Case History

A 72 year old male was referred to the Musculoskeletal diagnostic service by his general practitioner (GP) with right knee pain progressing over 20 years which had worsened over the last 6 month. He had pain while walking and during activities of daily living and occasionally at night as well as it preventing him playing golf and tennis for the last month. He reported 5/10 pain which worsened with activity and reported stiffness but no locking or giving way and had no major knee injuries in the past. He had previously received physiotherapy but had not engaged fully due to pain and this did not improve with paracetamol. His x-ray demonstrated moderate tricompartmental osteoarthritis (OA) with joint space narrowing and osteophytes. He was otherwise fit and well with no drug allergies.

He walked with an antalgic gait, had poor control on double leg and was unable to do a single leg squat due to the pain. He had reduced strength on single leg raise and had a range of motion between 0-130 degrees but exacerbation of pain at end range flexion and extension and some tenderness across the medial and lateral joint lines. A sweep test revealed an effusion and hip, and ankle screen were unremarkable. Ultrasound scan demonstrated an effusion in the suprapatellar recess (Fig 1&2) with some osteophytic changes of the medial and lateral joint lines and medial meniscal extrusion.

This presentation was in keeping with knee OA. A differential would include referred pain from hip OA.

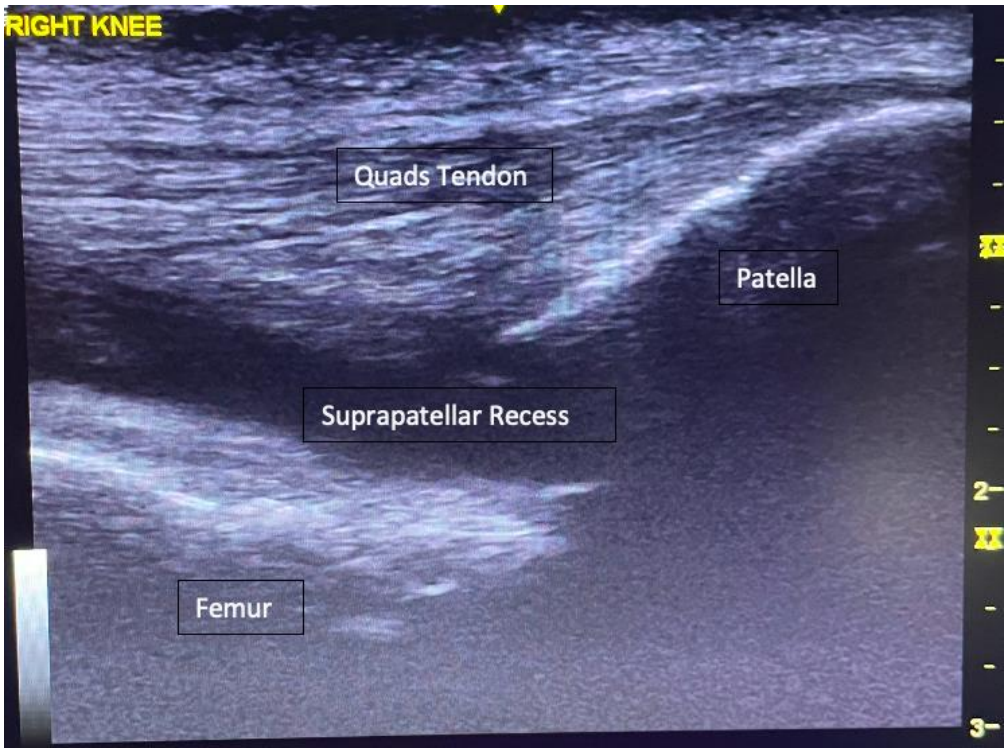

Figure.1-Sagittal ultrasound Image demonstrating an effusion within the suprapatellar recess.

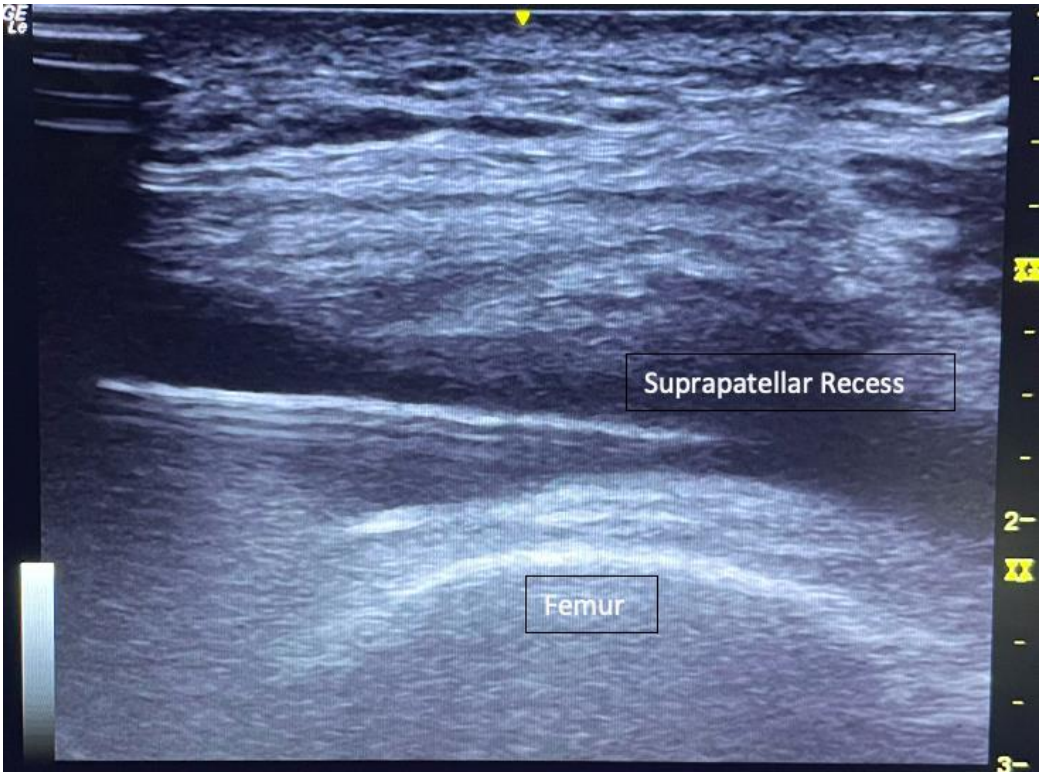

Figure.2-Transverse ultrasound demonstrating needle placement in the suprapatellar recess.

We discussed management options including physiotherapy, maximising analgesia, and surgery. However, he didn't want to take further tablets and was not keen on surgery and did not meet the referral criteria for this, so we agreed to trial an intraarticular corticosteroid injection (IA-CS) with local anaesthetic (LA) to provide some symptomatic relief and a window to engage with physiotherapy.

He provided informed consent as outlined below and was advised he might get some pain relief in the first few hours from the local anaesthetic (LA) and that the steroid would work over the next one to three weeks and the effect could be variable, but we hoped for three months or longer of symptom relief to provide opportunity for rehabilitation. He was advised to avoid strenuous activities over the next 48 hours and monitor for signs of infection including a more painful, red, swollen joint or developing a temperature and to seek medical attention should this happen. He was followed up four weeks post procedure.

Role of ultrasound in the diagnosis of Knee OA

OA can be diagnosed clinically if the presentation is typical which would include someone $\geq$ 45 with activity related pain, morning stiffness < 30 mins, crepitus, and bony enlargement, however imaging can be useful when the diagnosis is uncertain (1).

Conventional radiography is the most common form of imaging to aid diagnose and grade OA however other imaging modalities may be beneficial (Fig.3).

Imaging modality	Advantages	Disadvantages
X-ray	Low cost, reference technique Short testing time Wide equipment availability Screening or baseline assessment	Radiation Limitations in imaging soft tissue and subchondral structures
MRI	Sensitive Non-invasive technique No radiation burden 3D sectional imaging technique High spatial resolution Excellent soft tissue contrast High accuracy and reliability	High cost and low availability Scanning time can be prolonged Not dynamic Contraindicated in patients with implanted devices
US	Safety, non-invasiveness No radiation burden Low cost Absence of contraindications High temporal resolution Repeatability over the time Wide equipment availability Bedside procedure Optimal patient acceptance Real-time imaging with short acquisition time US-guided procedures	Limited number and width of acoustic windows Low contrast and strong boundary effects Operator dependency Long learning curve Lack of standardized definitions and scoring systems for findings

Figure.3-Advantages and disadvantages of different imaging modalities for OA (2).

Advantages of ultrasound include no side effects and dynamic scanning for multiple body regions in one sitting. Disadvantages include only tissues superficial to bone can be visualised and its operator dependant (2).

In knee OA US adds diagnostic information over radiographs in its ability to sensitively identify synovitis and effusions and visualise changes in the cartilage and meniscus – albeit only areas superficial not blocked by bone (3).

When compared to radiographs ultrasound has been shown to perform better or equally in the identification of tibiofemoral osteophytes, medial meniscal extrusion, and medial femoral cartilage morphological degeneration (4). Specifically medical meniscal extrusion is an important predictor of other structural damage and the likely progression of joint degeneration (3). Ultrasound identified medial meniscal extrusion, effusions and bakers' cysts correlate well with clinical and radiographic diagnosis (5,6).

Role of intra-articular injection therapy in Knee OA

A systematic review of 27 clinical practice guidelines concluded that IA-CS and Intra-articular Hyaluronic acid (IA-HA) are favoured within the knee OA treatment paradigm, while Intra-articular Platelet Rich Plasma (IA-PRP) currently has insufficient evidence to make a conclusive recommendation (7). NICE guidelines do not recommend IA-HA due to a lack of current evidence and make no mention of IA-PRP but do suggest IA-CS as an adjunct to core treatments for relief of moderate to severe pain in people with OA, generally for short term relief (1).

IA-HA

Hyaluronic acid (HA) is a high molecular weight polysaccharide and is an important component of synovial fluid and articular cartilage. It can lubricate joints, reduce pain, form a proteoglycan polymer and inhibit its precipitation from the cartilage matrix thereby reducing cartilage matrix loss and slowing joint degeneration (8).

IA-PRP

Platelet rich plasma (PRP) is obtained from autologous blood concentrated by aphereisis or centrifugation (9). Activation of the platelet concentrate induces the release of mediators (Granular secretion), including growth factors and soluble anti-inflammatory mediators like interleukin

receptor antagonists (IL-1) which appears to have a homeostatic, anabolic and anti-inflammatory impact on joint tissues and cells (9). A recent consensus statement recommended it as an effective treatment especially in early or moderate OA, although they recognise the low level of current evidence (9).

IA-CS

Corticosteroids (CS) work by producing anti-inflammatory, chondroprotective and analgesic effects through mechanisms including synovial blood flow reduction, synovial fluid composition alteration, gene suppression of leukocytes, protease and cytokine production and changes in collagen synthesis (10).

As stated, IA-CS are the only injectable recommended by NICE. Other guidelines including the American College of Rheumatology, the Osteoarthritis Research Society International and the French Society for rheumatology also support their use in knee OA (11). A recent meta-analysis demonstrated a medium effect of IA-CS on both pain and function in the short term (<6 weeks) (11). In the long-term the controls, especially physiotherapy, had a significantly better effect on function compared to IA-CS (11). This indicates the importance of seeing steroid injection as an adjunct to help manage acute pain and the importance of using physiotherapy alongside it or on its own.

A recent systematic review comparing IA-PRP, IA-HA and IA-CS demonstrated improvements in pain and function with all three at a minimum of 6 months follow up, however IA-PRP follow by IA-HA appeared to have the greatest effect over IA-CS (Fig.4). This evolving evidence perhaps suggests injectables other than IA-CS may have superior benefit in the longer term (12).

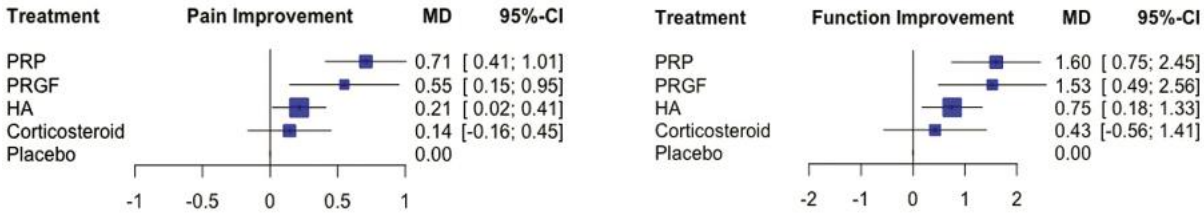

Figure.4– Forest plots demonstrating the mean difference (MD) and 9% Confidence Intervals (CI) in clinically significant pain and functional improvements for different treatments relative to placebo for knee OA, HA-hyaluronic acid, PRGF-plasma rich in growth factors, PRP-platelet rich plasma (12)

Stem Cells

Another area of research in recent years is Mesenchymal Stem Cells. Bone Marrow Mesenchymal Stem Cells from bone and cartilage tissue are considered the gold standard and It is believed these cells migrate from subcondral bone to areas of damage and differentiate into chondrocytes and osteoblasts integrating into new and surrounding tissues, thereby, it is thought, playing an important role in the repair of bone and cartilage (8). Stromal Vascular Fraction (SVF) found in adipose tissue and adipose mesenchymal stem cells are other potential sources that it is suggested provide stem cells that can differentiate into chondrocytes and may tolerate ischaemia and hypoxia found in articular cartilage (8). The evidence for these is mixed but some studies suggest that stem cells especially from SVF may be of benefit in OA Knee with significant improvements at 12 months follow up (13), however more research is needed.

Ultrasound Guided Injections (USGIs) V.S. Landmark Guided Injections (LMGIs)

A review demonstrated USGIs to be more accurate regardless of body location than LMGIs and were more efficacious in the glenohumeral joint, the subacromial space, the biceps tendon sheath and the joints of the hand, wrist, knee, ankle and foot. However improved outcomes were not demonstrated in the elbow, ACJ and hip joint (14).

A recent systematic review of randomised control trials (RCTs) of 1315 knees demonstrated that injections across every anatomical location were more accurate with ultrasound guidance with > 95% accuracy with all ultrasound guidance approaches compared to a range of 77.3 % and 95.74% for a landmark approach (15). Interestingly the most accurate landmark guided method was using an isometric quadriceps contraction with a superolateral approach (15).

A study using cadaveric injections demonstrated that LMGIs were between 55% and 100% accurate but were injector dependant compared to USGIs which were 100% accurate regardless of injector (16).

A systematic review looking at outcome data for USGIs compared to LMGIs looked at 715 patients (725 knee joints) and found a statistically significant reduction in pain with USGI compared to the LMGI group (2.24 greater reduction on the visual analogue scale (VAS) 2 weeks post injection) as well as an increased aspiration volume, and that the procedure was less painful (17).

Overall there appears to be good evidence for the use of ultrasound guidance in injection therapy for knee OA in terms of accuracy, clinical outcome, and procedural pain. Furthermore, the Position statement of the American Medical Society for Sports Medicine (AMSSM) suggests there is strong evidence that USGIs are more accurate and reported moderate evidence that they are more efficacious (18). There is preliminary evidence they are more cost effective than LMGIs (18).

Safety and medico-legal considerations

Informed consent as undertaken in this case is key to undertaking the procedure, this involved providing procedural information being sent prior to the appointment as well as during the appointment and the patient understanding the drug mode of action, potential risks and benefits and the likely experience during and post procedure. Alternative treatments were also considered as well as potential contraindications (Fig.5) and consideration given to any past medical history or drug and allergy history, including in diabetics, pregnancy and patients taking blood thinning medication, antiretrovirals. He was also assessed to have capacity to consent to the procedure.

a)
Indications
Inflammatory arthropathy
Degenerative arthropathy
Soft tissue/bursal inflammation
Transforaminal/epidural
b)
Absolute contraindication
Local or intra-articular sepsis
Broken skin or at site of injection
Fracture or joint instability
Allergy to constituents of injectate
Joint destruction
Unstable coagulopathy
Relative contraindication
Prosthetic joint
Sever juxta-articular osteoporosis
Injection three times within the preceding year or less than 2 weeks

Figure 5. Common indications (2a) and contraindications (2b) for corticosteroid injection (10)

It is important to consider and inform the patient of the possible deleterious effects of the drugs being used. It has been suggested that commonly used LAs (Lidocaine and bupivacaine) can cause chondrotoxicity and subsequent breakdown of articular cartilage (19,20,21), however there is a lack of RCTs and in vitro studies with the majority of evidence being in vivo observational with chrondrotoxity typically seen with higher concentrations and / or adrenaline (22). Therefore, currently there is no convincing clinical or in vivo evidence to contraindicate the use of LA in injections (10).

Lidocaine 1% has rapid onset and duration of action of 1-2 hours compared to bupivacaine 0.25% which has slower onset but can last 3-6 hours (23). Caution in patients with cardiovascular, liver, and renal disease is key as there may be minimal systemic absorption. (24)

Steroid arthropathy
Research reports possible radiographic progression of joint arthropathy with animal studies demonstrating chondrotoxic effect on cartilage with repeated injections (10). It has been hypothesised that proteolytic enzymes produced due to corticosteroid-induced synovitis could be the cause. This has not been clinically supported and it has also been suggested the anti-inflammatory effect of steroid may be protective (25).

Septic arthritis
This is a rare but catastrophic side effect it is important to inform patients about. Frequency ranges from 1:3000 to 1:100,000 (26,27). An aseptic technique and atraumatic procedure reduce infection risk and due to the potential immunosuppressive effects of steroids patients on antibiotics or with active infection should not have an injection (10).

Systemic effects
Facial flushing occurs in less than 1% of people and is more common with triamcinolone acenotide (Kenalog) and general requires no intervention (26). Vasovagals can also occur due to steroid systemic absorption and patient anxiety. In clinical practice up to 80 mg of steroid can be given without undue side effects. Over 50 mg of Kenalog has been demonstrated to reduce blood cortisol levels suggesting suppression of the hypothalamic axis (25). Hyperglycaemia may be induced by steroid injection and may last up to 3 weeks, so diabetic patients should be advised to monitor their blood sugars. USGIs can help ensure correct needle placement reducing systemic absorption.

Cutaneous effects
These are reported as less than 1% but can include subcutaneous tissue atrophy, hypopigmentation, and fat necrosis (25). These changes may be irreversible and are greater with Kenalog compared to methylprednisolone acetate (Depo-Medrone) potentially make the later more appropriate for superficial injections.

Steroid flare
This is a self-limiting steroid induced synovitis which presents with pain and swelling, and usually lasts less than 48 hours and is reported to occur in between 1-10% of cases (10).

Other side effects noted include joint capsule calcification, tendon rupture, allergy to drug additives, osteonecrosis causing joint destruction and hiccoughs (10).

Injections during pregnancy and breast feeding need to be considered carefully with informed consent received and the risks and benefits to mother and child clearly explained. Although corticosteroid have been found in small amounts in breast milk the small amount of systemic absorption from an intraarticular injection and small amount of infant gut absorption means no

significant impact on the hypothalamic-pituitary-adrenal axis. However, cases have been documented of lactation suppression after use of Kenalog (28,29).

Corticosteroids are a substrate of the CYP3A4 enzymes which is targeted and blocked by multiple drugs. It is therefore important to consider medications with caution as they may result in high levels of steroids and potential Cushing's syndrome and adrenal suppression (10). Furthermore, corticosteroids may induce the metabolism of protease inhibitors used in HIV treatment thus reducing plasma concentration, a good resource to check this is the Liverpool drug checker (30).

Steroid selection

There are multiple different corticosteroids injected, including triamcinolone acenotide (Kenalog-40), methylprednisolone acetate (Depo-Medrone), and dexamethasone. Microcrystalline agents such as Depo-Medrone and Kenalog stay in the injection site longer resulting in longer therapeutic duration, reported up to 21.1 days with Kenalog, the least soluble steroid (10). More soluble steroids can be rapidly reabsorbed.

Table 3
Our proposed guideline on the steroid preparation and the dose to select based on generic anatomical locations

Location	Dexamethasone (mg)	Depo-Medrone (mg)	Triamcinolone (mg)
Small joints			
Hand	-	10–20	
Wrist	-	40	
Elbow	-	40	
Acromioclavicular	-	20–40	
Sternoclavicular	-	20–40	
Fore and midfoot	-	20–40	
Large joints			
Glenohumeral	-	-	40
Hip	-	-	40
Knee	-	-	40
Tibiotalar	-	-	40
Subtalar	-	-	40
Superficial bursa/soft tissue	-	20–40	
Deep bursa/soft tissue	-	-	40
Tendons-superficial	-	40	
Tendons-deep			40
Transforaminal			
Cervical	4	-	
Lumbosacral	4	-	

Figure 6. Demonstrating usual type and location of steroid used for different body regions (10).

In terms of selection of corticosteroid type and dose it is important to consider trust policy body location and balance side effect profile and likely therapeutic benefit, figure 6 demonstrates suggested doses and types based on location. As such in this case I opted to use 40 mg of Kenalog with 4ml of 1% lidocaine.

USGI technique

I assessed the knee both clinically and using ultrasound prior to the procedure. For the ultrasound I used the "MSK Knee" pre-set and used a linear probe 14L5 with a frequency of 5-14 MHz. I adjusted the frequency, depth, gain and focus to best visualise the suprapatellar synovial recess just inferior to the quadriceps tendon and the synovial fluid which was compressible within it lying between the prefemoral fat pad and suprapatellar fatpad (Fig.7).

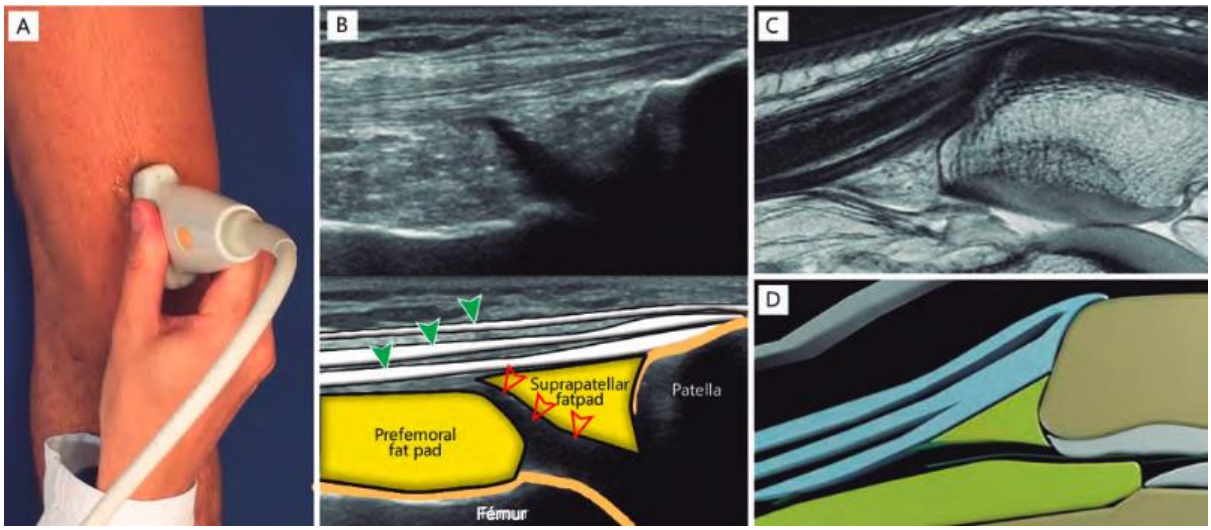

Figure.7-Demonstrating anatomy of the superior knee to identify the suprapatellar recess and location for injection (31).

After this an initial ultrasound was undertaken to visualise structures and identify the best approach for an injection and a sterile field was set up. Following this 1 ml of Kenalog 40 mg was drawn up with 4 mi of 1 % Lidocaine into a 5 ml luerlock syringe. A 21G 11/2 inch green needle was used. The technique was undertaken as follows.

1) Skin around the knee cleaned using chlorhexidine.
2) A sterile probe cover was placed over the probe which has ultrasound gel on it and then dipped into chlorhexidine solution.
3) Due to the effusion seen in the knee this was identified as the target and the probe was positioned in a superolateral position to the knee in a transverse plan to the femur.
4) The needle was inserted using an in-plane approach to access the suprapatellar recess.
5) The steroid and local were injected ensuring the flow was free and I could visualise the needle tip.
6) The needle was removed and the plaster was applied after ensuring no allergies and post procedure advice and a contact number were given to the patient.

In my practice I have found the superolateral approach much easier if there is fluid in the suprapatellar recess with the option for a medial patellar approach in a knee without an effusion, as well as the use of a two-syringe technique using local anaesthetic in the first syringe to create a suprapatellar effusion should there not already be one.

Outcome data

The VAS was used to assess pain and demonstrated an improvement of 6.8 to 1.1 four weeks post injection. He also completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) which is an extension of the WOMAC index for osteoarthritis and assess 5 areas, symptoms & stiffness, pain, function - daily living, function – sports and recreational activities, quality of life and provides a percentage for each section and an overall percentage with 0 representing extreme problems and 100 representing no problems. The overall improvement was 37.4% four weeks post injection indicating a significant improvement overall knee function as the minimal detectable change required being $\geq$ 20 (32).

Key learning points

- Knee OA can be diagnosed clinically without imaging if a typical presentation, but ultrasound can be useful to identify specific soft tissue pathology, effusions and synovitis using doppler.
- The importance of a full clinical assessment including considering PMH, allergies and drug history to ensure there is an appropriate indication for injection therapy and risks and contraindications have been considered.
- NICE suggests CSI may be used as an adjunct for knee OA. Currently they do not recommend other injections such as hyaluronic acid and PRP although recent systematic reviews suggest both, especially PRP, may be of benefit in selected patients.
- USGIs for knee OA appear to be more accurate, more effective, have less procedural pain and may be more cost effective than LMGIs
- It is key to consider the appropriate approach for each patient with the identification of the suprapatellar recess being good, often there is an effusion.

Word count (excluding references) = 2992

References

1) National Institute for Health and Care Excellence. Osteoarthritis: care and management. CG177. London: National Institute for Health and Care Excellence, 2014.
2) Wang X, Oo WM, Linklater JM. What is the role of imaging in the clinical diagnosis of osteoarthritis and disease management? Rheumatology (Oxford). 2018 May 1;57(suppl_4):iv51-iv60. doi: 10.1093/rheumatology/kex501. PMID: 29351654.
3) Roemer FW, Demehri S, Omoumi P, Link TM, Kijowski R, Saarakkala S, Crema MD, Guermazi A. State of the Art: Imaging of Osteoarthritis-Revisited 2020. Radiology. 2020 Jul;296(1):5-21. doi: 10.1148/radiol.2020192498. Epub 2020 May 19. PMID: 32427556.
4) Podlipska J, Guermazi A, Lehenkari P et al. Comparison of diagnostic performance of semi-quantitative knee ultra- sound and knee radiography with MRI: Oulu Knee Osteoarthritis Study. Sci Rep 2016;6:22365.
5) Malas FU, Kara M, Kaymak B, Akinci A, Ozcakar L. Ultrasonographic evaluation in symptomatic knee osteo- arthritis: clinical and radiological correlation. Int J Rheum Dis 2014;17:536–40.
6) Chan KK, Sit RW, Wu RW, Ngai AH. Clinical, radiological and ultrasonographic findings related to knee pain in osteoarthritis. PLoS One 2014;9:e92901.
7) Phillips M, Bhandari M, Grant J, Bedi A, Trojian T, Johnson A, Schemitsch E. A Systematic Review of Current Clinical Practice Guidelines on Intra-articular Hyaluronic Acid, Corticosteroid, and Platelet-Rich Plasma Injection for Knee Osteoarthritis: An International Perspective. Orthop J Sports Med. 2021 Aug 31;9(8):23259671211030272. doi: 10.1177/23259671211030272. PMID: 34485586; PMCID: PMC8414628.
8) Zhao D, Pan JK, Yang WY, Han YH, Zeng LF, Liang GH, Liu J. Intra-Articular Injections of Platelet-Rich Plasma, Adipose Mesenchymal Stem Cells, and Bone Marrow Mesenchymal Stem Cells Associated With Better Outcomes Than Hyaluronic Acid and Saline in Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. Arthroscopy. 2021 Jul;37(7):2298-2314.e10. doi: 10.1016/j.arthro.2021.02.045. Epub 2021 Mar 10. PMID: 33713757.
9) Eymard F, Ornetti P, Maillet J, Noel É, Adam P, Legré-Boyer V, Boyer T, Allali F, Gremeaux V, Kaux JF, Louati K, Lamontagne M, Michel F, Richette P, Bard H; GRIP (Groupe de Recherche sur les Injections de PRP, PRP Injection Research Group). Intra-articular injections of platelet-rich plasma in symptomatic knee osteoarthritis: a consensus statement from French-speaking experts. Knee Surg Sports Traumatol Arthrosc. 2021 Oct;29(10):3195-3210. doi: 10.1007/s00167-020-06102-5. Epub 2020 Jun 24. Erratum in: Knee Surg Sports Traumatol Arthrosc. 2020 Oct 24;: PMID: 32583023; PMCID: PMC8458198.

10) Shah A, Mak D, Davies AM, James SL, Botchu R. Musculoskeletal Corticosteroid Administration: Current Concepts. Can Assoc Radiol J. 2019 Feb;70(1):29-36. doi: 10.1016/j.carj.2018.11.002. PMID: 30691559.
11) Najm A, Alunno A, Gwinnutt JM, Weill C, Berenbaum F. Efficacy of intra-articular corticosteroid injections in knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. Joint Bone Spine. 2021 Jul;88(4):105198. doi: 10.1016/j.jbspin.2021.105198. Epub 2021 Apr 24. PMID: 33901659.
12) Singh H, Knapik DM, Polce EM, Eikani CK, Bjornstad AH, Gursoy S, Perry AK, Westrick JC, Yanke AB, Verma NN, Cole BJ, Chahla JA. Relative Efficacy of Intra-articular Injections in the Treatment of Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. Am J Sports Med. 2021 Aug 17:3635465211029659. doi: 10.1177/03635465211029659. Epub ahead of print. PMID: 34403285.
13) Anil U, Markus DH, Hurley ET, Manjunath AK, Alaia MJ, Campbell KA, Jazrawi LM, Strauss EJ. The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials. Knee. 2021 Oct;32:173-182. doi: 10.1016/j.knee.2021.08.008. Epub 2021 Sep 6. PMID: 34500430.
14) Daniels EW, Cole D, Jacobs B, Phillips SF. Existing Evidence on Ultrasound-Guided Injections in Sports Medicine. Orthop J Sports Med. 2018 Feb 22;6(2):2325967118756576. doi: 10.1177/2325967118756576. PMID: 29511701; PMCID: PMC5826008.
15) Fang WH, Chen XT, Vangsness CT Jr. Ultrasound-Guided Knee Injections Are More Accurate Than Blind Injections: A Systematic Review of Randomized Controlled Trials. Arthrosc Sports Med Rehabil. 2021 Jun 26;3(4):e1177-e1187. doi: 10.1016/j.asmr.2021.01.028. PMID: 34430899; PMCID: PMC8365196.
16) Curtiss HM, Finnoff JT, Peck E, et al. Accuracy of ultrasound-guided and palpation-guided knee injections by an experienced and less- experienced injector using a superolateral approach: a cadaveric study. PM R. 2011;3:507-515.
17) Wu T, Dong Y, Song Hx, Fu Y, Li JH. Ultrasound-guided versus landmark in knee arthrocentesis: A systematic review. Semin Arthritis Rheum. 2016 Apr;45(5):627-32. doi: 10.1016/j.semarthrit.2015.10.011. Epub 2015 Dec 17. PMID: 26791571.
18) Finnoff D, Hall MM, Adams E et al. American Medical Society for Sports Medicine (AMSSM) position statement: interventional musculoskeletal ultrasound in sports medicine. Br J Sports Med 2015; 49(3): 145– 150.
19) [5] Chu CR, Coyle CH, Chu CT, et al. In vivo effects of single intra- articular injection of 0.5% bupivacaine on articular cartilage. J Bone Joint Surg Am 2010;92:599e608.
20) [6] Chu CR, Izzo NJ, Papas NE, Fu FH. In vitro exposure to 0.5% bupi- vacaine is cytotoxic to bovine articular chondrocytes. Arthroscopy 2006;22:693e9.
21) [7] Piper SL, Kim HT. Comparison of ropivacaine and bupivacaine toxicity in human articular chondrocytes. J Bone Joint Surg Am 2008; 90:986e91.
22) Gulihar A, Robati S, Twaij H, Salih A, Taylor GJ. Articular cartilage and local anaesthetic: A systematic review of the current literature. J Orthop 2015;12(Suppl 2):S200e10.
23) Murakami, A. (2015) 'Ultrasound-guided injections - a technical review', Aspetar Sports Medicine Journal, 4, pp. 454-461.
24) NICE (2019a) Local Anaesthesia: British National Formulary. Available at: https://bnf.nice.org.uk/treatment-summary/anaesthesia-local.html (Accessed: 20 November 2021).
25) Gray RG, Tenenbaum J, Gottlieb NL. Local corticosteroid injection treatment in rheumatic disorders. Semin Arthritis Rheum 1981;10: 231e54.
26) Stephens MB, Beutler AI, O'Connor FG. Musculoskeletal injections: a review of the evidence. Am Fam Physician 2008;78:971e6.

27) Holland C, Jaeger L, Smentkowski U, Weber B, Otto C. Septic and aseptic complications of corticosteroid injections: an assessment of 278 cases reviewed by expert commissions and mediation boards from 2005 to 2009. Dtsch Arztebl Int 2012;109:425e30.
28) McGuire E. Sudden loss of milk supply following high-dose triam- cinolone (Kenacort) injection. Breastfeed Rev 2012;20:32e4.
29) Babwah TJ, Nunes P, Maharaj RG. An unexpected temporary sup- pression of lactation after a local corticosteroid injection for tenosyn- vitis. Eur J Gen Pract 2013;19:248e50.
30) University of Liverpool. HIV Drug Interactions. Available at: http:// www.hiv-druginteractions.org/checker. Accessed Nov, 2021. .
31) Iñigo Iriarte, Carles Pedret, Ramon Balius Consell Català de l'Esport, Luis Cerezal. Ultrasound of the Musculoskeletal System Anatomical Exploration and Pathology. Online ebook P270. (accessed on 22nd of November 2021).
32) Collins NJ, Prinsen CA, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. Osteoarthritis Cartilage. 2016 Aug;24(8):1317-29. doi: 10.1016/j.joca.2016.03.010. Epub 2016 Mar 21. PMID: 27012756.