CLINICAL NOTE

High-Resolution Ultrasound and Magnetic Resonance Imaging to Document Tissue Repair After Prolotherapy: A Report of 3 Cases

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High-resolution ultrasound imaging of musculoskeletal tissue is increasing in popularity because of patient tolerability, low cost, ability to visualize tissue in real-time motion, and superior resolution of highly organized tissue such as a tendon. Prolotherapy, defined as the injection of growth factors or growth factor production stimulants to grow normal cells or tissue, has been a controversial procedure for decades; it is currently gaining in popularity among physiatrists and other musculoskeletal physicians. This report describes imaging of tendons, ligaments, and medial meniscus disease (from trauma or degeneration). Although these tissues have been poorly responsive to nonsurgical treatment, it is proposed that tissue growth and repair after prolotherapy in these structures can be documented with ultrasound and confirmed with magnetic resonance imaging. Directions for future research application are discussed.

Key Words: Case report; Magnetic resonance imaging; Medial menisci; Rehabilitation; Sprains and strains; Tendinopathy; Ultrasound.

THE TERM *PROLOTHERAPY* was coined by Hacket[1] in the 1940s and 1950s to imply proliferation of normal tissue at ligamentous and tendinous entheses; the procedure has been described by other terms, such as sclerotherapy, regenerative injection therapy, and stimulated ligament repair. More recently, Reeves defined prolotherapy as injection of growth factors or growth factor production stimulants to grow normal cells or tissue.[2] The proliferant solution and technique varies according to physician training and preference. Commonly reported proliferants include 10% to 15% dextrose, P2G (phenol, glycerin, glucose), and sodium morrhuate. Opponents of prolotherapy have proposed that improvements are related to the placebo effect[3] and point out that randomized, controlled trials in low back pain (LBP) have had mixed results.[4] However, proponents of prolotherapy argue that needling and injection of saline into a ligament or tendon is an active, not a placebo, treatment[5] and that these injections have produced significant and sustained improvements in chronic LBP.[6] Proponents also point out that randomized controlled trials of knee osteoarthritis, in which needle trauma is minimal, have shown significant benefit of dextrose over anesthetic injection[7] and that machine measurements have shown tightening of ligaments objectively.[8] One recent physiatric study[9] reported full return to sport in 22 of 24 elite athletes with chronic groin pain and the inability to participate in their sport. Several crucial questions must be answered before prolotherapy can be accepted as a common medical practice. Does prolotherapy actually stimulate tissue growth? If so, is that tissue less organized (ie, scar) or more organized (ie, normal fibrous tissue)? Although definitions of prolotherapy imply growth of normal tissue, not scar, some are still using the term *sclerosing* to describe injection of proliferants,[10] which does not suggest normal fibrous tissue. High-resolution ultrasound now provides an accessible, inexpensive method for serial studies of these tissues to objectively evaluate tissue quality. The purpose of this report was to determine if ultrasonography can be a useful tool in evaluating tissue healing and organization in response to prolotherapy.

CASE DESCRIPTIONS

Prolotherapy involves injections of small amounts (0.5−1.0mL) of the proliferative solution at multiple enthesis points (for tendon, ligament, and fascia) and/or musculotendinous junctions. When joints are treated, an intra-articular injection is commonly performed. In most cases, 2 to 6 treatment sessions are required over 2 to 12 months to reach maximum effect.[11] Standard protocol includes restriction from nonsteriodal anti-inflammatory drugs 1 to 2 days before treatment and 10 to 14 days after treatment. All ultrasound imaging was performed by me, and I have more than 4 years of experience in musculoskeletal ultrasound imaging using real-time ultrasound equipment[a] with 10- to 22-MHz, 8- to 16-MHz, and 5- to 10-MHz broadband linear transducers. At each follow-up ultrasound study, patient and joint position were reproduced. The previous ultrasound image was visible next to the ultrasound machine to allow the reproduction of the exact machine settings (power and gain) and near exact probe position and angulation (using bone landmarks). Magnetic resonance images were obtained before and after completion of all treatments with readings by a board-certified radiologist who specializes in musculoskeletal radiology.

A brief review of ultrasound terminology will assist in interpreting the images in this article. Tissue appearance on ultrasound is determined by the density and organization of the tissue. Black tissue on ultrasound is described as anechoic; the tissue reflects no sound wave back to the transducer. Dense tissue such as bone appears bright white and is described as highly echoic. Tissue deep to normal cortical bone

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cannot be visualized because the bone reflects all the sound waves. Sound passes through water without reflection; thus, fluid collections and normal cartilage (which has high water content) appear black on ultrasound. Normal tendons and ligaments are described as echoic structures with a tightly packed, uniform fibrillar pattern on longitudinal images. The normal meniscus has mixed echogenicity because of its fibrocartilaginous histology. An abnormal tendon, ligament, or cartilage is more variable or heterogonous in appearance (eg, in tendinopathy, the linear fiber pattern breaks down becoming more difficult to identify). This fiber breakdown along with edema result in a tendon that is thicker than normal. Diseased tissue does not reflect sound wave normally and may be described as hypoechoic (reflecting less sound than normal, eg, an edematous tendon) or hyperechoic (reflecting more sound wave than normal, eg, a calcific tendon). This case series consists of patients who showed ultrasound abnormalities in tendon, ligament, and meniscus while also having a recent magnetic resonance imaging (MRI) of the same area to allow comparison after treatment was completed.

Case 1: Patellar Tendinopathy With a Partial Tear

A 34-year-old man with no significant medical history presented with intermittent, progressively worsening medial and anterior knee pain over the past 3 years. He relates the pain to 2 previous mild injuries. Three years before presentation, he felt a "pop" in the anterior knee while jumping in a pool; 1 year earlier he suffered a valgus sprain to the knee while playing basketball. Neither injury was associated with immediate-onset pain or swelling, but both contributed to his progressive pain with athletic endeavors. The pain worsened with sitting and playing tennis and volleyball; it interfered with sleep and has prevented him from jogging over the past year. The physical examination was significant for tenderness over the medial joint line and medial collateral ligament (MCL) without crepitus, whereas tenderness over the quadriceps tendon insertion and patellar tendon origin was associated with crepitus and mild edema. The McMurray sign, patellar ballottement, and ligament laxity testing were negative. An MRI ordered by a previous physician revealed "thickening of the medial collateral ligament consistent with an old injury, but not abnormal signal at this time" and "tendinosis and partial tearing of the patellar tendon at its insertion on the patella with associated reactive edema within the bone marrow of the patella" (figs 1A, B).

Ultrasound examination confirmed the MRI findings (figs 2A, B) and also revealed mild degenerative changes in the quadriceps tendon. Initial treatment sessions in November 2004, December 2004, and February 2005 involved injection of standard dextrose prolotherapy solution (15% dextrose/0.3% lidocaine) via 25-G, 2-in needles at enthesis points that were tender to palpation; these included MCL origin and insertion, quadriceps tendon insertion, and patellar tendon origin and insertion. At a follow-up in March 2005, the patient reported significant improvement in pain and stated "there haven't been any really bad pain days" despite increasing athletic activity. The patellar tendon was much less tender to palpation. Ultrasound at that time showed improved fibrillar pattern and echogenicity in the MCL, quadriceps tendon, and patellar tendon, (figs 2C, D). Because of continued pain with athletic activity

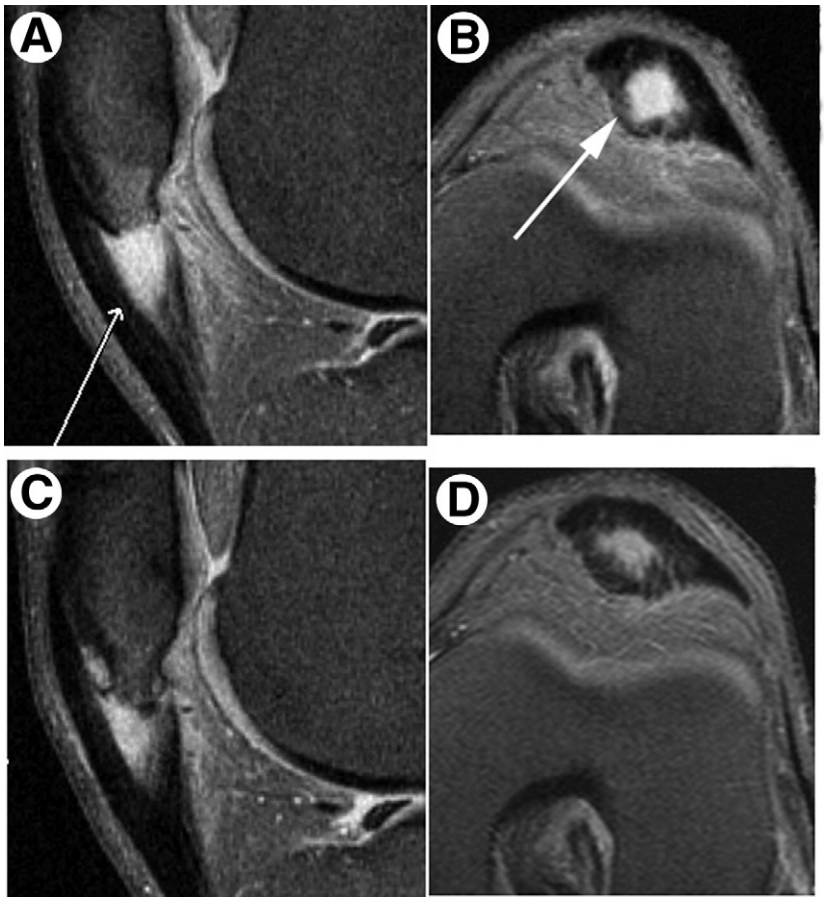

Fig 1. Proton density, fat saturation MRI of the knee (pre- and postprolotherapy). Top row, October 2004; bottom row, October 2005. (A and C) Sagittal views of left knee. The thin arrow (originally added by the interpreting radiologist) indicates a high signal in the deep, midportion of the patellar tendon consistent with partial tear. Note the reactive edema in the inferior pole of the patella (A) in 2004. Postprolotherapy, the edema is resolved and a subperiosteal cyst is noted (C). Images on the right (B, D) are axial views of the left knee through the patellar tendon; the large arrow in B points to the region of the thickened, abnormal tendon with high-signal intensity just distal to the patellar enthesis, indicating a partial patellar tendon tear. The postprolotherapy (D) shows new tendon growth and partial repair of the tear.

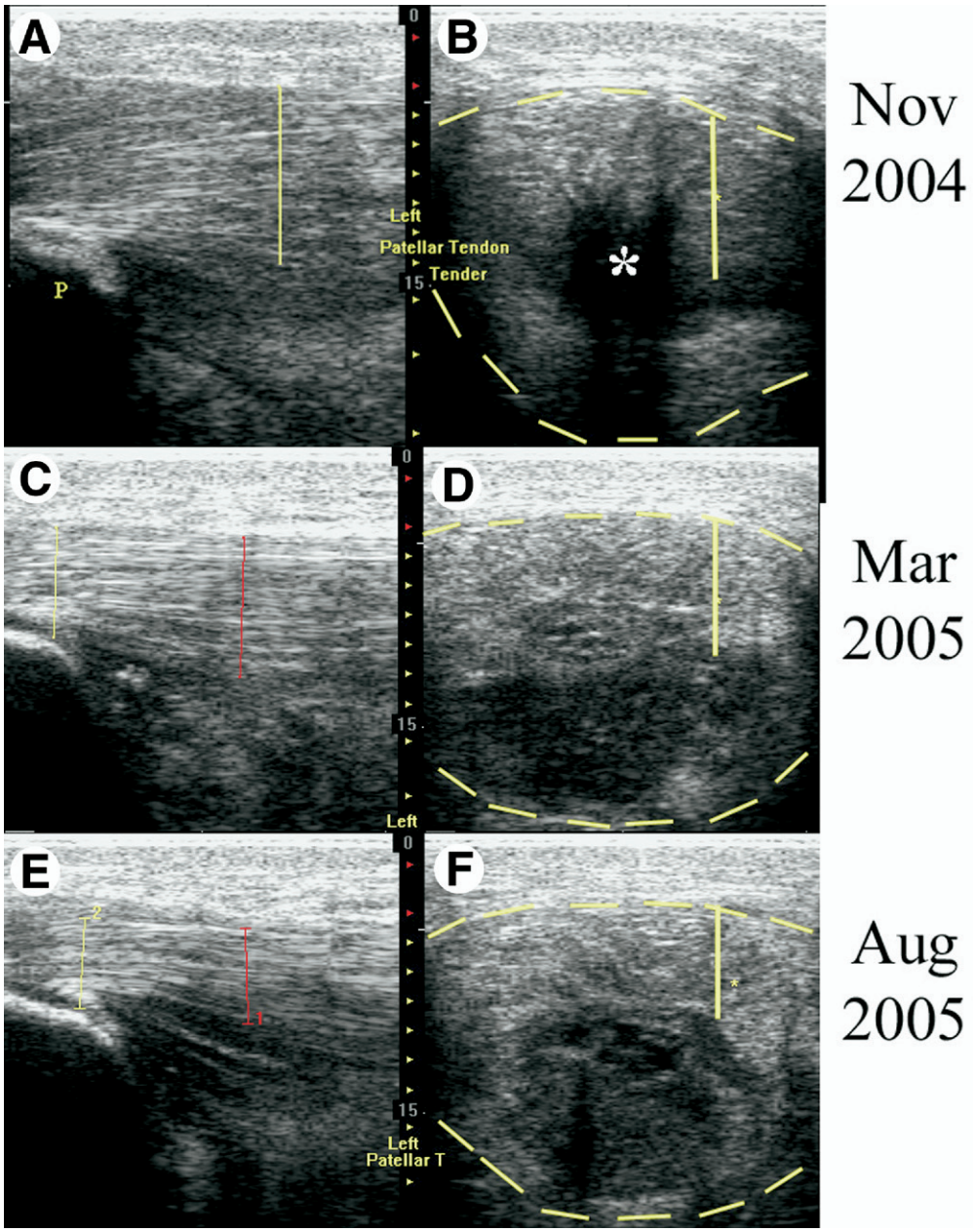

Fig 2. Patellar tendon ultrasound (pre- and postprolotherapy). Top row, November 2004; middle row, March 2005; bottom row, August 2005. A longitudinal view (A) shows a thickened (>10mm; normative, <4mm), hypoechoic tendon with a poor fibrillar pattern diagnostic of tendinopathy. A transverse image (B) confirms a thickened, hypoechoic tendon and reveals anechoic (black) deficit in the deep, midportion consistent with a tear (*). The images shown in C–F are at the same location after prolotherapy with dextrose and P2G, respectively. As treatment progresses, the tendon improves in tissue echogenicity, uniformity of signal, and fibrillar pattern. The anechoic tear has partially filled in with new tissue (ie, it is no longer anechoic), and the main portion of the tendon is near normal thickness. Abbreviation: P, inferior pole of patella. Legend: vertical yellow lines in the right images indicates position of probe just lateral to midline for the longitudinal images on left, and the dashed yellow lines outline the tendon in transverse views on the right.

and pain interfering with sleep, he elected to have a fourth treatment in May 2005, which included standard P2G solution (1.25% phenol, 12.5% dextrose, 12.5% glycerin, 0.5% lidocaine) in the same locations.

At a follow-up in August 2005, the patient reported significant improvement in knee pain with athletic activity and sleep. He had minimal tenderness to firm pressure over the proximal patellar tendon. Ultrasound on that date again showed an improved fibrillar pattern and echogenic signal (figs 2E, F). MRI in October 2005 was compared with images from the initial MRI. These showed marked improvement in tissue signal, reduction of the partial tendon tear, and resolution of the patellar edema (figs 1C, D).

During a telephone follow-up in January 2006, the patient reported complete resolution of nighttime pain and pain while exercising. He had returned to full participation in tennis, lower-extremity weight training, jogging, and yoga.

Case 2: An Anterior Talofibular Ligament Sprain

A 17-year-old female softball pitcher with no significant medical history presented with pain, swelling, crepitus, and sensation of instability in the left ankle 4.5 months after an ankle sprain from a motor vehicle collision (MVC). Radiographs in a hospital emergency department on the day of the injury revealed a small joint effusion but no fracture. She had received 6 weeks of physical therapy focused on strengthening the left ankle with only mild improvement in symptoms. Since the MVC in May 2004, she has required an ankle orthotic to pitch and run. At presentation to me in October 2004, the physical examination was remarkable for anterolateral ankle edema, tenderness, and palpable crepitus associated with a positive anterior drawer sign, an equivocal inversion stress test, and an equivocal distal tibiofibular compression test. Her orthopedic surgeon ordered an MRI in October 2004, which

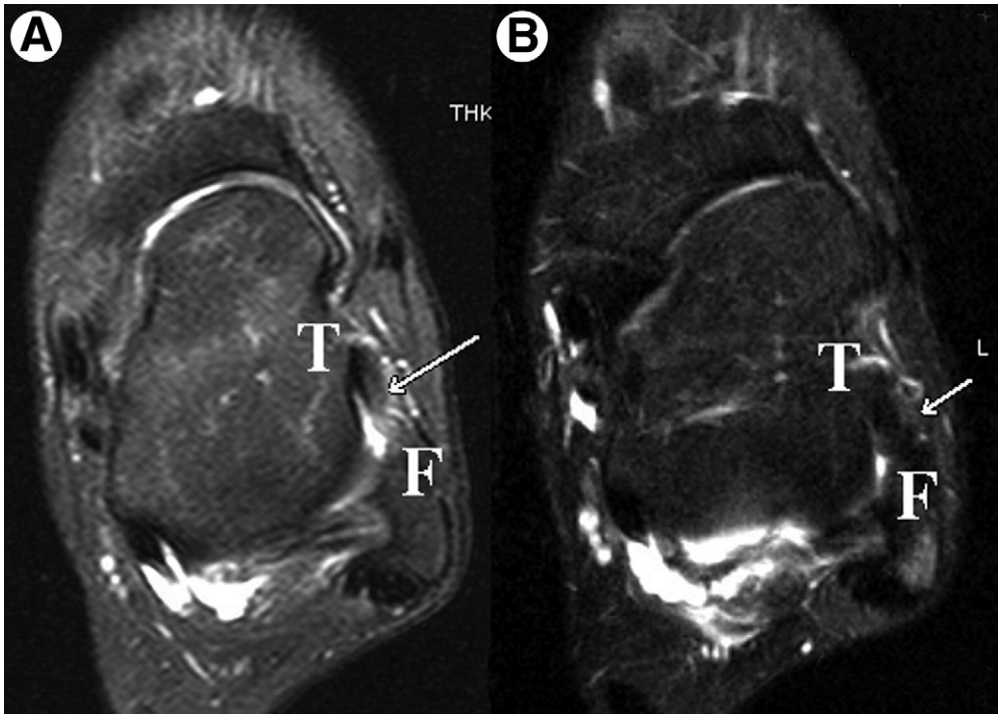

Fig 3. T2-fat saturated axial MRI of the left ankle. Left panel, October 2004; right panel, August 2005. (A) MRI 4.5 months after an injury from an MVC. The arrow indicates ATFL with high-signal intensity indicating a near complete tear. (B) MRI after 3 treatments with dextrose prolotherapy. The ligament remains abnormally thickened, but the high signal has resolved. NOTE. These images were obtained on different MRI machines by different technologists resulting in significant image-quality variability; the images have not been altered. Abbreviations: F, fibula at ligament enthesis; T, talus at ligament enthesis.

revealed "chronic appearing tear of the anterior talofibular ligament" (ATFL) with associated fibrosis (fig 3A), probable tear of the calcaneal fibular ligament, partial tear involving the deep fibers of the deltoid ligament, bone contusion of the medial talar dome and body, and small tibiotalar joint effusion." Ultrasound examination in October 2004 (figs 4A, B) confirmed a near full-thickness tear of ATFL on static and stress imaging as well as a mild distal, anterior tibiofibular ligament sprain.

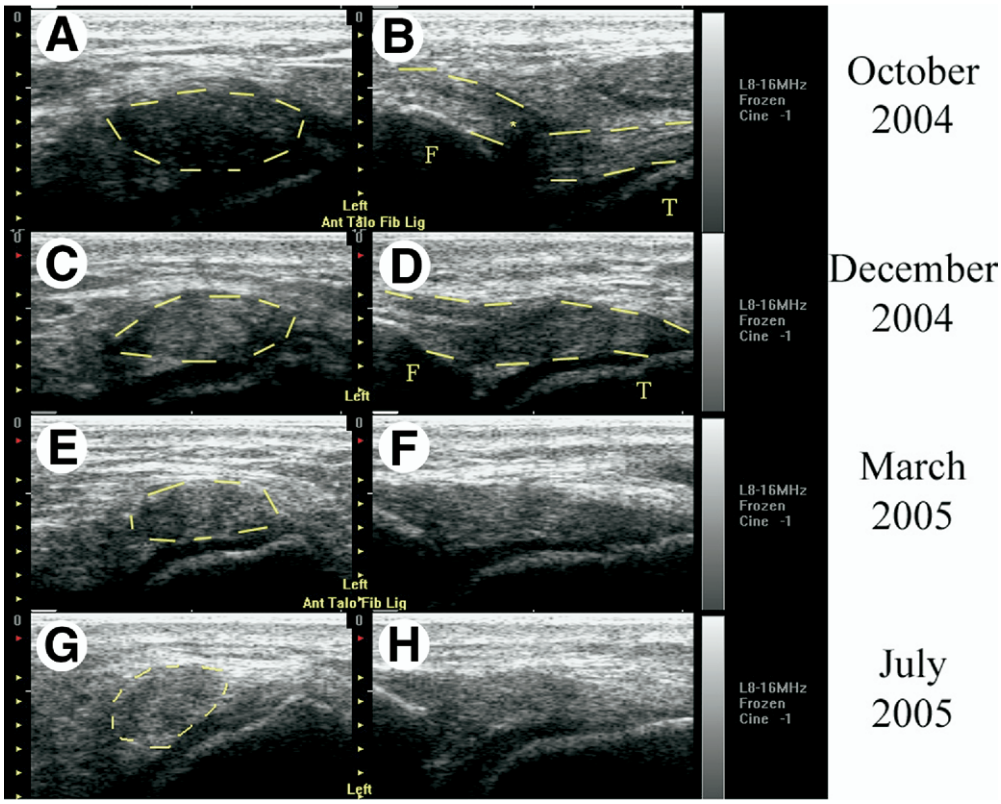

Fig 4. Sequential transverse (left column) and longitudinal (right column) ultrasounds of the left ATFL. Top images (A, B) (October 2004) of preprolotherapy showing free edges with anechoic cleft on longitudinal images indicating full-thickness tear (plane of probe for transverse view). The transverse view shows markedly thickened, hypoechoic, poorly defined ATFL. After 1 prolotherapy treatment (C, D) (December 2004), the longitudinal and transverse images have improved echogenicity and tissue plane definition. The anechoic cleft in the top image is identifiable only as a region of hypoechoic signal. After 2 prolotherapy treatments (E, F) (March 2005), the longitudinal view now shows identifiable fibrillar pattern bridging the previous anechoic gap. Both views show improved echogenicity and tissue plane definition. After 3 prolotherapy treatments (G, H) (July 2005), the longitudinal view shows improved fibrillar pattern and echogenicity. Abbreviations: F, fibula; T, talus. Legend: dashed yellow lines outline the ligament.

Her orthopedic surgeon released her for full participation in sport with ankle orthotic; however, she continued to complain of ankle weakness, pain, and instability. With her mother's consent, she agreed to try 1 treatment in November 2004 with standard dextrose prolotherapy solution. Injections of ligamentous entheses were performed via 27-G, 1.25-in needles as follows: anterior talofibular, anterior tibiofibular, calcaneofibular, anterior joint capsular ligament on talus, middle deltoid, and lateral talocalcaneal. At a follow-up in December 2004, the patient reported some reduction in swelling but no significant change in pain or instability. A physical examination confirmed reduction in edema and on anterior drawer testing; the patient remarked "it does not move nearly as far as it used to." Ultrasound on that date showed remarkable improvement in the ATFL (figs 4C, D).

She requested a second treatment, which was performed in January 2005, to the same locations except the middle deltoid ligament enthesis, which was no longer tender to palpation. At a follow-up in March 2005, she reported significant reductions in pain, swelling, and sensation of instability. A physical examination was remarkable for the absence of edema, reduced tenderness to palpation over the anterolateral ankle, and an equivocal anterior drawer sign. Ultrasound on that date again showed significant improvement (figs 4E, F).

She elected to delay further treatment because of the start of her final softball season as a senior in high school. She completed the season by using an ankle orthotic only during competition and intense practice but not during conditioning or running. She returned in May stating, "it feels so much better than it used to." A third treatment with the same solution and injection locations was performed in May 2005. At a follow-up in July 2005, she estimated she was "at 90%" of full function without using the ankle orthotic. Examination showed only mild tenderness to palpation over anterolateral ankle; the anterior drawer sign remained equivocal. Ultrasound on that date again showed improved echogenicity, tissue plane definition, and fibrillar pattern in the ATFL (figs 4G, H).

Before full release to participate in college softball, MRI was obtained in August 2005. This MRI was compared with images from the initial MRI. The report indicated "enlargement and fibrosis of the anterior talofibular ligament is noted consistent with healing of a prior ligament tear" (fig 3B), "A prior partial tear of the deltoid ligament has healed without evidence of abnormality," and "the adjacent reactive marrow edema in the talus has resolved." During a telephone follow-up in January 2006, she reported playing "full-speed" without pain, weakness, instability, and without need for the orthotic.

Case 3: A Degenerative, Complex Tear of the Medial Meniscus

A 59-year-old white woman with a history of coronary artery disease status post stent, remote uterine cancer treated by hysterectomy, and chronic LBP caused by lumbar degenerative disk disease, with sacroiliac joint dysfunction and osteoarthrosis of the right knee after arthroscopic débridement for degenerative meniscal tear presented in November 2003 with complaints of left knee pain, swelling, and sensation of instability. She felt that the left knee was "going to give out like the right one did last year." She denied trauma to the knee. A physical examination of the left knee was remarkable for antalgic gait, tenderness to palpation (over the medial joint line, MCL, tibial tuberosity, and pes anserine insertions), and positive McMurray sign. MRI in December 2003 revealed "complex tear of the medial meniscus includes horizontal cleavage tear of the posterior horn and body, as well as radial tear

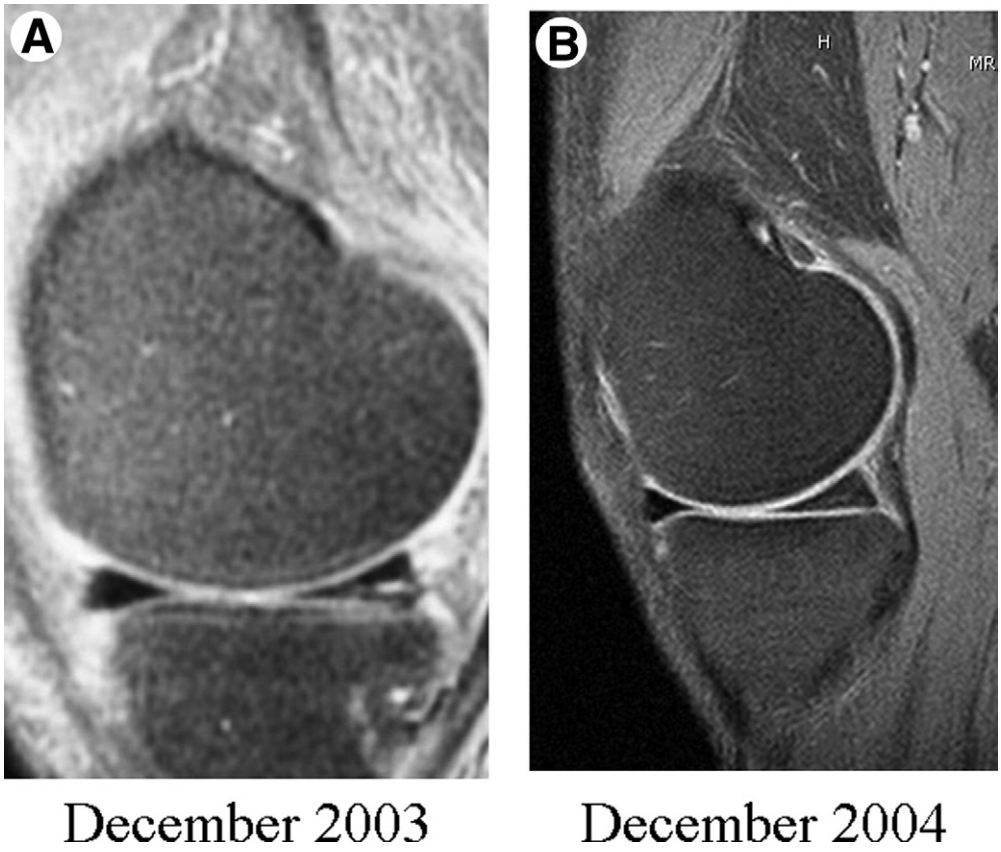

Fig 5. Sagittal proton density, fat saturation MRI of the left knee. (A) (December 2003) A preprolotherapy image showing a high signal in the posterior horn of the medial meniscus indicating a horizontal cleavage tear. (B) (December 2004) A postprolotherapy image showing only mild degenerative signal and no evidence of the previous tear.

which transverses the posterior horn-body junction; medial joint space degenerative chondromalacia with minimal reactive marrow edema adjacent to the meniscal pathology; prominent inflammation surrounding the medial collateral ligament, may be degenerative in the absence of recent trauma; mucoid degeneration signal is suspected within ACL" (figs 5A, 6A). Based on the examination and MRI, her orthopedic surgeon scheduled arthroscopic débridement in early 2004. Ultrasound imaging in December 2003 confirmed the degenerative changes in the MCL and complex, degenerative tears of the medial meniscus posterior horn and body (figs 7A, 8A).

After discussion, the patient agreed to 1 prolotherapy treatment before undergoing arthroscopic débridement in March; this first treatment was performed in January 2004. This treatment included standard dextrose prolotherapy with injections via 25-G, 2-in needles at tender entheses, including MCL (proximal and distal), coronary ligaments attaching the medial meniscus to the tibia (anteromedially, medially, and posteromedially), and pes anserine tendons. The day after the first treatment she slipped on a wet floor resulting in a nondisplaced fracture of the contralateral (right) patella. The right knee was immobilized during weight bearing for 6 weeks; during this time, she decided to delay the arthroscopy indefinitely. Subsequent treatments with dextrose prolotherapy occurred in April, May, and June. Follow-up ultrasounds were performed in March, May, and July (figs 7B–D, 8B–D). At the last office follow-up, she reported complete resolution of her left knee symptoms, and her knee examination was normal. During a telephone follow-up in December 2004, she denied any recurrence of her previous left knee symptoms and agreed to a follow-up MRI (figs 5B, 6B), which was read as "mild intrasubstance signal within the posterior horn of the medial meniscus but without criteria for tear. Otherwise unremarkable MRI of the left knee." During a telephone follow-up in January 2006, she again denied any recurrence of her previous left knee pain, instability, or swelling. She did volunteer that the right, postarthroscopy knee continued to have intermittent pain and feelings of weakness.

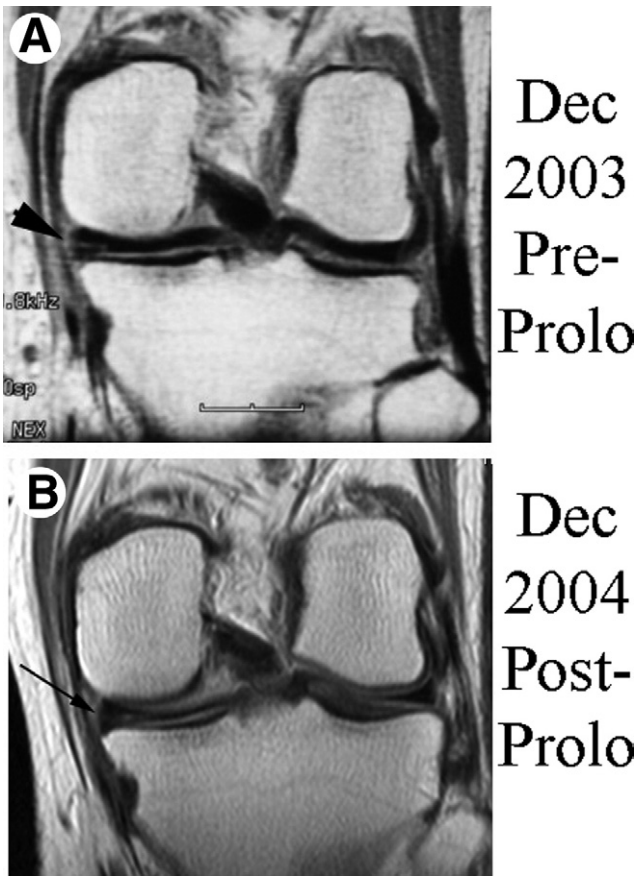

Fig 6. Coronal, T2-fat saturation MRI of the left knee (A) (December 2003, preprolotherapy). This image shows the linear high signal within the medial meniscal body, reaching the peripheral (large arrowhead) and possibly the articular surface, which is indicative of a tear. The lower image (B) (December 2004, postprolotherapy) shows healing of the peripheral tear (thin arrow).

DISCUSSION

These cases show the potential utility of high-resolution ultrasound to document pathology in soft tissues and tissue responses to treatment. Ultrasound images of animal tendons have been correlated with histology studies.[12] In the evaluation of tendons, Van Holsbeek has observed that "ultrasound has a significant advantage over MRI . . . tissues with few mobile protons emit little or no signal and, therefore, the internal architecture of the tendon is not well demonstrated [on MRI]."[13(p77)] The first patient in this report shows this advantage of ultrasound in evaluation of tendon organization. Both MRI and ultrasound show the tissue partially filling in the tear; however, only the ultrasound reveals the progressive improvement in fiber organization (on longitudinal images) over time. This advantage is vital in the evaluation of chronic tendinopathy because tendon degeneration (ie, progressive fiber disorganization over time) usually precedes tendon tear. The second case report shows similar issues in the evaluation of ligament. Normally, the complex, interlacing fiber patterns of ligaments result in a less regular fiber pattern on ultrasound. The ultrasound images show an identifiable fiber pattern within the anterior talofibular ligament, whereas the postprolotherapy MRI only shows a uniform mass of tissue. The third case report shows the limited application of ultrasound in evaluation of meniscus. Although clearly visible on MRI, the posterior horn tear was not well shown on ultrasound. The ultrasound, however, did clearly show healing of the medial body tear and progressive organization of the posterior horn. Healing of a complex, degenerative medial meniscal tear has not been reported in the literature previously.

Many past efforts to validate prolotherapy have focused on nonspecific LBP and have produced mixed results. Dagenais et al[10] recently surveyed spine prolotherapists and estimated the number of patients treated with prolotherapy "in the hundreds of thousands." This survey indicated that prolotherapy in the spine has a low incidence of reported adverse events and encouraged further prospective studies. Future research may focus on tissues readily visible with ultrasound, such as those described in this report. Although these cases are intriguing, reproducible imaging of musculoskeletal tissue with ultrasound is technically difficult. Ultrasound images of highly organized tissue such as a tendon can look vastly different with only slight changes in probe angulation; a phenomenon known as "anisotropy." This contributes to the operator dependence that currently limits clinical application of ultrasound in the musculoskeletal system. As training in ultrasound progresses, this concern should lessen. Anisotropy also casts doubt on serial imaging such as this case series; bias could be easily introduced on each subsequent image with a simple tilt of the probe. Thus, MRI, which is common and has proven reliability, is important to confirm tissue repair seen on ultrasound. Studies using ultrasound imaging of tendon response to various treatments have, thus far, used qualitative interpretations to determine tissue changes.[14] Valid, quantitative ultrasound techniques are needed. An ultrasound scale for grading tissue quality and organization in tendinopathy could be developed, similar to an

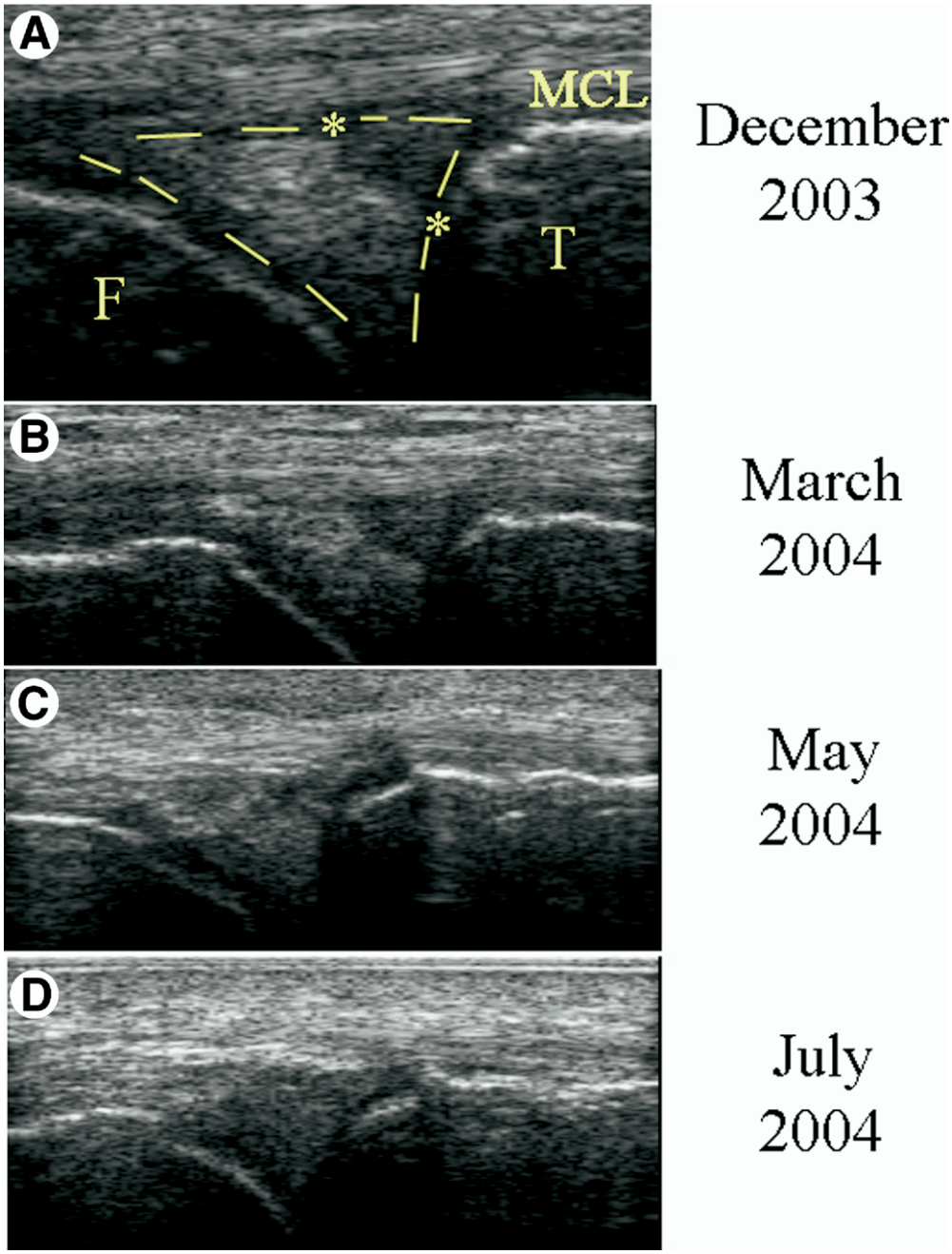

Fig 7. (A) This image (December 2003, preprolotherapy) shows that the normal, well-defined triangular shape of the medial meniscal body (yellow, dashed lines outline the meniscus) is partially defined and attached to the overlying MCL bridging the femur (F) and tibia (T). The oblique tear seen on MRI is reproduced well (*). The proximal MCL is markedly hypoechoic with a complete loss of normal, fibrillar pattern, indicating mucoid degeneration. (B) After 1 prolotherapy treatment (March 2004), the oblique tear is still visible. (C) After 2 treatments (May 2004), the tear is no longer visible. The MCL has improved echogenicity and fibrillar pattern. (D) After 4 treatments in July 2004, the meniscus has uniform signal with no evidence of a tear.

Ashworth Scale used for spasticity grading. Once validated, a scale would be useful in blinded evaluation of tendon quality pre- and postintervention, such as prolotherapy. Quantitative analysis of ultrasound images by using computerized texture analysis is being used in the evaluation of muscle[15]; similar techniques could be used on tendons. Also, ultrasound can be performed frequently and at low cost, providing multiple data points and potentially increasing statistical validity in a particular study.

Physiatry improves patient's lives by focusing on practical, functionally based treatments. However, rehabilitative interventions by their nature have been difficult to quantify and study. Advances in quantitative ultrasound and their application in rehabilitation research may lend more objectivity to physiatric interventions in general.

CONCLUSIONS

Ultrasound imaging can show tissue growth and repair. These case reports appear to confirm that prolotherapy does stimulate tissue growth in tendon (patellar), ligament (anterior talofibular), and meniscus (medial meniscus) and that this is an organized growth with a return toward a normal appearance on ultrasound. Further clinical studies with ultrasound confirmation are recommended. The development of quantitative methods to analyze ultrasound images will be valuable in blinded efficacy studies of prolotherapy and other rehabilitative interventions.

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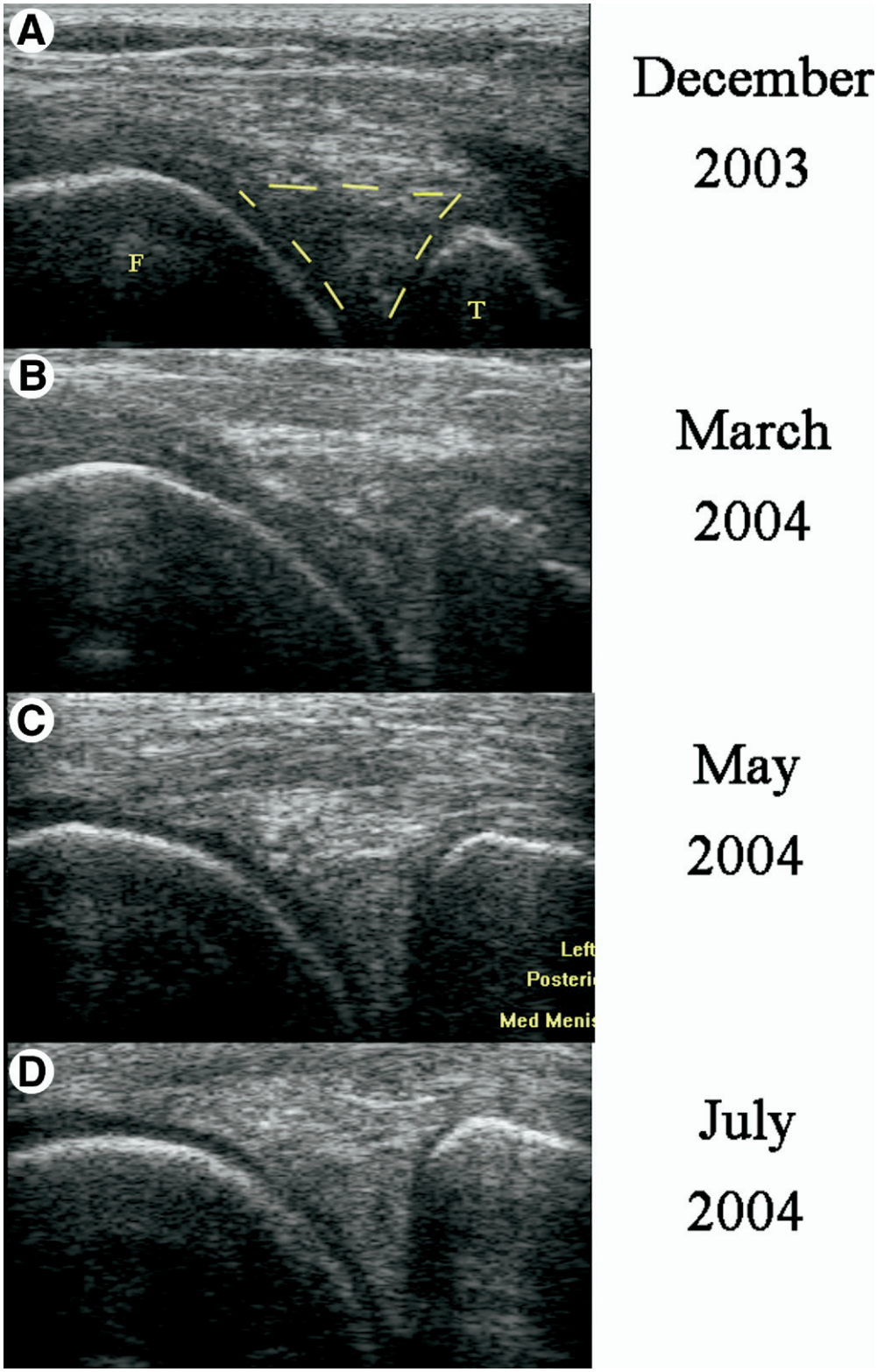

Fig 8. (A) In this image (December 2003, preprolotherapy), the normal, well-defined triangular shape of the posterior horn is poorly defined because of mucoid degeneration (yellow, dashed lines outline the meniscus). The horizontal tear seen on MRI is not visible on ultrasound. (B) After 1 prolotherapy treatment (March 2004), the normal triangular shape is evident and the meniscal signal is more homogenous. (C) After 2 treatments (May 2004), echogenicity, homogeneity, and tissue definition continue to improve. (D) After 4 treatments (July 2004), the meniscus has normal echogenicity, uniform signal, and clear definition. Abbreviations: F, posterior femoral condyle; T, posterior tibia.

References

1. Hacket GS. Ligament and tendon relaxation treated by prolotherapy. Springfield: CC Thomas; 1956.
2. Reeves KD. Prolotherapy: regenerative injection therapy. In: Waldman SD, editor. Pain management. Philadelphia: WB Saunders; 2007. p 1106-27.
3. Loeser JD. Point of view. Spine 2004;29:16.
4. Kim SR, Stitik TP, Foye PM, Greenwald BD, Campagnolo DI. Critical review of prolotherapy for osteoarthritis, low back pain, and other musculoskeletal conditions: a physiatric perspective. Am J Phys Med Rehabil 2004;83:379-89.
5. Reeves KD, Klein RG, DeLong WB. Re: Yelland MJ, Glasziou PP, Bogduk N, et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized study. Spine. 2003;29:9-16. [letter]. Spine 2004;29:1839-40; author reply 1842-3.
6. Yelland MJ, Glasziou PP, Bogduk N, Schluter PJ, McKernon M. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. Spine 2004;29:9-16.
7. Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. Altern Ther Health Med 2000;6:68-74, 77-80.
8. Reeves KD, Hassanein K. Dextrose injection prolotherapy for ACL laxity. Altern Ther Health Med 2003;9:58-62.
9. Topol GA, Reeves KD, Hassanein K. Efficacy of dextrose prolotherapy in elite male kicking-sport athletes with chronic groin pain. Arch Phys Med Rehabil 2005;86:697-702.
10. Dagenais S, Ogunseitan O, Haldeman S, Wooley JR, Newcomb RL. Side effects and adverse events related to interligamentous injection of sclerosing solutions (prolotherapy) for back and neck pain: a survey of practitioners. Arch Phys Med Rehabil 2006;87:909-13.
11. Reeves KD. Prolotherapy: basic science, clinical studies and technique. In: Lennard TA, editor. Pain procedures in clinical practice. 2nd ed. Philadelphia: Hanley & Belfus; 2000. p 172-90.
12. Martinoli C, Derchi LE, Pastorino C, Bertolotto M, Silvestri E. Analysis of echotexture of tendons with US. Radiology 1993;186:839-43.
13. Van Holsbeek M. Musculoskeletal ultrasound. 2nd ed. St Louis: Mosby; 2001.
14. Ohberg L, Lorentzon R, Alfredson H. Eccentric training in patients with chronic Achilles tendinosis: normalised tendon structure and decrease thickness at follow-up. Br J Sports Med 2004;38:8-11.
15. Nielsen PK, Jensen BR, Darvann T, Jorgensen K, Bakke M. Quantitative ultrasound tissue characterization in shoulder and thigh muscles—a new approach. BMC Musculoskeletal Disord 2006;7:2.

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a. Diasus; Dynamic Imaging Ltd, 9 Cochrane Sq, Brucefield Industrial Pk, Livingston, Scotland, EH54 9DR.