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Musculoskeletal Ultrasound in Orthopedics

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Abstract

Context: Musculoskeletal ultrasound (MSUS) utilization has increased significantly over the last decade with the largest growth observed in non-radiologist. The advancement of ultrasound technology has created a safe, effective, and affordable tool that provides theorthopedic physician the ability to imagemusculoskeletal structures in real-time, assisting in the diagnosis and treatment of diseases. It is postulated that the use of MSUS is an accurate diagnostic tool and delivers accurate interventional therapies. However, the clinical outcomes of these therapies are not clear.

Evidence acquisition: Medline and PubMed where utilized to find articles published in English from 1980 to 2015. Additional articles were acquired from reference lists of research articles.Textbooks were utilized asbasic science principle reference.

Results: The body of data reviewed supports the postulate that MSUS is and accurate diagnostic tool that also delivers guided therapies effectively. However, there are data that suggest that there is no significant difference in clinical outcomes between injecting corticosteroids with or without the use of MSUS. More study is needed to make definitive conclusions about the outcomes ofother specific therapies utilizing MSUS.

Conclusions: MSUS is an accurate diagnostic and interventional treatment tool, but may not provide superior clinical outcomes compared to palpation-guided injections of corticosteroids in many cases. However, more study is needed before a definitive conclusion can be drawn concerning the clinical outcomes of other specific treatments utilizing MSUS.

Strength-of-Recommendation Taxonomy (SORT):

a. Diagnostic and interventional accuracy of MSUS = A,

b. Treatment outcome of MSUS interventional therapies = B

Keywords: *Ultrasound; Sonography; Musculoskeletal; Physics; Accuracy*

Introduction

Musculoskeletal ultrasound (MSUS) is becoming a ubiquitous tool in a growing number of orthopedic physician's hands. The appreciation of ultrasound imaging of musculoskeletal structures has gained much popularity recently in the United States and has been recognized as a tool that offers a great amount of accurate diagnostic information. In addition, it has been found to improve accuracy of certain interventional techniques, thusenhancing patient care. Much technological advancement has been made since Pierre Curie's discovery of the piezoelectric effect in 1880. Improvements in image quality have been paramount in the development of MSUS, allowing the practitioner to image tissues dynamically and in greater detail than ever before. In many cases producing higher resolution images than comparative magnetic resonance imaging (MRI). [21] The creation of the linear array transducer helped reduce tendon and ligament artifact when compared to the original curvilinear transducer configuration. Additionally, conversion from analog to digital signal processing has allowed new capabilities that improve resolution and enhancement to image quality such as displaying multiple focal zones, video capturing, compound, panoramic and harmonic imaging. [47] With these technical advancements and the increased affordability of ultrasound equipment many providers are integrating this tool into their practices today. [59] Organizations such as American Institute of

Ultrasound in Medicine (AIUM) and the American Registry for Diagnostic Medical Sonography (ARDMS) have recognized this trend early and have supported practitioners by providing general guidance, educational resources, accreditation for practices, and credentialing for providers.

Ultrasound Basics

Understanding the basic physical characteristics of acoustic energy and how it is transferred through tissues is paramount to producing a high quality ultrasound image and avoiding the pitfalls generated by sonographic artifacts. Acoustic energy is a physically observable event produced by a vibrating mass that transfers its energy from one point in space to another. The frequency of the ultrasound beam used in medical ultrasound image generation is between 1 and 30 MHz and for reference human hearing is in the range of 20 Hz to 20 KHz. [43]

Image Generation

An ultrasound image is generated by a computer processor housed in the ultrasound machine that generates alternating electrical pulses and transmitsthem through wires to an array of crystalsin the transducer (or probe). Here the electrical energy is converted to acoustic energy (ultrasound) by the crystal elements that vibrate at certain frequencies, a process termed the piezoelectric effect. This acoustic energy is then transmitted through a medium (aqueous gel) into the body of tissue. Some of the ultrasound beam will be reflected back by the tissues to the piezoelectric crystals in the transducerand the acoustic energy will then convert into electrical energy, by the reverse piezoelectric effect, whichis then transmitted back to the computer's processor where it will generate an image on a video display. [38, 43]

Image Optimization

When ultrasound is transmitted through tissue it will encounter an acoustic interface and some of the sound will be reflected back toward the transducer forming echoes that are useful in producing a clear image of the tissue. However, most of the acoustic energy will be absorbed or refracted by the tissue and will not contribute to the image. [38] Furthermore, a portion of the ultrasound beam may contribute to image artifacts (discussed later in this paper) and typically are undesirable because it may degrade the image quality.

The depth of ultrasound beam is inversely related to the frequency of the ultrasound beam. [43] High frequency beams create high-resolution images of superficial structures (e.g. tendons crossing at the wrist), but provide very poor images of deep structures (e.g. hip joint) secondary to sound attenuation properties of tissue. Low frequency beams provide better ability for sound to penetrate to deeper tissue structures creating echoes on the image display. [43]

The computer processor determines the position of each point where sound is reflected in the tissue and displays it accurately in the image by determining what point on the horizontal plane of the crystal array a reflected sound strikes and using the velocity equation ($v = d/t$, where average v in human tissue is 1540 m/s) to determine its depth. The echoes are also displayed ona grey-scale spectrum of brightness that is directly proportional to the intensity or amplitude of the echo. [43] This type of scanning is referred to as B-mode or "brightness modulation". As stated before, much of the sound generated by the transducer is lost in the tissue and does not help form the image. To remedy this an amplifier in the computer can increase the electrical pulse returned from the transducer producing a brighter signal of the entire image, *termed overall gain*, a function found on all modern ultrasound machines. Furthermore, this can also be completed based on the velocity equation to amplify signals coming from certain depths, termed *time gain compensation* (TGC) or *depth gain compensation* (DGC). [38,43]

An additional intricacy of the computer's processor and the transducer's array of multiple piezoelectric crystals allows for the ability to focus the ultrasound beam at multiple levels in the tissue improving spatial resolution of the image, termed electronic focusing. [43] Spatial resolution is composed of lateral and axial resolution and is inversely related to the wavelength (l) and directly related to frequency (f) (i.e. $l = c/f$: c = velocity of sound in human tissue = 1540 m/s). Lateral resolution is the ability to perceive two or more objects side-by-side and axial resolution is the ability to perceive two or more structures that are separated in the axis of the beam. [21,43]

However, the complexity and time needed to form each focal zone will increase the data load to the processor and thus as one increases the number of focal zones the frame rate decreases, reducing temporal resolution, loosing the ability to produce a real-time image. [38]

The amount of sound reflected by the body is directly proportional to the tissues density and the angle of the ultrasound beam in relationship to a particular mass construct, such as a tendon.1For example, if denser tissue (e.g. tendon) is adjacent to less dense tissue (e.g. muscle), more sound is reflected back to the transducer from the tendon and it appears brighter than muscle on the image-viewing screen. In addition, if the ultrasound beam is directed in a perpendicular plane to the tendon (90 degrees) more sound is reflected from it and it will appear brighter, improving the generated ultrasound image. This type of image optimization technique requires the sonographer to dynamically manipulate the transducer to optimally align the angle of incidence. The angle of incidence is themeasure angle between the vector of the emitted ultrasound beam and the perpendicularline from the reflective surface of the specific tissue being interrogated. This angle should be close to zero, angles over 5-10 degrees typically will produce less echoes on the display. [2,6]

Blood flow in large vessels can be indentified and quantified readily by the use of the ultrasound machines color Doppler function. Smaller vessels can be indentified with a more sensitive option termed power Doppler ultrasound (PDU). Both of these methods use data in each frame of an image looking for a Doppler shift in each ultrasound beam sent to detect movement caused by blood flow. [43,47] The color Doppler function has the ability to detect average speed and direction of blood flow, whereas PDU demonstrates the size of the reflections from blood flow. [47,50]

Image Artifacts

It is important for the sonographer to understand how sonographic artifacts (aberrancies in ultrasound images) are generated and how they can lead to misdiagnosis. On the other hand, understanding the nature of these artifacts can be beneficial to the astute scanner. The following are descriptions of common sonographicartifacts encountered when performing MSUS and common techniques to either avoid these scanning pitfalls or making the artifact useful by exploiting it.

Anisotropy is a hypoechoic area within a fibrillar structure such as a tendon or ligament that is caused by reflection of sound away from the transducer due to the increased angle of incidence.This typically occurs when scanning curved surfaces such as the distal portion of the supraspinatus tendon. If the angle of incidence is greater than 5-10 degrees the normal echo intensity is lost producing a hypoechoic area within the structure (i.e. tendon or ligament) that may be misinterpreted as a tendon or ligament tear. [2,6] In some instances this can be used to the sonographer's advantage. For instance, in the foot, the plantar heel consists of hyperechoic skin, fat pad, plantar fascia (that has a similar echotexture to ligament) and bone. Often it is difficult to discriminate the differences between the fat and plantar fascia. But by employing the principles of anisotropy one can make the plantar fascia more conspicuous by increasing the angle of incidence in reference to the plantar fascia thereby making it appear hypoechoic compared to the fat pad. Fat does not create anisotropy artifact and thus its echo appears similar at varying angles of the transducer in relation to the structure being scanned. This technique can be used in other anatomical locations that have fatty structure adjacent to tendons and ligament, such as the wrist and ankle. [6,45]

Shadowing is an artifact phenomenon caused by one or a combination of ultrasound beam being absorbed by the tissue, reflected away from the transducer or refraction through the tissue, resulting in an anechoic region deep to the acoustic interface in the image viewing field. [43] This artifact phenomenon has also been termed to by some as "posterior" acoustic shadowing, because it appears behind or deep to the structure in question. [3,22] These acoustic interfaces that display shadowing are dense structures such as bone or calcific deposits that reflect nearly all of the sound back strictly limiting the sound penetration to areas deeper than the bone or calcification, thus producing no echoes beyond its interface creating the anechoic region deep to it. In some instances this phenomenon can be useful to the sonographer when diagnosing tears in tendons because the torn edges refract the ultrasound away from the transducer producing an anechoic region deep to the pathologic region. [27]

Posterior acoustic enhancement (or increased through-transmission) is an artifact that occurs when the ultrasound beam passes through with less attenuation than surrounding tissue, reflecting more intense echoes deep to the fluid structure (e.g. cyst).

Posterior reverberation artifact is a series of similar appearing echoes deep to a multilayer eddense and flat surface (i.e. metal needle). Thisoccurs when acoustic energy is transmitted back and forth between the surfaces of the object. Repetitive images appear deeper to the objects true reflection point secondary to the time delay in the reverberation echoes reaching the transducer. [43] Metal objects tend to produce uniform reverberation echoes and is further termed ring-down artifact. [43] Gas bubbles in soft tissue produce reverberation echoes as well, but these echoes appear to narrow farther away from the transducer, termed *comet-tail* artifact. [43]

Diagnostic and Interventional Imaging

MSUS utilization has increased significantly over the last 10 years among all user groups. Interestingly, non-radiologists have seen the largest growth in the use of this technology in their private offices over this time period. [59] Overall this development is linked to the decrease in cost of ultrasound machines and the widening scope of indication for use, opening the door to orthopedic physicians. [32,56] It is expected that this group will continue to adopt musculoskeletal ultrasound into their practices and appears to be directly related to the decreasing cost, technological improvements, patient satisfaction and the development of formal training and testing.

The AIUM in conjunction with the American College of Radiology (ACR), the Society for Pediatric Radiology (SPR), and the Society of Radiologist in Ultrasound (SRU) has developed practice guidelines specifically outlining the performance and recording of the musculoskeletal ultrasound examination. [3] These guidelines specifically review the indications and specifications for anatomical region examinations and requirements for interventional methods, among other important attributes that will not be duplicated in this review paper. However, the accuracies of diagnostic and effectiveness of interventional methods of musculoskeletal ultrasound in a broad representation of anatomical sites are reviewed here.

Normal Versus Abnormal Appearances of Common Musculoskeletal Structures

With a clear understanding of the basic principles of ultrasound physics as described earlier in this paper, one will better understand the images generated when scanning normal and abnormal tissues.

Recognizing a tissues specific ability to produce an echo will allow the observer to differentiate musculoskeletal structures such as vessels, nerves, muscle, tendons, ligaments, fascia and bone. In addition, it is of significant importance that the scanner have an in depth knowledge of musculoskeletal anatomy of the specific region being scanned.

The echoes produced by specific structures can be characterized in terms of their echogenicity (i.e. ability to reflect sound: hyperechoic, hypoechoic, anechoic, isoechoic), echotexture (i.e. pattern of reflected sound: fibrillar, fascicular, pinnate, honeycomb, broom end, starry night), ability to produce anisotropy, ability to be compressed with transducer pressure and blood flow. [2,63] The following are specific ultrasonographic characteristics of normal and abnormal musculoskeletal structures that can be accurately visualized with ultrasound:

Vessels (veins and arteries) in the normal state appear tubular and anechoic or hypoechoic. They demonstrate flow on Doppler scanning and are compressible (compressibility: vein > arteries). In the abnormal state there may be a hypoechoic mass within the thickened vessel wall andreduced or absenceblood flow on Doppler examination representing a vessel thrombosis. [11,33,49] Additionally, there may be an enlarged region of the vessel that would be consistent with an aneurysmor pseudoaneurysm. [46,51,69] PDU is particularly helpful in MSUS imaging when one is attempting to detect small amounts of blood flow within small vessels scanned in tendinopathic tissue. [60] The prognostic value of PDU has been studied in many tendinopathic conditions. It is thought that the presence of neovascularization in the tendon may be associated with poorer outcomes. One such study looked for presence of neovascularization in the mid-portion of the Achilles tendon of 634 asymptomatic runners and found the likelihood of developing symptomatic disease within 1 year in those with neovascularization was 6.9 fold (P = 0.0001). [29]

Furthermore, an earlier study showed that there was no significant correlation between the presence or absence of neovascularization and pain/dysfunction at baseline testing of symptomatic patients. But after 12 weeks of physical therapy this correlation was present. Moreover, there was no correlation in the presence or absence of neovascularization at baseline and treatment outcome. [15] This would support earlier studies that suggested that there is no prognostic value for clinical outcome using PDU in symptomatic patients with Achilles tendinopathy. [74] However, another investigation looking at chronic tennis elbow patients, interrogating the common extensor tendon origin at the lateral epicondyle with PDU and comparing it togrey-scale findings found that a positive PDU finding in the tendon alone had a positive likelihood ratio of 45.39 of accurately diagnosing tennis elbow. [67] Furthermore, they found a negative likelihood ratio of 0.05 of diagnosis in those with negative PDU and grey-scale findings. Positive grey-scale findings alone are not as diagnostically accurate as PDU findings. [67] However, another study of tennis elbow demonstrates that the positive findings on PDU do not coordinate well with change in severity of pain and dysfunction, and therefore may not be good predictor of clinical outcomes as seen in the aforementioned Achilles tendon studies. 9 Additionally, when looking at the neovascularization in the patellar tendon associated with jumper's knee and potential treatments early study showed that interrupting the new vessels with injection of a sclerotic agent, polidocanol, may be an effective solution for patients. [25,30] However, long-term study of outcomes showed only moderate improvement at 24 months post treatment with polidocanol injection and that other invasive treatmentsuch as arthroscopic shaving of the tendinopathic area may be superior. [31,73] These observations would suggest that presence of neovascularization on PDU in tendons is helpful in making an accurate diagnosis but may not be a good predictor of treatments outcomes.

Nerves have mixed echogenicity (hyperechoic/hypoechoic) based on the differences in echo generation by the nerve fascicles high fluid content (hypoechoic) versus the denser epineurium (hyperechoic). This generates two types of echotexture depending on the plane in which the nerve is scanned. Along the longitudinal axis it has a fascicular pattern and in the transverse axis it appears to have a "honeycomb" pattern. In addition, nerves display much less anisotropy than tendon requiring less attention to the angle of insonation by the sonographer. [45] Large peripheral nerves such as the median and ulnar nerves can easily be traced in the transverse plane with good differentiation from adjacent tendons.45 This technique can be used with the addition of physical examination techniques to elicit signs and symptoms such as Tinel's sign or limb manipulation to elicit nerve subluxation and dislocation (e.g., ulnar nerve subluxation from the cubital tunnel). With nerve entrapment syndromes (e.g. Carpal Tunnel Syndrome) the nerve will appear hypoechoic and swollen proximal to the compression. [45,70] Meta-analysis has shown that the cross-sectional area of the median nerve at the carpal tunnel inlet equal to or greater than 9 mm^2 is the single best diagnostic decisive factor, having a diagnostic odds ratio of 40.4, a sensitivity of 87.3% and a specificity of 83.3%. [66] However, other studies have demonstrated that US is not as accurate as electro-diagnostic testing, which remains the gold standard. [16,17,56] Moreover, new advancements in insonation technology are allowing even smaller peripheral nerves, such as those in the hand and wrist area, to be interrogated with good accuracy in diagnosing peripheral neuropathies. [65,70] Furthermore, ultrasound guided injection into or around peripheral nerves for treating conditions such as inter digital neuroma and providing nerve blocks is very accurate. [2,20]

Muscle has mixed echogenicity (hypoechoic muscle fascicles > hyperechoic perimysium and epimysium). In the longitudinal axis it has a "pinnate" or feather-like echotexture and in the transverse axis, a "starry night" echotexture. [63,70] In the injured state the normal patterns are disrupted. In mild grade injuries there may be regions of slight hypoechogenicity and loss of the normal pinnate echotexture. In higher grade injuries there may be larger regions of more conspicuous hypoechogenicity or anechoic areas consistent with hematoma formation. In more advance injury there may be complete disruption of the muscle fiber with intervening hematoma of which typically will occur at the myotendinous junction. [10,70]

Tendons appear hyperechoic and have a fibrillar arechotexture in the longitudinal axis and have a broom-end appearance on the transverse axis image. Tendon tissue is comprised of densely packed linear collagen bundles that are not compressible and reflect sound uniformly creating susceptibility to anisotropy. [1,6,45] An acutely injured tendon may result in a partial or full thickness tear. Here the scanner would see possible thinning of the tendon and/or disruption of the fibrillar structure and an intervening hypoechoic or anechoic region representing the tear, which can be confirmed in two orthogonal planes. [1,6,45,62] Furthermore, dynamic study may reveal gapping of the tendon parts in high-grade partial tears and full thickness tears. In addition, shadowing artifact may occur deep to the tear secondary to refraction of the torn edges of the tendon. [27] In chronic conditions of the tendon or tendinosis, the affected area of the tendon appears hypoechoic and enlarged and may be hyperemic as detected by PDU examination. [1,45,60] Tenosynovitis can be simple or complex in nature. Simple tenosyonvitis has the appearance of an anechoic region (simple fluid) surrounding a

Whereas, in cases of complex tenosyonvitis, a mixed echogenic fluid mass is seen surrounding the tendon. A thickened synovial membrane may also accompany it with the presence of hyperemia detected by PDU examination. [1,45] It is important to keep in mind that ultrasound cannot rule out infectious conditions and one must use good clinical judgment and consider aspiration of the complex fluid for culturing to rule out infectious synovitis. [63]

Ultrasound diagnostic accuracy of tendon pathology has been extensively investigated. In the Achilles tendon the differential diagnostic accuracy, comparing ultrasound to surgical findings, of full versus partial thickness tears or tendinosis is 92%, with a 100% sensitivity and specificity of 83%. [27] When comparing accuracy of magnetic resonance imaging (MRI) to ultrasound diagnosis of the patellar tendinopathy, ultrasound was found to be more accurate than MRI. [72] Whereas when considering the diagnostic accuracy of sonographic measurements of the common extensor tendon (CET) in tennis elbow, an early study showed that increases in CET cross-sectional area equal to or greater than 32 mm^2 (accuracy 84.2%; sensitivity 86.3%; specificity 82.5%) and thickness of 4.2 mm (accuracy 87.7%; sensitivity 78.4%; specificity 95.2%) correlated with the presence of tendinosis, but further study is needed to determine the utility of these measurement and correlation to severity of symptoms. [40] Furthermore, the accuracy of detecting full-thickness tears of the long head of biceps tendon is 97% (sensitivity 88%; specificity 98%), whereas it was only found to have an88% accuracy rate for partial tears. [61] Finally, the diagnosis of rotator cuff pathology has been the focus of many studies. Particularly comparing the accuracy of MRI versus MSUS in detecting rotator cuff tears. One meta-analysis evaluating 65 articles focusing on accuracy of MRI, magnetic resonance arthrography (MRA), and MSUS found that MRA is the most sensitive and specific imaging modality for full and partial-thickness rotator cuff tears. But also elicited that MSUS and MRI have comparable sensitivity and specificity. [14] Another meta-analysis evaluating 62 studies focusing on accuracy of MSUS and either arthroscopic or open surgical findings, in regards to rotator cuff tears, found MSUS to be accurate in diagnosing partial thickness tears (sensitivity 84%; specificity 89%) and full-thickness tears (sensitivity 96%; specificity 93%).[64]

Ligament in its normal state appears similar to tendon and can be differentiated simply by scanning end-to-end over the structure and observing the attachments. However, the collagen fibers of the ligament are not as uniform as tendon making it slightly less vulnerable to anisotropy. In the low-grade injured state this fibrillar structure may be thickened and hypoechoic. Moreover, in the high-grade injury state the ligament may have a partial or full-thickness tear represent sonographically by disruption of the fibrillar structure that may be made more conspicuous by stress testing. [37]

Bone is very dense and is an excellent reflector of acoustic energy and therefore is hyperechoic. As stated earlier, ultrasound cannot visualize structures deep to bone or highly calcified structures. Therefore, ultrasound is limited only to evaluation of the boney surface. When performing an ultrasound scan it is very common to use bone as an anatomical landmark or reference point to other anatomical structures such as the lateral epicondyle and its relationship to the common extensor tendon. Moreover, multiple studies have shown that ultrasound is a good imaging modality for fracture detectionin non-intra-articular long bones, nasal bones, ribs, sternum, and phalanges. [4,19,26,34,71] One recent prospective study assessing 86 patients presenting to an ER with clinically suspected fractures were evaluated with X-ray and ultrasound. They showed that US had a sensitivity of 94% and a specificity of 92% when looking at long bones fractures. [4]

Accuracy of Ultrasound Guided Injections

Historically, injections into musculoskeletal soft tissues (e.g., joints, peri-tendinous, muscle and peri-neural regions) have been performed by palpation-guided injection (PGI). PGI uses the finger tip(s) to palpate anatomical landmarksin attempts to accurately place the needle tip into the intended target. MSUS allows the sonographer to visualize the needle tip within the body, in many cases, and has great potential of accurately guiding a needle to target tissue. Over the last 10 years the use of MSUS to guide procedures, especially injections, have significantly increased among non-radiologist as described earlier in this paper.This may be particularly beneficial for patients with difficult anatomy, deep non-palpable target areas, or those on anticoagulants. However, one controlled laboratory study concluded that the accuracy rate for ultrasound guided placement of a compartment pressure needle into the deep posterior compartment of the leg was 88% compared to the 90% accuracy rate of palpation-guided placement. [53] Nevertheless,it is thought that USGI is more accurate than PGI. Choudur, et al. demonstrated a 99% accuracy rate of injection of contrast into the wrist, shoulder, knee, and hip joints. [8] In review of multiple studies evaluating USGI in patients and cadaveric specimens of multiple anatomical regions in the upper and lower extremities demonstrate high accuracies rates that are superior to PGI. [8, 13, 23, 24, 28, 36, 42, 48, 52, 54, 55] However, not all studies revealed superior USGI accuracy rates in all target areas. Khosla, et al. reported equally superior accuracy rates for USGI and PGI in the tibiotalar and subtalar joints. [36] Rutten., *et al*. also demonstrated equally high accuracy rates for USGI and PGI in the subacromial-subdeltoid bursa. [57]

Even though the accuracy of placement of injectate utilizing USGI appears to be better than PGI in most studies, the superior efficacy measured by clinical outcomes has not been demonstrated with much vigor in the current body of literature. Cunnington., *et al*. showed in a double-blind, controlled investigation that there was no significant difference between clinical outcomes of patient receiving USGI and PGI of corticosteroid for inflammatory arthritis in the wrist, elbow, shoulder, ankle, or knee joints. [12] Dogu., *et al*. demonstrated no difference in either accuracy rate of USGI versus PGI or difference in clinical outcome of the delivery of cortisone by either method into the subacromial region for subacromial impingement syndrome. [18] In addition, Bloom., *et al*. concluded in their 2012 Cochrane review that the literature up to June 2011 does not support any advantage of USGI of cortisone into the shoulder for common pathologies. [5]

Conclusion

As orthopedic physicians actively adopt MSUS into clinical practiceit is paramount to understand how acoustic energy interacts with human tissue in order to create high-quality images. This complex technology, which has been refined and simplified over many years, in its current form has proven to be an accurate tool fordiagnostic and interventional imaging of musculoskeletal tissues. However, more study is needed to definitively demonstrate the efficacy of such specific interventions on clinical outcomes.

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