrasound) in sports medicine applications. Exclusion criteria include studies that do not involve PAI or photoacoustic tomography; those that do not focus on sports medicine or address diseases or injuries outside the scope of sports medicine (e.g., cancer and dermatological conditions), unless directly related to musculoskeletal health; abstracts, conference papers, or non-peer-reviewed articles that lack sufficient methodological detail regarding the application of PAI in sports medicine; and studies not published in English or those lacking accessible English translations of key content. The flowchart is shown in Figure S2. The studies included in this review are of high quality, with a comprehensive search conducted across PubMed, Web of Science, and Google Scholar, covering both preclinical and clinical research on PAI in sports medicine. The research adhered to strict inclusion criteria, emphasizing PAI's effectiveness in diagnosing and monitoring musculoskeletal injuries, and compared PAI with traditional imaging methods (MRI, CT, and ultrasound). The exclusion criteria ensured that only high-quality studies with sufficient methodological details and relevance to sports medicine were included, strengthening the reliability of the evidence.

2.1 | General Characteristics of PAI

PAI is a non-invasive, contrast-agent-free optical imaging technology that provides high-resolution images of blood vessels and soft tissues. Its temporal and spatial resolution is comparable to that of ultrasound imaging, and it has been developed and tested in various preclinical and clinical applications [19–23]. PAI's visible to near-infrared (NIR) optical absorption contrast, which is inherently sensitive to the content of oxy- and deoxyhemoglobin, shows broad application potential in the field of sports medicine. PAI can be used to diagnose diseases of the skeletal and joint systems, including fractures and other structural abnormalities. Due to its high contrast imaging capability for soft tissues, PAI is particularly suitable for detecting injuries to tissues such as cartilage, ligaments, tendons, menisci, and muscles. These soft tissues are often difficult to clearly display in traditional x-ray imaging, and while visible in CT and MRI, PAI offers a faster and more cost-effective alternative. Furthermore, PAI offers distinct advantages in vascular imaging, enabling the clear visualization of minute blood vessels and alterations in blood flow. This has significant importance in the assessment of vascular responses resulting from exercise and the recovery of blood flow following treatment.

The application of PAI in sports medicine encompasses the assessment of tissue oxygenation and metabolic activity. This is of particular importance in the monitoring of biological

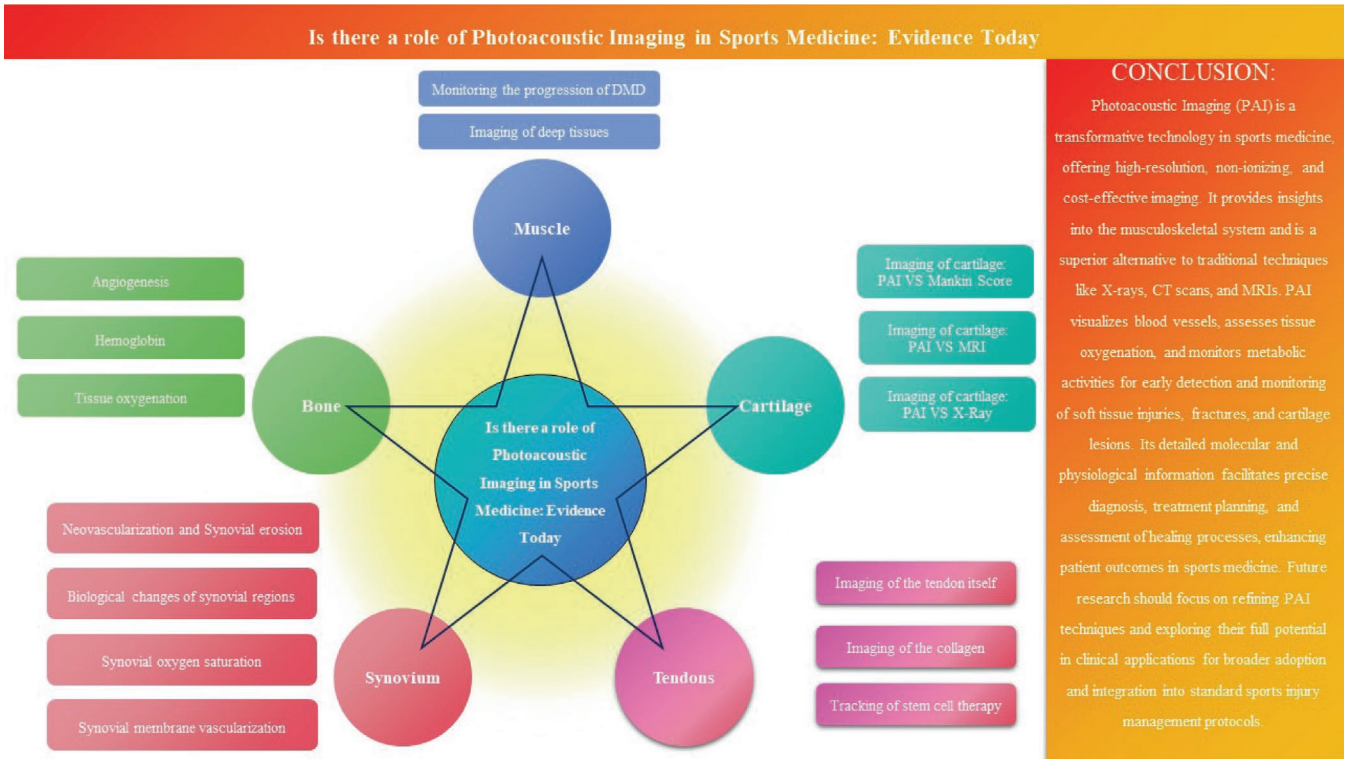

FIGURE 1 | Applications of photoacoustic technology in various tissues in sports medicine.

changes during the recovery process from sports injuries. For instance, the measurement of oxygenation levels in the injured area allows for the assessment of the healing progress of the tissue, thereby providing guidance for rehabilitation treatment.

In comparison to traditional imaging techniques, the advantage of PAI lies in its capacity to provide more comprehensive physiological and metabolic information, including blood oxygen saturation and blood flow dynamics. These are essential for comprehending the nature of sports injuries and monitoring the rehabilitation process. Additionally, the operation of PAI is relatively simple and low in cost, making it a promising tool for rapid diagnosis and tracking of treatment effects in the field of sports medicine. Although PAI is still in the research stage and not widely applied in clinical practice, its unique imaging advantages and potential for application make it a strong candidate for future diagnostics and treatment in sports medicine (Table S1).

2.2 | Photoacoustics in Bone and Fracture Healing

Photoacoustic technology has demonstrated potential for identifying molecular changes in bone tissue and visualizing tissue microstructure. PAI employs light to penetrate bone and then generates acoustic pressure that produces highly sensitive optical absorption contrast in deep biological tissue. PAI has unique advantages in areas such as bone cancer, joint pathology, spinal disorders, osteoporosis, and guidance for bone-related surgeries (Figure 1).

A fracture is defined as a break in the integrity and continuity of the bone. The primary cause of fractures is typically trauma resulting from external factors, such as falls, automobile accidents, or collisions during sports. In addition to injuries, other causes such as osteoporosis, tumors, or other diseases may render bones susceptible to weakness or vulnerability, thereby increasing the risk of fractures that are more severe. In certain instances, fractures may arise from stress injuries resulting from prolonged exposure to repetitive or excessive stress, a phenomenon commonly observed in high-intensity sports such as long-distance running and basketball [24, 25].

PAI plays a role in the detection of prognosis. Fracture healing is a complex but carefully planned process leading to the regeneration and functional recovery of bone [26]. Fracture nonunion is a serious complication arising from fractures, and it is a persistent clinical problem. As a serious fracture complication, nonunion has a significant impact on the quality of life and economic status of patients and may be associated with severe functional and psychological impairment [27]. Although delayed unions can still heal without surgical intervention, a nonunion does not, and often causes prolonged pain and disability with negative effects on mental and physical health and general quality of life [28]. Recent studies have shown that the average risk of bone nonunion per fracture is 1.9%, with the risk of nonunion being as high as 9% for specific fracture types (tibia and clavicle fractures) and in elderly patients [29].

To investigate the role of cilostazol in promoting angiogenesis and bone regeneration in the context of fracture non-union in a mouse model, Menger et al. established a fracture non-union model by creating segmental defects in the mouse femur and using a pin-clip fixation technique. This was studied using PAI, radiography, and ultrasound imaging. PAI directly reflects angiogenesis and tissue oxygenation levels by measuring total

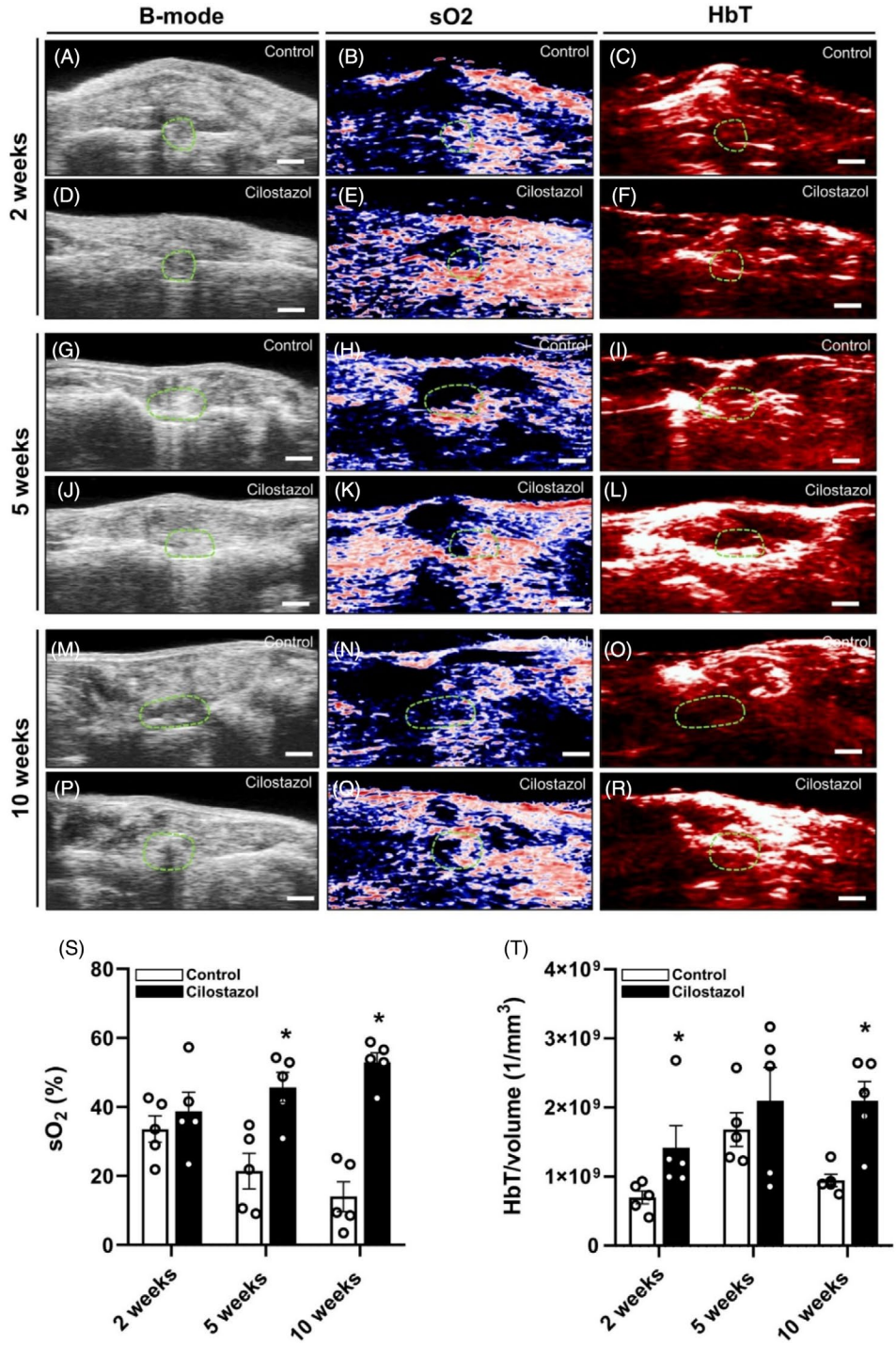

FIGURE 2 | At 2 weeks post-surgery, photoacoustic analysis did not reveal any difference in the oxygen saturation (sO2) within the callus tissue between the control group and animals treated with cilostazol. In contrast, significantly higher sO2 levels within the callus were detected in the cilostazol-treated mice at 5 and 10 weeks post-surgery compared to the control group. Additionally, we observed a significant increase in the total hemoglobin (HbT)/volume quantity at 2 and 10 weeks post-surgery. Notably, at 5 weeks, the HbT/volume was only slightly increased compared to the respective control groups. In the control group animals, ultrasound imaging showed a persistent osteotomy gap throughout the observation period, whereas in the cilostazol-treated mice at 10 weeks post-surgery, some callus formation could be seen [30].

hemoglobin content and oxygen saturation within the tumor tissue at 2, 5, and 10 weeks after surgery. These metrics are critical to understanding how cilostazol promotes blood vessel formation and bone regeneration. The research team's study evaluated the efficacy of Cilostazol in promoting angiogenesis and improving tissue oxygenation by comparing the differences in PAI metrics between the Cilostazol-treated group and the control group. This approach supports the potential use of Cilostazol in the treatment of fractures (Figure 2) [30]. In brief, Menger et al. used PAI to study the role of cilostazol in promoting angiogenesis and bone regeneration in a fracture non-union mouse model, demonstrating its potential for fracture treatment.

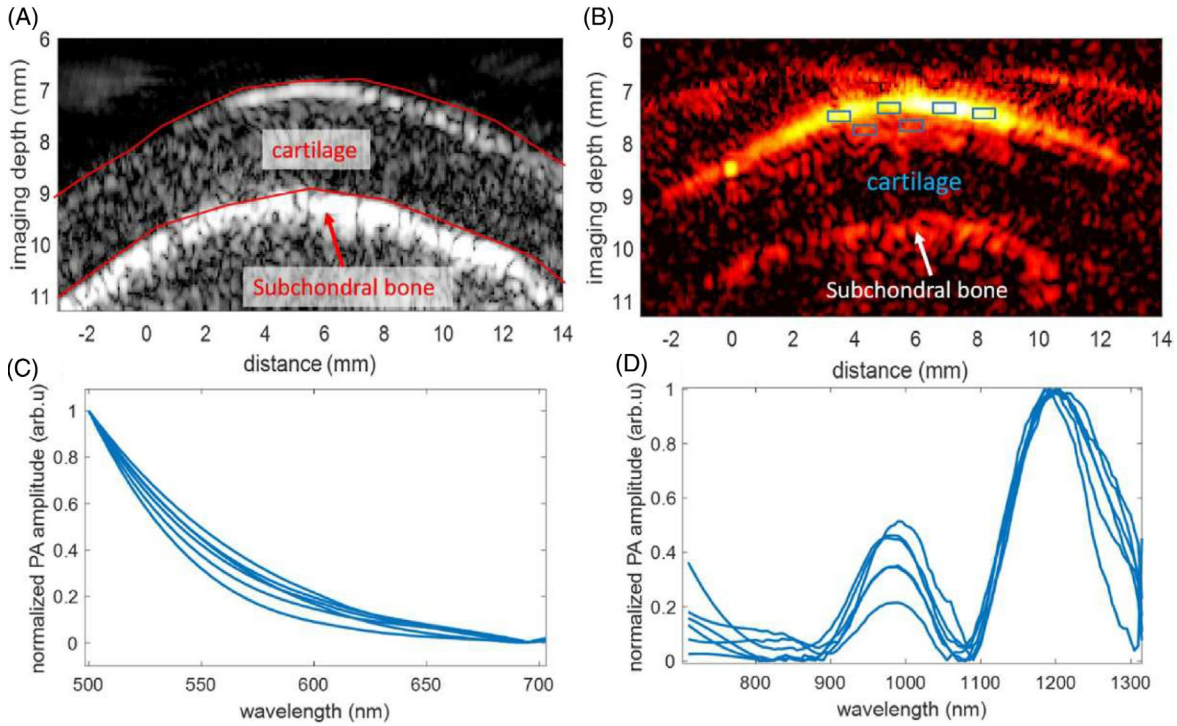

FIGURE 3 | Examples of ultrasound and photoacoustic imaging of human cartilage samples and their corresponding photoacoustic spectra. B-mode ultrasound images of the cartilage samples and the corresponding photoacoustic imaging [35].

Similarly, Histing et al. evaluated the effects of sildenafil on bone regeneration and angiogenesis in a mouse model of atrophic nonunion fractures using PAI and the Vevo LAZR system. The team conducted ultrasound and PAI in control and sildenafil-treated mice at 2, 5, and 10 weeks after surgery. This was done using pulsed lasers at 750 nm and 850 nm wavelengths to induce thermoelastic expansion, and the acoustic signals of hemoglobin and oxyhemoglobin were recorded. The results demonstrated that denafide significantly enhanced bone regeneration by augmenting angiogenesis and oxygenation to the bone scab tissue [31]. In short, Histing et al. used PAI to show that sildenafil enhances bone regeneration and angiogenesis in a mouse model of atrophic nonunion fractures.

In conclusion, PAI offers significant value in sports medicine, particularly for assessing bone fractures. It provides detailed insights into molecular changes, angiogenesis, and tissue oxygenation, which are essential for understanding fracture healing. Compared to traditional methods like x-ray, MRI, and CT, PAI offers unique advantages, including its noninvasive nature, sensitivity to tissue contrast, and ability to monitor vascular formation and oxygenation. This makes it especially useful for evaluating bone recovery and detecting complications like nonunion. With advancements in imaging depth and resolution, PAI holds great potential for improving fracture diagnosis and treatment in sports medicine.

2.3 | Photoacoustics and Cartilage

Cartilage is a tough and flexible tissue that serves as a cushioning material for the body's joint surfaces, reducing friction between bones and protecting them from damage. It is composed of specialized cell types, chondrocytes, which secrete an abundance of type II collagen and proteoglycans to form a unique extracellular matrix [32]. Cartilage lacks the vascular supply of bone, resulting in a slower repair process. This poses a significant challenge in the treatment of sports injuries and joint disease [33]. The limitations of existing imaging modalities for cartilage applications are primarily due to resolution and contrast limitations in soft tissue. For example, MRI provides images of soft tissue but with limited resolution, and CT scans do not visualize cartilage structures well. In contrast, PAI, which is non-invasive, provides high-resolution, high-contrast images that more clearly reveal the microstructure and biochemical state of cartilage. This imaging technique offers new perspectives and tools for early diagnosis and treatment of cartilage lesions.

Lopata et al. [34] sought to investigate the potential of spectral PAI (sPA imaging) technology in the detection and assessment of cartilage damage, with a particular focus on its suitability for early diagnosis and monitoring of osteoarthritis (OA). Human cartilage samples were imaged using sPA imaging over a broad spectral range from 500 to 1300 nm. The spectral characteristics of the photoacoustic signals were analyzed and compared with histological findings and Mankin Score (the gold standard for cartilage damage assessment) to assess the extent of cartilage damage. This study demonstrated that sPA was able to identify photoacoustic spectral changes in collagen associated with different degrees of cartilage damage (Figure 3). To put it simply, Lopata et al. used spectral photoacoustic imaging (sPA) to assess cartilage damage and monitor osteoarthritis, showing its potential for early diagnosis.

Itoi et al. [35] attempted to use a PAI system to simultaneously evaluate the articular cartilage and subchondral bone of an

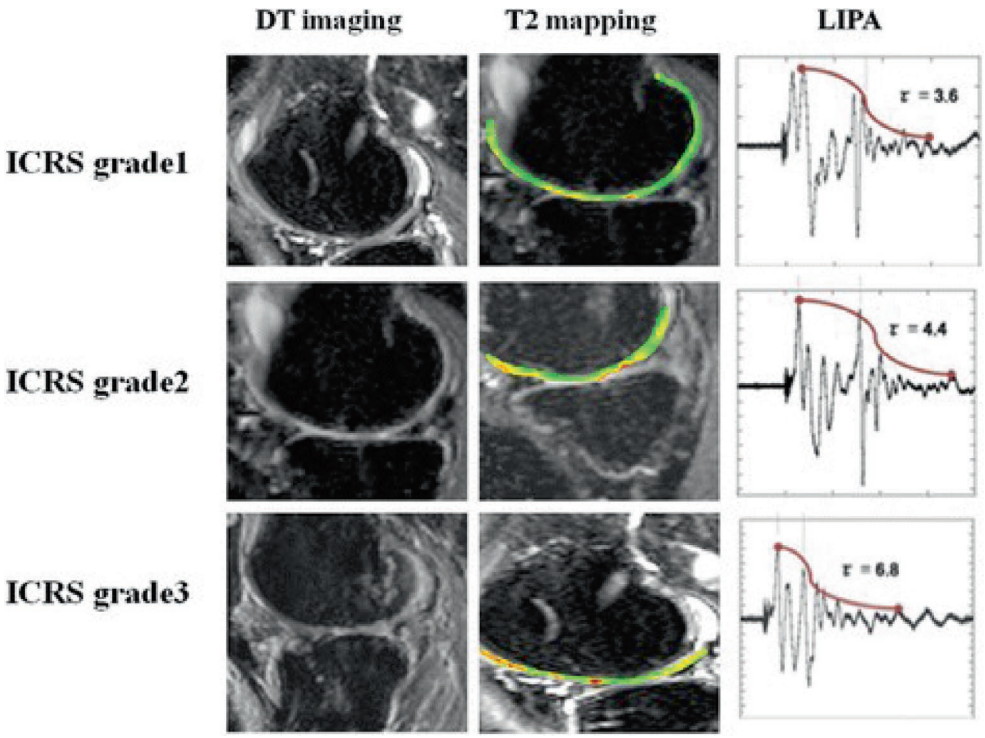

FIGURE 4 | Diffusion tensor imaging, T2 mapping, and Laser-Induced Photoacoustic Imaging (LIPA) for early, moderate, and severe cartilage damage. DT represents Diffusion Tensor, and LIPA stands for Laser-Induced Photoacoustic (Imaging) [36].

immobilized rat knee joint. The team scanned the entire proximal third of the rat's tibia with the PAI system, and the results showed that the photoacoustic signals from the articular cartilage and subchondral bone increased with immobilization time, with a significant difference compared to the control group. This indicates that the PAI system can effectively evaluate both articular cartilage and subchondral bone. Simply put, Itoi et al. used PAI to evaluate articular cartilage and subchondral bone in a rat knee joint, demonstrating its effectiveness in assessing both tissues.

In a study conducted by Mochida and colleagues, the validity of cartilage damage in the knee was assessed by comparing the use of laser-induced photoacoustic measurements (LIPA) with 3.0 Tesla magnetic resonance imaging (MRI) techniques, including T2 mapping and diffusion tensor imaging (DT imaging) [36]. The study used the International Cartilage Repair Society (ICRS) classification to categorize 29 osteochondral samples removed during surgery. In addition, LIPA measurements were performed at sites corresponding to areas of cartilage damage, and preoperative MRI scans were performed to assess T2 values and apparent diffusion coefficients (ADCs). The study showed that while LIPA may not be as effective as some MRI techniques (e.g., ADC measurements) in differentiating early cartilage damage, it demonstrated significant differences in the assessment of moderate to severe cartilage damage, suggesting that LIPA has potential for assessing the viscoelastic properties of cartilage. This study demonstrates that the LIPA technique provides a more comprehensive assessment of cartilage damage when used in conjunction with MRI techniques to evaluate cartilage damage in the knee, particularly its viscoelastic properties (Figure 4). To summarize briefly, Mochida et al. showed that laser-induced photoacoustic measurements (LIPA) can complement MRI in assessing moderate to severe cartilage damage and evaluating its viscoelastic properties.

Osteoarthritis is among the most common orthopedic disorders that not only affect a large population, but also are associated with large healthcare costs [37]. OA results from long-term degeneration that is often symptomatic in the later stages of the disease [38]. Patients present with pain, crepitus on moving the joint, stiffness, and a limited range of motion [39].

Chen et al. [40] improved the sensitivity of PAI to cartilage changes by developing cationic nanoprobes targeting anionic glycosaminoglycans (GAGs) in articular cartilage. This provides a novel approach for early detection and monitoring of OA. The research team synthesized PLL-MNPs by electrostatic attraction between polylysine and melanin. They then conducted in vitro and in vivo experiments. In vitro experiments were conducted by incubating PLL-MNPs with cartilage dissection specimens of different GAG concentrations to investigate the relationship between GAG content and PA signal intensity. An osteoarthritis model (DMM mouse model) was used for in vivo studies to monitor OA progression by injecting PLL-MNPs and performing PAI over time. A comparison of PAI with radiographic imaging validated the findings of PAI and demonstrated that PAI was able to detect cartilage changes at an earlier stage than conventional radiographic methods. Histological examination confirmed a decrease in GAG content, which correlated well with PAI results, further validating the efficacy of PLL-MNP-enhanced PAI in monitoring OA progression. The results of this study indicate that the use of cationic nanoprobe-enhanced PAI to detect changes in GAG content provides a sensitive and consistent method for visualizing OA progression. This approach

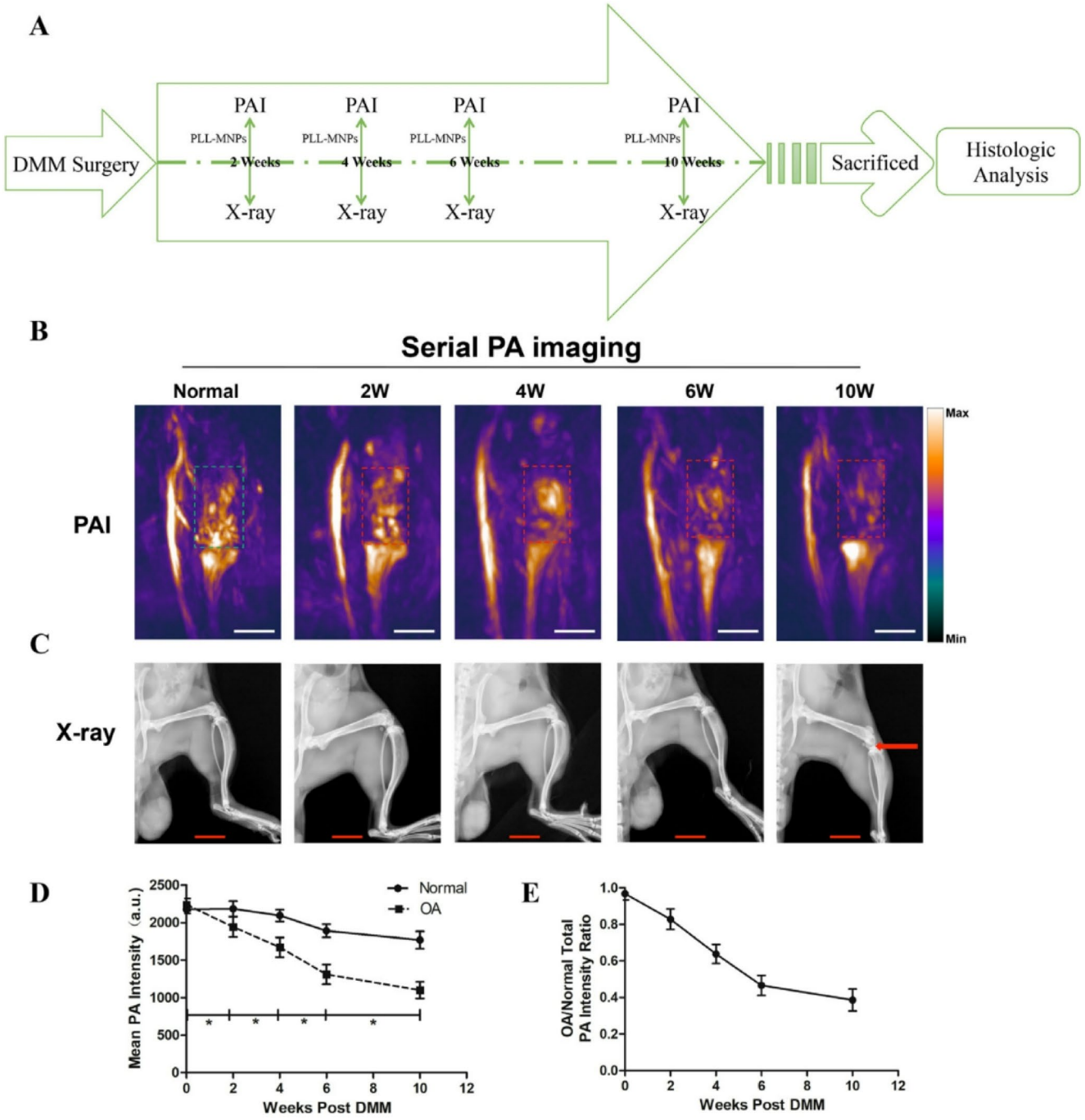

FIGURE 5 | (A) DMM surgery was performed on mice to model osteoarthritis, utilizing photoacoustic imaging to live-detect the development of osteoarthritis (OA) in comparison with x-rays, and conducting Histologic Analysis. (B) Representative PAI of an OA knee joint after intra-articular injection of PLL-MNPs. The scale is 10 mm. (C) x-rays of the OA knee joint show no significant changes in joint morphology at 2 and 4 weeks. Red arrows indicate noticeable irregularities in the joint surface, narrowing of the joint space, or formation of osteophytes, indicating cartilage damage at 10 weeks. The scale is 10 mm. (D) Average photoacoustic intensity collected from the knee joint of each mouse, quantified from the collected PAI [40].

may significantly advance the diagnosis and treatment of OA by providing a more timely and accurate method for monitoring disease progression and assessing treatment efficacy. The ability to non-invasively visualize cartilage changes at the molecular level is an important advancement for personalized therapy in OA treatment (Figure 5). Briefly, Chen et al. developed cationic nanoprobe-enhanced PAI to detect early cartilage changes in osteoarthritis, offering a sensitive, non-invasive method for monitoring disease progression and treatment efficacy.

However, although meniscal injuries are one of the most common sports injuries of the knee joint, there is no literature reporting the application of PAI in the meniscus [41, 42]. The meniscus is primarily composed of fibrocartilage, which is made up of Type I collagen, while the articular cartilage is made of transparent cartilage, which is constituted by Type II collagen [43, 44]. Given the extensive use of PAI in bones, tendons, and muscles (tissues rich in Type I collagen), photoacoustic technology is highly suitable for the diagnosis of meniscal injuries(Table S2).

In summary, PAI holds significant application value in sports medicine, particularly for the early diagnosis and monitoring of cartilage damage, such as osteoarthritis (OA). Compared to traditional methods like MRI and CT, PAI provides high-resolution images that better reveal the microstructure and biochemical changes of cartilage. Its non-invasive nature allows for early detection, improving intervention and treatment outcomes. PAI can also assess both cartilage and subchondral bone, providing a comprehensive view of joint health. With the use of nanoprobes to enhance sensitivity, PAI shows great potential in monitoring OA progression and treatment efficacy. As the technology advances, PAI will play an increasingly important role in diagnosing and treating sports-related joint injuries.

2.4 | Photoacoustics and Synovium

The synovial tissue lines the inner cavity of the joint and has many functions, including the secretion of synovial fluid, shock absorption, nutritional support, modulation of the immune response, and promotion of tissue repair [45]. The synovial tissue maintains the volume and composition of the synovial fluid by secreting substances such as hyaluronic acid (HA) and lubricin, which provide nutrients and lubrication to the cartilage [46]. The synovial tissue consists of an inner layer (lining) and an outer layer (matrix). The lining is mainly composed of fibroblast-like synoviocytes (FLS) and CX3CR1+ macrophages, while the matrix is composed of fibroblasts, adipocytes, blood vessels, lymphocytes, and macrophages [47, 48].

Hu et al. [49] used dual-modality photoacoustic/ultrasound (PA/US) imaging to monitor neovascularization and synovial erosion in rheumatoid arthritis (RA) in their study. The team used PA/US imaging based on a subjective scoring system to assess synovial erosion and vessel visualization within the knee joint in real time and with high spatial resolution in various disease states. In addition, the system quantitatively monitored subcutaneous vascular physiology and morphology in the hind paws of mice by measuring the area of vascular proliferation and photoacoustic signal intensity and showed a positive correlation with disease grading. PA/US imaging is more sensitive than traditional subjective scoring of arthritis severity; that is, vascular signal and synovial erosion can be observed early in the arthritic process (Figure 6). In summary, Hu et al. used dual-modality photoacoustic/ultrasound imaging to monitor neovascularization and synovial erosion in rheumatoid arthritis, showing it is more sensitive than traditional scoring methods for early disease detection.

Chen et al. [50] used PAI to monitor the distribution of M@P-siRNAsT/I nanoparticles in a rat model. Using near-infrared spectroscopy, PAI was able to track the localization and aggregation of these nanoparticles in the joint region in real time. Notably, multispectral PA imaging could be used to evaluate the potential effect of M@P-siRNAsT/I as a therapeutic regimen for RA without any labeling. The changes in the photoacoustic signals reflected the biological changes in the synovial and cartilage regions before and after treatment. Briefly, Chen et al. used PAI to track M@P-siRNAsT/I nanoparticles in a rat model, demonstrating its potential for evaluating RA treatment effects without labeling.

Jiang et al. [51] used PAI to measure synovial oxygenation status in patients with rheumatoid arthritis (RA) and to investigate its correlation with disease activity. The team used PAI to measure synovial oxygen saturation (SO_2) at two wavelengths, 750 nm and 830 nm. These two wavelengths were chosen because they can provide critical information about the state of tissue oxygenation, which can help determine blood oxygen levels in the synovium. The study provides valuable insight into the use of PAI in the management of RA, particularly in the non-invasive monitoring of synovial oxygenation status and disease activity. This may help improve the diagnosis of RA, therapeutic decisions, and monitoring and evaluation of disease activity. In brief, Jiang et al. used PAI to measure synovial oxygenation in rheumatoid arthritis, providing valuable insights for non-invasive monitoring of disease activity and treatment decisions.

Wang et al. [52] devised a study to examine the capability of PAI in distinguishing between inflammatory arthritic joints and normal joints and gathered imaging results from 16 patients and 16 healthy controls. The single- and double-wavelength PAI on human subjects in this study demonstrated increased vasculature, intensified tissue metabolism, and consequently hypoxia in the arthritic finger joints. Notably, the single laser wavelength PAI showed higher sensitivity to the increased vascularity (i.e., hyperemia) in the arthritic finger joints. They concluded that PAI combined with US could potentially warrant the study of supplementary physiology biomarkers of inflammatory arthritis in vivo. In short, Wang et al. used PAI to distinguish inflammatory arthritic joints from normal ones, showing increased vascularity and hypoxia in arthritic joints, with potential for studying biomarkers of inflammatory arthritis.

Zhao et al. [53] performed a study that used a multimodal PA/US imaging system to obtain images of the joints of RA patients in order to judge the correlation of multimodal PA/US articular imaging scores and relative oxygen saturation values of lesions with varying disease activity measurements of RA. They found that PAI was potentially able to more accurately reflect the disease activity of the individual patients, which is especially useful for active lesions. In short, Zhao et al. used multimodal PA/US imaging to assess rheumatoid arthritis, finding that PAI more accurately reflects disease activity, especially in active lesions.

To enable imaging of synovial membrane vascularization in the synovial joints of the hands, the research team developed a photoacoustic (PA) imaging system based on a ring-array ultrasound transducer [54]. The system was validated by design simulations and phantom experiments, demonstrating its ability to image small objects with diameters of approximately 0.1–0.5 mm, and the half-maximum width of the system in the slice direction was within 2 mm, consistent with simulation results. In addition, when applied to healthy volunteers, the system successfully imaged vascular structures within the finger, including vessels approximately 0.26 mm in diameter and the locations of the distal and proximal interphalangeal joints. The development and validation of this system demonstrate the potential of PAI to visualize synovial vascularization, an early lesion feature of RA. By providing high-contrast, high-resolution images of the synovial

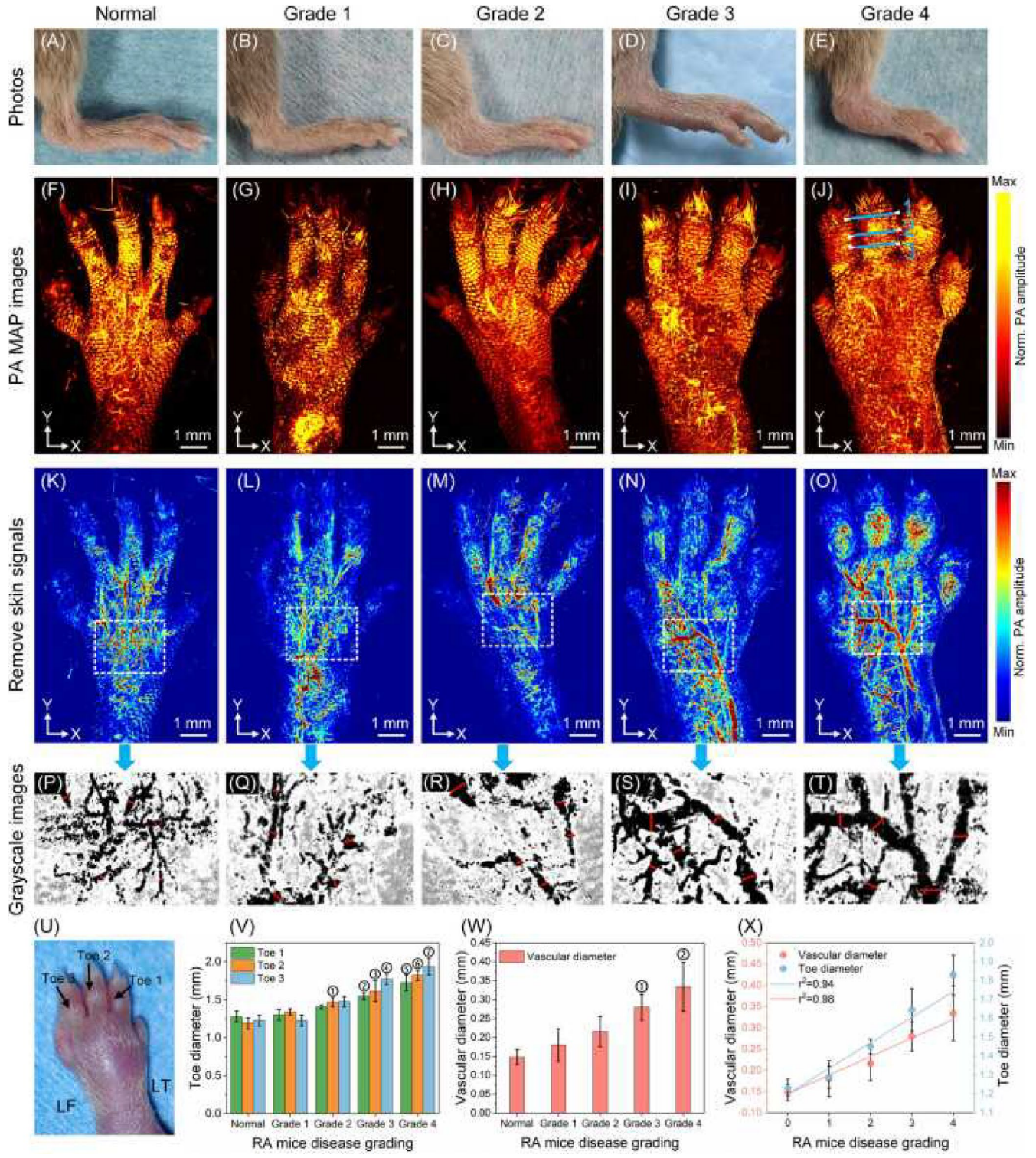

FIGURE 6 | Photoacoustic imaging (PAI) of the mouse hind paw was displayed. These images demonstrate the impact of different disease stages on the mouse hind paw, allowing analysis of the vascular diameter within the paw and the degree of swelling of the paw. (A)–(E) show macro photographs of normal DBA/1 mouse hind paws and those with different ratings (grades 1–4). (F)–(J) present maximum amplitude projection (MAP) images from photoacoustic imaging, showing the morphology of the mouse hind paw, such as the bone surface and superficial skin vessels. (K)–(O) after removing strong photoacoustic signals from the skin surface, display more vessels. (P)–(T) provide grayscale images of the vascular pathways and morphology in the mouse hind paw, with vascular morphology highlighted through image processing techniques [49].

membrane and surrounding tissues, it provides important information for early diagnosis and treatment of RA. In the future, the system is expected to be further developed for clinical applications, particularly for assessing synovial vascularization and monitoring disease activity. Briefly, The research team developed a PAI system that successfully visualizes synovial vascularization in hand joints, demonstrating potential for early rheumatoid arthritis diagnosis and monitoring.

To summarize, PAI plays a significant role in monitoring synovial tissue and joint diseases, such as rheumatoid arthritis (RA). Compared to traditional methods like x-ray and MRI, PAI provides high-resolution, high-contrast images that effectively detect early changes in synovial tissue and vasculature. It is capable of assessing tissue oxygenation and vascularity at different wavelengths, enhancing the monitoring of disease progression. The combination of PAI with ultrasound further improves diagnostic capabilities. As PAI technology advances, it is set to become an essential tool for early diagnosis, monitoring, and therapeutic decision-making in joint injuries and diseases in sports medicine.

2.5 | Photoacoustics and Tendons

The health of tendons, the key biological structures that connect muscle and bone, is critical to human motor function [55]. However, tendon injuries, whether due to overuse or acute impingement, can severely impact an individual's athletic ability and quality of life. Existing diagnostic imaging tools have several drawbacks, including the fact that the signal intensity of normal tendons in MRI sequences is low because the alignment of water and collagen molecules in the tendon structure creates dipolar interactions that significantly shorten the T2 relaxation time by up to 1–2 ms [56]. In addition, tendons produce characteristic angle-dependent MRI signals. T2 begins to increase in T2 when the angle between the tendon and the magnetic field is greater than 20° and maximizes at about 55° (the "magic angle" phenomenon) [57–59]. Tendons show higher MRI signal intensity in the direction of the collagen at this "magic angle" depending on the sequence type and echo time. Therefore, changes in the orientation of tendon fibers can cause signal degradation and lead to misdiagnosis of these injuries. In contrast, PAI provides detailed information about the structure of the tendon and its functional state, offering new possibilities for early diagnosis and monitoring of tendon injuries.

Tendons are composed of a high density of type I collagen, which is arranged in a cross-linked triple-helical structure [60]. The collagen present in tendons not only endows them with their characteristic mechanical properties, such as strength and flexibility, but also allows them to exhibit a clear endogenous absorption contrast in the near-infrared spectral range. Consequently, tendons are able to generate strong photoacoustic signals during PAI due to their collagen-rich structure. Taking advantage of this property, Tae et al. [61] employed a pulsed near-infrared fiber laser with a central wavelength of 780 nm for imaging, successfully providing a wide field of view ($5 \times 5\,mm^2$) of a mouse tendon and reconstructing three-dimensional in vivo images of tendons in the paws of mice. The PAI system allows for a clear distinction between tendons and other tissues, such as epidermis, dermis, glands, and muscles. The technique is not susceptible to angular dependence between the laser beam and the tendon orientation during imaging, thus preventing signal fluctuations due to changes in tendon orientation, which is known as the "magic angle" phenomenon.

Tae et al. [62] measured the peak PA absorption spectra of collagen in the short-wave infrared region (SWIR, defined as 1100–2000 nm) at 1200, 1550, and 1700 nm. The optimal wavelength for collagen imaging was identified as 1550 nm, and 3D PA images of the collagen patches were obtained using a pulsed fiber laser with an output wavelength of 1560 nm. This confirms the utility of an effective PA absorption spectrum and optimal wavelength for PAI of collagen-based tissues, which helps to improve the sensitivity of PA images. PAI of both the tendon itself and collagen demonstrates the great potential of PAI in the diagnosis of tendon injuries. In brief, Tae et al. used PAI with near-infrared lasers to create high-resolution 3D images of tendons and collagen, demonstrating its potential for diagnosing tendon injuries.

PAI is not only employed for the imaging of tendons but also for the tracking of stem cell therapy. Given that tendon stem cells (TSCs) have been employed to facilitate the repair of rotator cuff injuries, the fate of these cells following transplantation remains unknown [63, 64]. Lu et al. employed polylactic acid-hydroxyacetic acid copolymers (PLGA)/iron oxide microparticles (IO MPs). The tendon stem cells (TSCs) were labeled, and the rats were subjected to dual-modal magnetic resonance imaging (MRI) and PAI techniques to track the TSCs transplanted in the rat rotator cuff location and to ascertain the status of the transplanted TSCs in a rat rotator cuff injury model. PAI was employed to track the transplanted TSCs in this study, thereby corroborating the feasibility and safety of labeling TSCs using PLGA/IO MPs. Moreover, it provided an effective method for non-invasive, long-term tracking of TSCs. Through PAI, the researchers were able to observe the distribution and status of transplanted TSCs in the rotator cuff injury model at different time points, thereby supporting the value of PAI in sports medicine [65, 66]. Briefly, Lu et al. used PAI to track tendon stem cells (TSCs) in a rat rotator cuff injury model, demonstrating its effectiveness for non-invasive, long-term monitoring of stem cell therapy.

Anterior cruciate ligament (ACL) injuries are a common type of sports-related injury, especially in sports that involve sudden stops, quick changes of direction, or direct impacts, such as football, basketball, and skiing [67]. The ligament is primarily composed of Type I collagen, a protein that is both strong and elastic, providing the necessary mechanical strength and stability to the ligament [68]. Although there is no literature reporting the application of PAI technology in ligaments, PAI is very suitable for diagnosing ligament injuries.

Overall, PAI offers significant value in diagnosing and monitoring tendon injuries. Compared to traditional imaging methods like MRI, PAI provides high-resolution, detailed images of tendon structure and function, overcoming the limitations of MRI, such as signal degradation due to tendon orientation (the "magic angle" phenomenon). PAI's ability to visualize collagen-rich tissues and track stem cell therapy in tendon repair further enhances its diagnostic and therapeutic potential. As PAI technology evolves, it will become an increasingly important tool for early detection, monitoring, and treatment of tendon and ligament injuries, offering a non-invasive, precise approach in sports medicine.

2.6 | Photoacoustics and Muscle

Muscles play a central role in movement and are a key area of study in sports medicine [69, 70]. However, currently, in addition

to magnetic resonance imaging (MRI), there are no effective imaging methods for muscles [71]. Photoacoustic Elastography (PAE) is a novel muscle imaging technique that combines PAI technology with the principles of Elastography. PAE employs short-pulse lasers to irradiate biological tissues, which absorb the light and produce a thermal effect, causing instantaneous volume expansion and generating ultrasound waves (photoacoustic waves). These ultrasound waves are received by an ultrasound probe and converted into images. In elastography, external pressures or vibrations are applied to deform the tissue, and the tissue's response to these forces is observed. The elastic properties of the tissue affect the degree of deformation, allowing the tissue's elastic properties to be inferred by measuring the deformation (or strain). Therefore, Wang and others applied a known external pressure (12 millinewtons) to a mouse's leg, and they used a 680 nm wavelength laser pulse before and after compression to generate photoacoustic waves, which were detected by an ultrasound probe array and reconstructed into images for PAI. This compression causes tissue deformation, resulting in alterations to the photoacoustic signal. Given that PAI provides a high degree of optical absorption contrast, PAE can generate high-contrast images of tissue elasticity. In comparison to optical imaging, PAI can achieve imaging depths of several millimeters to several centimeters in biological tissues, rendering PAE an appropriate technique for elasticity imaging of deep tissues. PAE maintains the high spatial resolution of PAI, enabling clear differentiation of small structures and lesions [72]. In summary, Wang et al. used photoacoustic elastography (PAE) with external pressure and laser pulses to generate high-contrast images of tissue elasticity, offering deep tissue imaging with high spatial resolution.

Knieling and others have employed multispectral optoacoustic tomography (MSOT) to detect and quantify the distribution of collagen in the muscles of patients with Duchenne muscular dystrophy (DMD). MSOT employs multi-wavelength lasers ranging from 680 to 1100 nm to capture changes in biomolecules within tissues, particularly the increase in collagen, which is a key marker of muscle fibrosis. The non-invasive nature and high-resolution imaging capabilities of this technique render it a valuable tool for monitoring the progression of DMD and its response to treatment. It provides a novel perspective on assessing muscle pathological states and treatment efficacy [73]. In short, Knieling et al. used multispectral optoacoustic tomography (MSOT) to detect and quantify collagen distribution in Duchenne muscular dystrophy, offering a non-invasive, high-resolution tool for monitoring disease progression and treatment response.

In the study conducted by Yang et al. [74], they checked the feasibility of PAT for measuring the hemodynamic changes in the forearm muscle during cuff occlusion. They presented high-resolution photoacoustic tomography (PAT) images cross-verified by ultrasound images and showed that photoacoustic tomography is efficient for tracing hemodynamic changes during rotator cuff occlusion, and it can accurately resolve the signals among different depths/layers in muscle with high resolution. In summary, Yang et al. demonstrated that photoacoustic tomography (PAT) effectively measures hemodynamic changes in forearm muscles during cuff occlusion, providing high-resolution, depth-resolved imaging.

In experiments conducted by Chen et al. [75], to quantitatively detect the extent of increased microvascular permeability, they used Evans blue (EB), an agent that strongly binds to albumin in blood, to act as a molecular probe for PA imaging of leaked albumin, to estimate the extent of local microcirculation injury. Depending on the extent of ischemic injury advancement, a significant increase in the PAI signal could be seen in the damaged muscle of all rats in which edema was evident in pathologic results. They compared the PAI results with the pathological evaluations of muscle injury. The results obtained by quantitative analysis showed a continuous increase in muscle injury, which strongly correlated with the time of ischemia. They concluded that PAI can act as a real-time effective diagnostic modality in determining the degree of limb and muscle ischemic injury. Briefly, Chen et al. used PAI with Evans blue to quantitatively assess muscle ischemic injury, demonstrating its effectiveness as a real-time diagnostic tool for evaluating microvascular permeability and injury progression.

To conclude, PAI and elastography (PAE) provide significant value in muscle imaging. PAE delivers high-resolution, deep-tissue imaging with superior contrast compared to MRI, allowing for precise differentiation of small structures. PAI effectively monitors muscle properties, hemodynamic changes, and microvascular injury, thereby improving the diagnosis and treatment of muscle injuries. As a non-invasive, real-time technique, PAI is poised to become an essential tool in diagnosing and managing muscle injuries, offering strong potential for personalized care in sports medicine.

3 | Discussion

Over the past decades, PAI has demonstrated great potential in clinical applications, especially in the diagnosis and treatment of thyroid disorders [76, 77], breast disorders [78–81], dermatologic disorders [82–84], and prostate disorders [85, 86]. These tissues and organs are located in the superficial region, and the depth of penetration of existing PAI techniques is sufficient for the needs of these applications. However, to date, no applications of PAI in sports medicine have been reported, except for applications in fingers. The main reason for this is that the penetration depth of PAI techniques is still insufficient [20]. Although PAI offers greater depth compared to purely optical imaging techniques, the inherent attenuation of light energy limits its penetration depth to only ~0–3 cm [87]. This depth limitation is particularly problematic when attempting to image deeper tissues in the locomotor system, such as muscles, tendons, and joints, which are essential in sports medicine. As a result, imaging these deeper tissues remains a challenging task.

The depth limitation of PAI arises from the scattering and absorption of light as it travels through tissue. Although techniques like near-infrared light provide a better penetration depth than visible light, the energy loss due to scattering still limits its effectiveness in deeper tissues. Current advances in laser technology and signal processing techniques, such as the development of higher-energy pulses, adaptive optics, and enhanced light delivery methods, may help overcome some of these depth limitations. Furthermore, emerging technologies such as high-frequency ultrasound or the combination of PAI

with other modalities could enhance the overall imaging depth and resolution. For instance, combining PAI with MRI or CT scans could compensate for the limited penetration depth of PAI by integrating complementary strengths from each modality.

In addition, contrast agent identification is an important challenge. Although there are multiple endogenous contrast agents (e.g., hemoglobin, water, lipids, and melanin) [88], their absorption spectra often overlap, making it challenging to distinguish them even with multispectral photoacoustic tomography (MSOT). As previously discussed in this paper, PAI techniques can be used to image the motor system using collagen. However, because collagen is ubiquitous in the motor system, precise discrimination is difficult to achieve using collagen as an endogenous contrast agent for tissue imaging. To overcome some of these limitations, targeted exogenous molecular agents can be employed. These agents possess high absorbance and unique spectral characteristics, allowing them to be easily distinguished from the background. Furthermore, such agents can provide crucial clinical information, such as the presence of specific biomarkers or the activity level of enzymes, which are essential for clinical decision-making.

Unfortunately, despite the existence of a large number of preclinical studies reporting on the potential utility of such agents, to date, such targeted drugs have not been approved by the U.S. Food and Drug Administration (FDA). It is noteworthy that fluorescent optical imaging agents have begun to receive FDA approval. While they are not the optimal choice for PAI, they may still be utilized for PAI applications under certain circumstances. This represents a potential expansion of the clinical use of targeted imaging agents and opens up new possibilities for the further development and clinical application of PAI technology.

To validate the applicability of PAI in sports medicine, comprehensive measurements and recordings are essential. First, the resolution of the PAI system at different depths should be measured and documented to assess its performance in various tissue types (e.g., muscles, ligaments, joints, etc.). Additionally, the maximum depth of penetration of PAI in different tissues must be evaluated. Advanced systems that incorporate adaptive optics or other depth-enhancing technologies should be prioritized for testing.

Subsequently, the duration of the imaging procedure should be recorded to assess its efficiency in clinical practice, as faster imaging times will be crucial for real-time diagnostics. Furthermore, the accuracy and sensitivity of PAI in the diagnosis of sports injuries should be evaluated by comparing it with conventional imaging techniques (e.g., MRI, CT, ultrasound, etc.). This will help identify the strengths and limitations of PAI, especially its ability to detect soft tissue injuries such as strains, tears, and inflammation, which are common in sports medicine.

In the future, the integration of PAI with other imaging modalities could significantly enhance diagnostic capabilities in sports medicine. For example, combining PAI with ultrasound could provide real-time imaging with high spatial resolution, allowing for both structural and functional assessments of tissues such as muscles, tendons, and ligaments. Additionally, hybrid PAI with MRI could provide deeper tissue imaging while retaining the molecular insights offered by photoacoustic techniques. These multimodality systems may offer a more comprehensive approach to diagnosing and monitoring sports injuries, potentially improving both accuracy and patient outcomes.

Finally, it is necessary to document the effectiveness of PAI in monitoring the treatment process, such as tracking injury healing or assessing treatment response. The collection of specific clinical case data will demonstrate the performance and benefits of PAI in real-world applications, providing strong evidence to support its adoption in sports medicine.

4 | Conclusion

PAI emerges as a transformative technology in sports medicine, offering unparalleled insights into the musculoskeletal system. Its ability to provide high-resolution, non-ionizing, and cost-effective imaging positions PAI as a superior alternative to traditional techniques like x-rays, CT scans, and MRIs. PAI's unique capability to visualize blood vessels, assess tissue oxygenation, and monitor metabolic activities makes it invaluable for early detection and monitoring of soft tissue injuries, fractures, and cartilage lesions. The detailed molecular and physiological information provided by PAI facilitates precise diagnosis, treatment planning, and assessment of healing processes, ultimately enhancing patient outcomes in sports medicine.

To further strengthen the integration of PAI into sports medicine, future research should focus on the standardization of PAI protocols for specific sports injury applications. This includes developing specialized PAI equipment tailored to the unique demands of different sports injuries, ensuring optimized imaging and diagnostic accuracy. Additionally, combining PAI with other imaging modalities such as MRI or ultrasound could enhance its diagnostic potential and expand its clinical utility. These efforts will help ensure broader adoption and integration of PAI into standard sports injury management protocols.

Author Contributions

C.M. and J.J.G. conceived the ideas. All authors discussed the content of the Review. C.M. and A.N.C.prepared the figures. C.M. and A.N.C. wrote the paper with input and comments from all authors. C.W. and J.J.G. supervised the project. All authors reviewed and edited the manuscript before submission.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

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