NORTHERN OHIO FOOT & ANKLE FOUNDATION

The Northern Ohio Foot and Ankle Journal *Official Publication of the NOFA Foundation*

Osteochondral Lesions of the Talus: Literature Review

by Neil Younce, DPM

The Northern Ohio Foot and Ankle Journal 5 (1):1

Osteochondral Lesions of the Talus or OLT's are a result of articular cartilage damage to the talar dome. These lesions are frequently painful and debilitating. Several theories have been reported as to the cause of these lesions, but currently is theorized to be the leading cause. Several different treatment options are available based on location of the lesion and severity of the lesion. This article aims to review the background, etiology, diagnoses, and standard treatment for Osteochondral lesions of the talus.

Key words: Osteochondral Lesions of Talus, OLT, OCD, Osteochondral Dissecans, Osteochondritis Dissecans, Talar Arthritis.

Accepted: April, 2016 **Published:** May, 2016

Osteochondral lesions of the talus, or OLT's, are injuries or abnormalities of the talar articular cartilage and adjacent bone (20,21). Previously these lesions were referred to as OCD's, or osteochondritis dissecans which broken down means "inflammatory process in the joint" and "to separate." It is now believed that this process is not due to inflammation, but rather trauma. These lesions are also frequently referred as osteochondral defects or fractures (21).

Osteochondral lesions were first reported in 1888 by Konig, who described a loose body formation with articular cartilage and subchondral bone fractures. In 1922 Kappis first described this process in the ankle joint (21). In 1932, Rendu was the first to recognize the trauma is the main cause of these lesions (21). The initial classification of talar lesion was first described by Berndt and Harty in 1959 and not until 2001 was a 5th stage added to this classification by Scranton and McDermott (24).

Anatomy

The anatomy of the talus, or astragalus, is important for understanding the mechanism of injury and the healing potential for injuries to the talus. The talus receives its blood supply in a retrograde fashion from 3 main arteries: the perforating peroneal artery, the anterior tibial artery, and the posterior tibial artery. The perforating peroneal artery supplies the lateral aspect of the talus, the anterior tibial artery supplies the head of the talus, and the posterior tibial artery supplies the most of the body of the talus (28). There are no muscular attachments to the talus, only ligamentous attachments.

60% of the talus is covered by hyaline cartilage, which is made of type II cartilage, however when injured the cartilage is replaced by type I cartilage (7). A 12 cadaver study looked at the areas of thickness of the cartilage and found the greatest thickness of the

Address correspondence to: NXYounce@mercy.com. Department of Foot and Ankle Surgery, Mercy Health Regional Medical Center
[1]Podiatric Resident, Department of Foot and Ankle Surgery

talar cartilage is located at the anterior lateral and posterior medial. They found the average max thickness of the cartilage was 2.38 +/- 0.4 mm at the thickest areas. They concluded that these areas of maximal thickness occur in clinically relevant regions that are common to injury and that these thick areas of cartilage are the response to mechanical conditions in the ankle joint (22).

Etiology and Epidemiology

As mentioned before, the current belief that OLT's are caused by trauma, but other hypotheses include inflammation (osteochondritis), avascular necrosis, or just normal arthritic changes of the ankle joint.

The talus is the 3rd most common site for osteochondral lesions. It is reported that OLT's account for 1% of all talar fractures and 0.09% of all fractures. Additionally, they account for 4% of all reported cases of osteochondritis. These injuries are most common during the 2nd through 4th decades of life, with the average age at time of injury being 25 years of age with a higher predilection for males (21).

The average length of time between the injury and the time to diagnosis is about 36 months. This is concerning since there is such a delay between injury and the time it's recognized. The association between ankle fractures and OLT was studied by Leontaritis et al and saw 73% (61/84) patients had an OLT who presented with an ankle fracture (18).

Mechanism of Action

The historical belief was that these injuries occurred via 2 types of mechanism with ankle injuries. This system was referred to as "DIAL a PIMP." This theory uses the position of the foot in relation to the leg at time of injury as the predictor for the location of the OLT on the talus. Thus, a dorsiflexion (D) and inversion (I) injury leads to an anterior (A) and lateral (L) location on the talus. Where a plantarflexion (P) and inversion (I) leads to a medial (M) and posterior (P) location on the talus. This theory concludes that the anterior lateral and posterior medial are the 2 most common locations for OLT's. Two separate articles, by Raikin et al and Hembree et al, looked at location of these lesions and tested this belief.

The article by Raikin et al reviewed 424 patients by a radiologist and orthopedic surgeon between 1999-2003. To provide locations for these lesions, the talar dome was divided into a 9 zone area (like a tic tac toe diagram with 1 medial the top left area, 5 the central area, and 9 being the bottom right area). They looked at the size of the lesions and location of these lesions as well as the age and gender of the patient. The results of this article showed that zone 4 and 6 were the 2 most frequent sites of lesions at 227 and 110 total respectively. The central column had the fewest being zones 2,5, and 8 with a total number of 2 8, and 6 for the zones respectively. In terms of surface area and depth zones 2 and 1 had the two largest surface areas and depth, zone 2 surface area of 219.0 mm^2 and depth of 7.5 mm and zone 1 having a surface area of 146 mm^2 and depth of 6.8 mm. Overall they concluded medial lesions were more frequent than lateral and central lesions, zones 4 and 6 were most common, the central column lesions (zones 2, 5, and 8) were the deepest and the medial column lesions (1,4,7) were the largest in terms of surface area (24).

Another article by Hembree et all looked at location of OLT's based on MRI findings. A total of 77 patients were retrospectively reviewed again using the 9 grid system that Raikin used. They found that the medial central (54.5%) and lateral central (31.3%) were the most common sites of OLT's. However, they did not find a correlation with location and size that Raikin had found in their article (13).

Classification Systems

Several classifications have been created based on the various imaging techniques such as x-ray, magnetic resonance imaging or MRI, computed tomography or CT scans as well as arthroscopic evaluation.

The x-ray classification system that is classically used and referenced is the Berndt and Harty classification system from their 1959 article. That breaks down Osteochondral lesions into 4 categories. In this classification system a stage 1 lesion is a small area of subchondral compression on the talar dome cartilage, a stage 2 lesion is a partial fragment detachment or partial fracture with a portion still attached to surrounding cartilage, a stage 3 lesion is a complete fragment detachment that is not displaced, and a stage 4 lesion is a complete fragment that is displaced (21). This classification system had a stage 5 added in 2001 by Scranton and McDermott that is a subchondral cyst (Scrantong et al).

Hepple et al and Anderson et al both came up with MRI classification systems. The Hepple MRI classification has 6 stages; stage 1 is simply articular cartilage edema, stage 2a is cartilage injury with underlying fracture and surrounding bony edema, stage 2b is the same as 2a except without the surrounding bone edema, stage 3 is a detached non displaced fragment, stage 4 is a displaced fragment, and stage 5 is a subchondral cyst (21). The Anderson MRI classification system has 5 stages; stage 1 consists of bone marrow edema, stage 2a is a subchondral cyst, stage 2b is an incomplete separation of the osteochondral fragment, stage 3 has fluid around an undetached fragment, and stage 4 is a displaced osteochondral fragment.

Ferkel and Spangione developed a computed tomography classification for OLT lesions that consists of 5 stages. Stage 1 is a cystic lesion within the dome of the talus with an intact roof on all views, stage 2a is a cystic lesion communicating to the talar dome surface, stage 2b is an open articular surface lesion with overlying nondisplaced fragment, stage 3 lesions are a displaced lesion with lucency, and stage 4 is a displaced fragment.

An arthroscopy classification system was developed in 1995 by Cheng and Ferkel that consisted of 6 grades based on the status of the articular cartilage during arthroscopy. In grade A the talar cartilage is smooth and intact, but soft. Grade B has a rough surface, grade C has fissures in the cartilage, grade D has a flap or exposed bone, Grade E has loose and non displaced fragment, and Grade F is a displace fragment (21).

Clinical Presentation

Patients presenting with OLT's report various subjective and objective findings that are not specific for OLT's, but give a better clue that a lesions may be present. Subjective complaints include pain to the ankle that can feel deep within the joint, swelling to the ankle joint, ankle joint stiffness, and the feeling of "catching." Objective complaints include pain with palpation to the ankle joint and the ankle gutters, effusions, decreased ankle joint range of motion, and pain with inversion, dorsiflexion or plantarflexion (21)

Conservative Treatment

Conservative options for OLT's include non-weight bearing, bracing, orthotics, casting, and non-steroidal anti-inflammatory drugs.

A study by Klammer evaluated 48 patients who were all treated with nonoperative treatment options. These patients were followed for 2 years and improvement based on patient questionnaires, x-rays, and MRI assessment. At the end 43 out of 50 ankles had no pain at the end of the 2 year study. On x-ray no OLT showed progressive worsening. On MRI 84% were unchanged, 12% had progression to osteoarthritis, and 4% had improved. From their results, non-operative treatment options are a viable option for OLT's (14).

Another article by Tol et al did a systematic review of treatment options for OLT's. They reviewed 32 studies from 1966-1998 and looked at success rates based on excellent/good results based on patient's reports. Non-operative treatment options included rest and restriction of activities of ankle, NSAIDs, or cast immobilization for 3-4 weeks. Surgical options included arthroscopic surgery and open techniques that include excision, excision and curettage, or microfracture drilling. In the article they found out of the 32 studies there was only a 45% success rate of all studies that looked at non-operative treatments compared surgical treatment success rates of 41% with open excision, 59% with open excision and curettage, and 83% with open microfracture drilling (27).

Surgical Treatment

There are multiple surgical options for repairing OLT's that involve open and arthroscopic techniques. Options include excision, excision and curettage, abrasion, microfracture drilling, retrograde drilling, transmalleolar drilling, OATS or osteochondral autograft transfer system, allografts, and ACI or autologous chondrocyte implantation

Arthroscopic Treatment

For arthroscopic surgical treatment of OLT's, the general consensus for which lesions should have arthroscopic intervention are failed stage I, II, and III medial lesions as well as all stage III lateral lesions and stage 4 lesions (21). A study by McGahan showed that OLT's that are between 0.25 cm and 4 cm have the best results with arthroscopic surgical management and the rest should be open (20). Several other studies also recommend arthroscopic surgery for OLT's if the lesions are under a diameter or 1.5 cm^2 and an area of 150 mm^2 (4,6).

A study by Ferkel et al reviewed 50 patients with an average of 71 months who were surgically treated with drilling only, excision and abrasion, or excision and drilling. Each patient had an x-ray and a MRI or CT evaluation pre operatively to evaluate the OLT's. They concluded that there was a 72% excellent or good results with these procedures and overall the AOFAS scores were 84 and Weber scores were 78. From this article they developed the arthroscopic grade system for OLT.s. They were unable to correlate pre-operative imaging staging with post operative success. They did, however, find that arthroscopic evaluation findings with worse lesions as defined by their own grading system, the worse Weber and AOFAS scores post-operatively (10).

Another study by Schuman et al, reviewed 38 patients for an average of 4.8 years who all underwent arthroscopic curettage and microdrilling. 22 patients had no prior surgeries and 16 had failed a previous treatment. They found 86% good results in patients who had previously not had surgery and only 75% in the revisional groups. In the end, the authors recommended arthroscopic curettage and microdrilling as primary and revisional surgery for OLT's (25).

A level III retrospective study by Goh et al reviewed 61 patients who underwent arthroscopic chondroplasty, loose body removal, and microfracture. Patients were included in the study if they had unilateral lesions, lesions less than 2 cm, no ankle instability, and no history of ankle surgery or ankle trauma. Follow up only was pre operatively, at 6 months and 12 months. They found AOFAS scores went from 53 preoperatively, 77.8 at 6 months, and 83.1 at 12 months. Overall 74% of patients were satisfied with surgery at 12 months. They concluded that arthroscopic treatment of ankle joint OLT's was successful in the right surgical candidate (12).

Retrograde and Transmalleolar Drilling

Retrograde drilling and transmalleolar drilling of OLT's are an option for surgical treatment. Retrograde drilling involved drilling through the talus without entering the ankle joint. These options are great for subchondral bone without overlying injury to the cartilage. Typically done laterally and either posteriorly or anteriorly through the talus. One must avoid the sural nerve through the posterior lateral portal and the anterior talofibular ligament and the mechanoreceptors through the anterolateral portal. Transmalleolar drilling is done via a kirschner wire through the medial malleolus to reach the OLT. The use of an Arthroscope is utilized through an anterolateral portal to visualize the kirschner wire. It is important to note that this technique can damage the tibial articular cartilage with insertion of the kirschner wire and also that a previously undetached OLT can become detached.

Both techniques were compared in a study by Kono et al where a total of 30 patients were reviewed with ankle pain. All patients underwent MRI and arthroscopic evaluation to determine extent of the OLT. 11 of the patients underwent retrograde drilling and 19 patients underwent transmalleolar drilling and average follow up was 24-49 months. At 1 year a repeat arthroscopic evaluation was performed to determine amount of deterioration of cartilage after each procedure was performed and no patients had signs of deterioration in either group. There was also no difference between AOFAS scores between either the retrograde or transmalleolar drilling groups (15).

Osteochondral Autograft Transfer System (O.A.T.S.)

This technique is a procedure for OLT's that are larger lesions or have failed previous conservative and surgical treatments (32). This procedure requires removing a cartilage graft from another source on the patient's body and transferring the graft to the area of the lesion on the talus. The source of the donor site is usually from the ipsilateral knee (intercondylar notch, or medial/lateral femoral condyle), but can be from or talus (anterior, medial or lateral facet)(20). An article by McGahan et al showed that there is a donor site morbidity of 0-55% after the graft is removed from that site (20). It is important to note that when removing the graft from the donor site and applying the donor site that the graft must be taken and placed at perpendicular to articular surface.

Woefle et al published a level 4 study on 32 patients who underwent an OATS procedure with an average follow up of 29 months. All donor grafts were harvested from the ipsilateral lateral femoral condyle. Grafts varied in size based on the size of the lesions on the talus, which included ten 6 mm grafts, thirty six 8 mm grafts, and one 10 mm graft. They found no difference with results based on graft size. They had an overall AOFAS score of 86 and a HSS Patella score of 95. They found no difference in patients who had previous surgery, received more than 1 graft, had a body mass index (BMI) greater than 25, history of ankle arthritis, or whether the lesions was medially or laterally located. They did find a decreased HSS patella score in patients over 40 for ipsilateral knee pain (31).

A study by Yoon et al did a retrospective study looking at 22 patients who underwent an OATS procedure versus 22 patients who underwent a repeat arthroscopic procedure either by excision and drilling or by abrasion. All 44 patients had previously undergone a failed arthroscopic marrow stimulation. The results showed that after 6 months there was no difference in terms of AOFAS scores at 6 months where the OATS procedure was 82.8 and arthroscopic surgery was 83.7. However there was an improvement in the OATS procedure at 12 months of 85.3 compared to arthroscopy, which showed worse results at 69.6. Patients also reported more good and excellent results in the OATS group, 18 of 22, compared to arthroscopic group where only 7 of 22 patients reported good or excellent results. They also reported that no patients in the OATS groups required revisional surgery, where 14 of 22 in the arthroscopic group required a revisional surgery (32).

An article by Lee et al looked at multiple osteochondral autografts or mosaicplasty in 18 patients who had Berndt Harty stage III and IV lesions. They used a medial malleolar osteotomy and at least 2 to 3 osteochondral grafts. All patients had an arthroscopic evaluation between 12 and 18 months. They found that 16 had excellent functional results and 2 had good functional results and 16 of 18 had cartilage had cartilage consistent with normal talar cartilage. They concluded that multiple autografts is a good procedure with 87.5% of grafts had consistency of normal talar cartilage (17).

A level 1 prospective randomized study comparing chondroplasty, microfracture drilling, and the OATS procedure with 11, 9 (10 ankles) and 12 patients in each of the respective groups. They followed up patients on average of 53 months and looked at various scoring systems as well as post op MRI's. They concluded that microfracture and OATS had better results with smaller lesions and chondroplasty had mixed results. They saw no difference in long term function and pain comparing each of the 3 procedures. Their recommendations based on these results are to 1). Start with arthroscopy first and then follow with the OATS procedure (11).

Allograft Transplantation

Allograft transplantation is similar to OATS except using chondrocytes from another human donor source. In an article by Williams et al, they recommend harvesting graft from the donor's site within 24 hours of death and implanted ideally within a week, usually 14-21 days(29). At 14 days, chondrocytes viability decreases by 1.7% and at 28 days it decreases at 28.5% (30)

The indications for using allografts in the ankle joint are large osteochondral defects greater than 2 cm^2 and 6-10 mm deep, poor shoulder lesions, failure of other regenerative techniques, partial degenerative disease, severe ankle arthritis. Contraindications include serious joint deformity or anatomy disruption, ligamentous instability and malalignment of the limb, and inflammatory disease, vascular pathologies, and severe neurologic disorders (29).

It is important to note that allografts are generally not matched to human leukocyte antigen or blood type of the donor and the recipient because acellular cartilage matrix is believed to protect chondrocytes from host immune surveillance (29). Vannini did a systematic review and found that allograft transplantation is increasing in popularity and the results from the 13 articles they reviewed had good results, but most have short term follow up, small number of patients in the study and low evidence are all a problem and more studies are needed with more patients and longer follow up (29).

Raiken et al had 15 patients with average lesion volume of 6059 mm^3 and all underwent allograft transplantation. The average AOFAS score improved from 38 preoperatively to 83 post operatively and pain decreased from 8.5 to a 3.3. They concluded that fresh osteochondral allograft is viable (9). El Rashidy et al performed osteochondral allograft transfer in 38 patients with an average size lesion of

1.5 cm^2. Patients in the study had their pain improve from a 8.2 to a 3.3, and AOFAS scores improve from 53 to 79. MRI follow up also was done and showed that graft incorporation was good in all but 4 of the patients. They concluded that allograft is a viable option (9).

Autologous Chondrocyte Implantation (A.C.I)

ACI is a new procedure for OLT's that requires 2 surgeries. The first surgery requires harvesting hyaline cartilage from the patient's talus or femoral condyle. The chondrocytes are then harvested and cultured in a lab and then approximately 3 weeks later the harvested and cultured chondrocytes are re-implanted into the OLT, and then fixated to the periosteum of the tibia (20). McGahan et al reviewed six level 4 studies that dealt with lesions between 0.5 cm and 6.25 cm who underwent ACI. They found an average return to normal activity of 8-12 months and average AOFAS scores of 88.4-90.5 after the procedure was performed. Overall 82-92% of patients reported excellent or good results (20).

Conclusion

Osteochondral lesions of the talus are a cause of ankle pain in many patients. The treatment options for these lesions are expanding and more studies need to be developed for the new methods of surgical treatment. Even those these injuries are only 0.09% of all fractures, these injuries need to ruled out because these injuries can be debilitating for patients.

References

1. Al-Shaikh, Raad "Autologous osteochondral grafting for talar cartilage defects." *Foot & ankle international* 23.5 (2002): 381-389.

2. Baltzer, Axel WA, and Juergen P. Arnold. "Bone-cartilage transplantation from the ipsilateral knee for chondral lesions of the talus." *Arthroscopy: the journal of arthroscopic & related surgery* 21.2 (2005): 159-166.

3. Berlet, Gregory C., et al. "Does fresh osteochondral allograft transplantation of talar osteochondral defects improve function?." *Clinical Orthopaedics and Related Research®* 469.8 (2011): 2356-2366

4. Choi WJ, Park KK, Kim BS, Lee JW. Osteochondral lesion of the talus: is there a critical defect size for poor outcome? Am J Sports Med. 2009;37(10):1974-1980.

5. Chuckpaiwong B, Berkson EM, Theodore GH. Microfracture for osteochondral lesions of the ankle: outcome analysis and outcome predictors of 105 cases. Arthroscopy. 2008; 24(1):106-112

6. Cuttica DJ, Smith WB, Hyer CF, Philbin TM, Berlet GC. Osteochondral lesions of the talus: predictors of clinical outcome. Foot Ankle Int. 2011; 32(11):1045-1051.

7. Dixon A, Morgan M. "Talus" Radiopaedia.org.

8. Easley, Mark E., and Pierce E. Scranton Jr. "Osteochondral autologous transfer system." *Foot and ankle clinics* 8.2 (2003): 275-290.

9. El-Rashidy, Hany, et al. "Fresh osteochondral allograft for the treatment of cartilage defects of the talus: a retrospective review." *The Journal of Bone & Joint Surgery* 93.17 (2011): 1634-1640.

10. Ferkel, Richard D., et al. "Arthroscopic Treatment of Chronic Osteochondral Lesions of the Talus Long-term Results." *The American Journal of Sports Medicine* 36.9 (2008): 1750-1762.

11. Gobbi, Alberto, et al. "Osteochondral lesions of the talus: randomized controlled trial comparing chondroplasty, microfracture, and osteochondral autograft transplantation." *Arthroscopy: The Journal of Arthroscopic & Related Surgery*22.10 (2006): 1085-1092.

12. Goh, Graham Seow Hng, Hamid Rahmatullah Bin Abd Razak, and Amit Kanta Mitra. "Outcomes Are Favorable After Arthroscopic Treatment of Osteochondritis Dissecans of the Talus." *The Journal of Foot and Ankle Surgery*54.1 (2015): 57-60.
13. Hembree, Walter C., et al. "Magnetic resonance imaging features of osteochondral lesions of the talus." *Foot & ankle international* 33.7 (2012): 591-597.
14. Klammer, Georg, et al. "Natural history of nonoperatively treated osteochondral lesions of the talus." *Foot & ankle international* (2014): 1071100714552480.
15. Kono, Michihaya, et al. "Retrograde drilling for osteochondral lesions of the talar dome." *The American journal of sports medicine* 34.9 (2006): 1450-1456.
16. Kwak, Steve K., et al. "Autologous Chondrocyte Implantation of the Ankle 2-to 10-Year Results." *The American journal of sports medicine* 42.9 (2014): 2156-2164.
17. Lee, Chian-Her, et al. "Osteochondral autografts for osteochondritis dissecans of the talus." *Foot & ankle international* 24.11 (2003): 815-822.
18. Leontaritis, Nikoletta, Lauren Hinojosa, and Vinod K. Panchbhavi. "Arthroscopically detected intra-articular lesions associated with acute ankle fractures." *The Journal of Bone & Joint Surgery* 91.2 (2009): 333-339.
19. Medscape: http://emedicine.medscape.com/article/1237723-overview
20. McGahan, Patrick J., and Stephen J. Pinney. "Current concept review: osteochondral lesions of the talus." *Foot & ankle international* 31.1 (2010): 90-101.
21. Mcglamry, E. Dalton. *Comprehensive textbook of foot surgery*. Vol. 1, 4th Edition. Williams & Wilkins, 1987.
22. Millington, S. A., et al. "Quantification of ankle articular cartilage topography and thickness using a high resolution stereophotography system." *Osteoarthritis and cartilage* 15.2 (2007): 205-211.
23. Raikin, Steven M. "Fresh osteochondral allografts for large-volume cystic osteochondral defects of the talus." *The Journal of Bone & Joint Surgery* 91.12 (2009): 2818-2826.
24. Raikin, Steven M., et al. "Osteochondral lesions of the talus: localization and morphologic data from 424 patients using a novel anatomical grid scheme." *Foot & Ankle International* 28.2 (2007): 154-161.
25. Schuman, L., P. A. A. Struijs, and C. N. Van Dijk. "Arthroscopic treatment for osteochondral defects of the talus RESULTS AT FOLLOW-UP AT 2 TO 11 YEARS." *Journal of Bone & Joint Surgery, British Volume* 84.3 (2002): 364-368
26. Southerland, Joe T., et al. *McGlamry's comprehensive textbook of foot and ankle surgery*. Lippincott Williams & Wilkins, 2012
27. Tol, J. L., et al. "Treatment strategies in osteochondral defects of the talar dome: a systematic review." *Foot & ankle international* 21.2 (2000): 119-126.
28. Trueta, J. "The blood supply of the talus." (1970).
29. Vannini, Francesca, et al. "Osteochondral Allografts in the Ankle Joint State of the Art." *Cartilage* 4.3 (2013): 204-213
30. Williams SK, Amiel D, Ball ST, Allen RT, Wong VW, Chen AC, et al. prolonged storage efforts on the articular cartilage of fresh human osteochondral allografts. J Bone Joint Surg Am. 2003; 85 (11) 2111-20
31. Woelfle, Julia V., H. Reichel, and M. Nelitz. "Indications and limitations of osteochondral autologous transplantation in osteochondritis dissecans of the talus." *Knee Surgery, Sports Traumatology, Arthroscopy* 21.8 (2013): 1925-1930.
32. Yoon, Hang Seob, et al. "Osteochondral autologous transplantation is superior to repeat arthroscopy for the treatment of osteochondral lesions of the talus after failed primary arthroscopic treatment." *The American journal of sports medicine* 42.8 (2014): 1896-1903.