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Review

Imaging-based measures of synovitis in knee osteoarthritis: A scoping review and narrative synthesis

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ABSTRACT

Background: Synovitis has emerged as a tissue target of importance in OA research and is commonly evaluated with medical imaging.
Objectives: The purpose of this scoping review was to identify and describe the medical imaging techniques and definitions used by knee OA researchers to assess synovitis, summarize their advantages and disadvantages, and identify opportunities for future work.
Eligibility criteria: We included full-text peer-reviewed English publications including adults diagnosed with knee OA. Studies were included if one or more medical imaging modalities were used to assess synovitis in the knee. Studies of inflammatory arthritis, joint replacement, and synovial joints other than the knee were excluded. Animal studies and literature syntheses were also excluded.
Sources: MEDLINE, SCOPUS, and Google scholar databases were systematically searched for publications (2000–2023) using the following medical subject headings (MeSH): "osteoarthritis, knee", "magnetic resonance imaging", "ultrasonography", "synovitis".
Results: 1154 articles were identified from searching medical databases. After removal of duplicates, abstract screening, and full text reading, 251 articles were included in the final review. MRI is the most common modality employed to assess knee synovitis, followed by US imaging. Varied imaging techniques used in the assessment of joint synovitis may be targeting divergent constructs of synovial remodeling and inflammation, which complicates interpretation of results.
Conclusions: There is no consensus on the best method for imaging of knee synovitis in OA. Future work may benefit from the evaluation of synovitis separate from joint effusion, and their associations with histologic findings to discriminate between features of synovial inflammation and remodeling.

1. Introduction

Knee osteoarthritis (OA) is a highly prevalent [1] and complex disease, with multi-tissue involvement of the whole joint, including articular cartilage, subchondral bone, synovium, tendons, ligaments, and menisci [2]. Degenerative changes to articular cartilage and bone have long been the focus of research efforts in the field of OA, but new data points to the synovial membrane as a tissue of interest in OA pathogenesis, symptomology, and progression.

Early work [3] has confirmed that thickening of the synovial membrane on MRI is correlated with histological evidence of papillary hyperplasia, mononuclear cell infiltrate, fibrosis, edema, and angiogenesis. As a result, synovitis is a term often used to refer to this imaging construct and is thought to represent inflammation of the synovial membrane. Over the last two decades, spurred by technological advances in medical imaging, much work has been done to establish the biological associations of synovitis with OA outcomes; synovitis has been found to be an independent risk factor for incident knee OA [4], and is associated with knee pain [5] and accelerated disease progression [6]. However, the role of synovitis in knee OA pathogenesis remains controversial, given that other studies of its biological associations produce conflicting results. One study of 87 women by Baert et al. found limited associations

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between MRI features of OA and pain/function [7]. Another case-control study of 243 participants of varied OA severity found significant associations of synovitis on ultrasound (US) with radiographic severity, but not with pain [8]. This may be attributable in part to the clinical heterogeneity of the knee OA population, and also in part due to multiple definitions and measurement methods used by knee OA researchers, which complicates comparisons between otherwise similar studies.

The aims of this scoping review are to describe the medical imaging techniques and definitions used by knee OA researchers to quantify synovitis, summarize their strengths and weaknesses, and identify opportunities for future work.

2. Methods

A systematic electronic literature search was performed in June 2023 to identify studies that described imaging-based measures of synovitis in knees with OA. The search and selection of articles was guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist. MEDLINE, SCOPUS and Google Scholar databases were searched for peer-reviewed, English-language articles reporting the measurement of synovitis in knees of adult participants with OA. We elected to include only articles published after 2000 in order to focus on the most contemporary methods consistent with our current understanding of synovitis in OA. Various combinations of the following medical subject heading (MeSH) terms were used for the search; "osteoarthritis, knee", "MRI", "ultrasonography", "synovitis". Studies involving animal models of OA, human participants with inflammatory arthritis or arthroplasty appliances, or studies that measured synovitis in other peripheral joints were excluded, as these topics include various disease models that affect how image findings are interpreted and involve different joints that are physiologically and anatomically distinct.

After extraction and pooling of articles, the primary reviewer (RD) cross-referenced and deleted duplicates. Then, the primary reviewer screened titles and abstracts, excluding articles based on the pre-specified inclusion and exclusion criteria. The full texts of remaining articles were then reviewed by the primary and secondary reviewers (RD and MEE) for final decision on inclusion or exclusion. Discrepant cases between the primary and secondary reviewer were resolved by consensus. Finally, the primary reviewer manually searched the reference lists of included articles to identify and include relevant articles missed in the search strategy.

No review protocol was registered prior to undertaking this scoping review. The full list of extracted studies, full list of search terms, and structured data extraction form are provided in Appendices A through C.

3. Results

1154 articles were identified using the search strategy. After removal of duplicates and screening of titles and abstracts, 273 articles remained. After conducting secondary screening in duplicate, 31 articles were excluded. These excluded articles consisted of literature syntheses, editorials, articles on pigmented villonodular synovitis, inflammatory or acute arthritis, arthritis in animals, and studies measuring synovitis in areas other than the knee. One study was removed from the analysis due to having been retracted from the journal of publication. Nine articles were included following a manual search of reference lists, resulting in 251 articles included in the final review (Fig. 1).

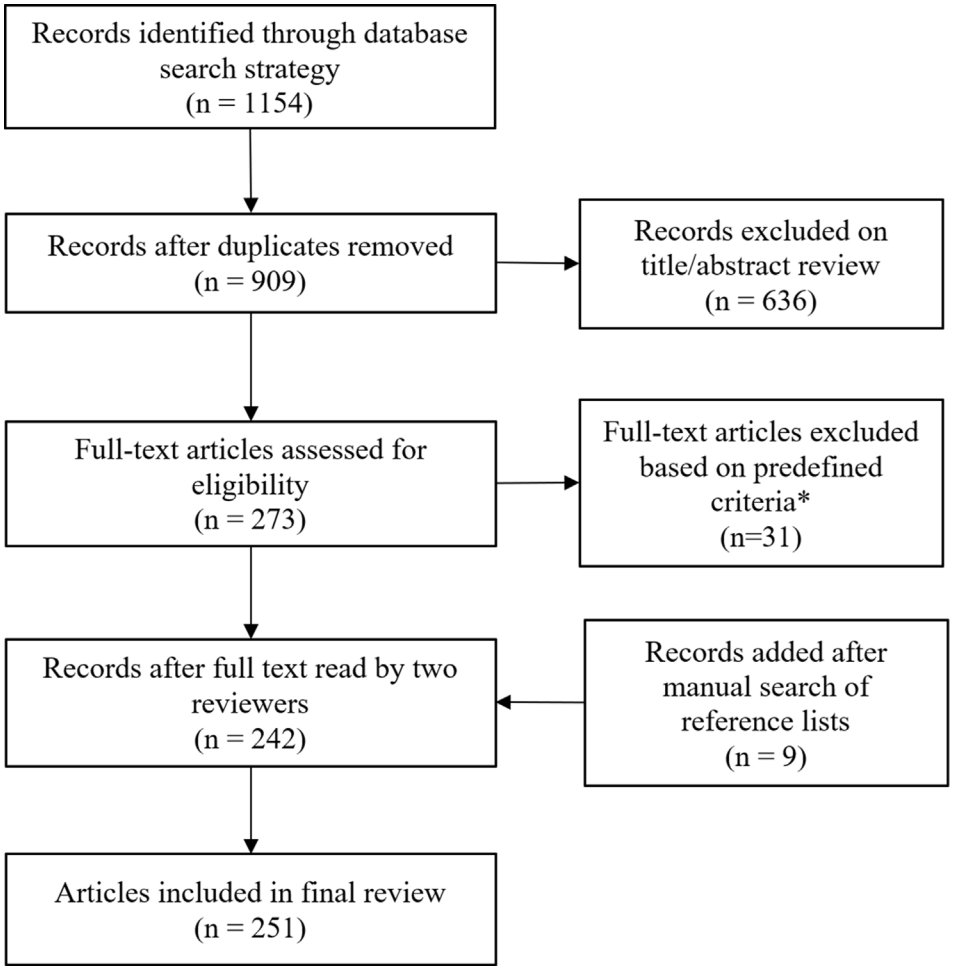

Fig. 1. PRISMA-ScR flow diagram of included studies.

3.1. Synovitis terminology

The synovial membrane is a vascular, semi-permeable connective tissue that lines the inner surface of the joint capsule. The main function of the synovial membrane is to produce synovial fluid through ultrafiltration of blood plasma [9]. In OA, the synovial membrane is infiltrated by inflammatory cells and undergoes hyperplastic thickening secondary to the release of pro-inflammatory cytokines. As a result, the term "synovitis" refers to the characteristically thickened appearance of the synovial membrane, normally invisible on medical imaging modalities. Synovitis has also been used to refer to areas of the synovial membrane that appear vascularized on medical imaging [10,11], under the hypothesis that tissue vascularization betrays underlying inflammation. However, histologic and immunohistochemical evidence suggests that a spectrum of both inflammatory and remodeling features are present in OA-associated synovitis [12], meaning that not all synovial thickening in OA indicates active inflammation.

In OA, the knee joint may also become distended with excess synovial fluid, resulting in joint effusion (swelling) [13]. Despite being separate pathological processes, effusion and synovitis are often grouped together and measured as "effusion-synovitis" on non-contrast MRI.

Finally, alterations in the signal intensity or size of the infrapatellar fat pad (IPFP) have also been described as "IPFP-synovitis" or equivalently, "Hoffa-synovitis". Inflammatory changes in the IPFP have been correlated with measures of effusion-synovitis and inflammatory biomarkers [14], pain [15], and OA progression [16].

3.2. Magnetic resonance-based measures of synovitis

MRI is commonly used for the assessment of synovitis in knee OA, due to its ability to image the entire knee joint with excellent soft tissue contrast resolution. Of the 251 studies included in this review, 206 (82 %) used MRI for the assessment of synovitis.

3.2.1. Conventional pulse sequences

Fluid-sensitive sequences such as fat-suppressed proton density or fat-suppressed T2-weighted are the most common protocols used to evaluate effusion-synovitis. Because synovium and joint effusion both demonstrate high signal on conventional pulse sequences, these separate features cannot be differentiated from each other without administration of contrast agent.

Semi-quantitative (SQ) grading schemes have been developed and validated for grading effusion-synovitis and Hoffa-synovitis on conventional MR sequences [4,13,17–112]. The Whole Organ MRI Score (WORMS) grades effusion-synovitis in terms of the maximal distension of the synovial joint cavity from zero to three [113]. Compared to knees without effusion-synovitis, the presence of WORMS effusion-synovitis is associated with increased cartilage defects and decreased cartilage volume [22]. Suprapatellar pouch effusion-synovitis graded by WORMS is also significantly and independently associated with increased total and non weight-bearing knee pain [45]. The MRI Osteoarthritis Knee Score (MOAKS) similarly provides an effusion-synovitis score (zero to three) based on the size of effusion-synovitis in the axial plane [60]. MOAKS also provides a Hoffa-synovitis score [7,114–123] based on the size of diffuse hyperintense signals in the IPFP on sagittal T2 fat-suppressed sequences; the fat pad is graded from zero (normal) to three (severe). MOAKS measures of effusion-synovitis and Hoffa-synovitis are associated with radiographic progression [93] and knee pain [30].

Quantitative measures of effusion-synovitis [6,124–147] and Hoffa-synovitis [14,16,148–152] can be obtained on conventional MR sequences by summing select regions of interest on a section-by-section basis. Quantitative measures of IPFP signal intensity are reproducible and correlated with SQ measures of IPFP signal intensity and MR features of OA including cartilage defects [148].

Conventional MR sequences are a mainstay of effusion-synovitis evaluation in knee OA, and multiple methods are available to researchers. These techniques are especially attractive given the existence of publicly available databases of T1/T2-weighted knee MRI sequences such as the Osteoarthritis Initiative.

3.2.2. Static contrast-enhanced imaging

Contrast enhancement (CE) refers to the use of contrast agents to exaggerate the visible differences between structures on imaging studies [153]. CE-MRI involves the intravenous (IV) injection of a gadolinium-based contrast medium which produces an increased signal intensity within perfused tissues. Tissues demonstrating increased signal after enhancement with a gadolinium-based contrast medium do so as a result of both intravascular and interstitial enhancement [154] and are termed extracellular fluid contrast agents. CE-MRI allows excellent morphological assessment of synovitis because perfused synovium is enhanced by the contrast agent whereas adjacent joint fluid is not (Fig. 2).

SQ grading of synovitis on CE sequences involves the assessment of synovial thickness at multiple sites around the knee [137,155–171], and has been shown to correlate moderately with microscopic and macroscopic features of synovitis [162]. Others simply grade whole-joint synovitis as either present or absent [171].

Quantitative measures of synovitis on CE-MRI sequences are obtained by segmentation of enhancing synovium on post-contrast images [172–188]. Total volume, reported as "synovial tissue volume" (STV) or "synovial membrane volume" (SMV) is calculated by summing these areas across slices, with consideration given to the slice thickness of the MR images used. In their seminal study of synovitis changes following intra-articular corticosteroid (IACS) injection, O'Neill et al. employed a semi-automated approach to synovitis segmentation on CE-MRI. They

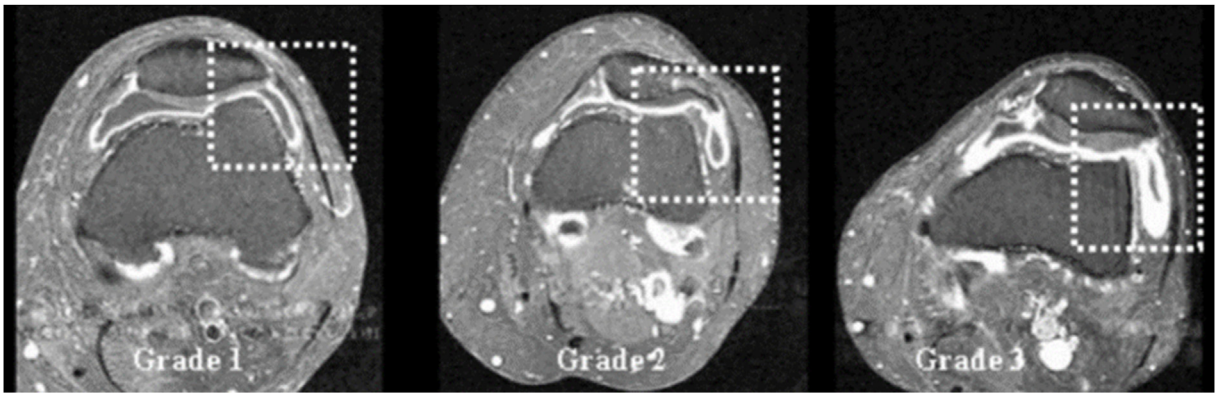

Fig. 2. Adapted from Rhodes et al., 2005 The validation of simple scoring methods for evaluating compartment-specific synovitis detected by MRI in knee osteoarthritis. Contrast-enhanced T1-weighted post-gadolinium fat-saturated images demonstrating increasing SQ grades (left to right) of synovitis in the lateral parapatellar pouch of a patient with knee OA.

found that STV was reduced significantly after IACS, and that this change was statistically significantly associated with reduced knee pain [186].

Static CE-MRI has also been used to investigate Hoffa-synovitis as enhancing areas within the IPFP. High signal-intensity areas are segmented and summed in a similar fashion to the measurement of STV, and these quantitative measures are associated with knee pain, function, and total scores on validated PROMs [189]. The IPFP can also be graded in a SQ manner on CE sequences similar to the MOAKS approach [15,190]. In one study, SQ grading of the IPFP on CE-MRI was found to be more strongly related to activity-induced knee pain compared to grading on non-CE-MRI [15].

3.2.3. Dynamic contrast-enhanced imaging

Dynamic CE (DCE) imaging allows for the derivation of time intensity curves by acquiring a series of CE images over time. These TICs quantify the temporal enhancement of tissue, which allows the inference of physiologic properties related to microvascular blood flow. DCE analysis of synovitis and Hoffa-synovitis requires the identification of enhancing synovium via segmentation, followed by the generation of TICs on a voxel-by-voxel basis within regions of interest. DCE parameters can be extracted directly from the TICs (heuristic parameters) or from mathematical models [191] which describe the underlying physiological phenomena between parenchymal cells, blood vessels, and extra-cellular extravascular space (pharmacokinetic parameters). In the current review, 16 studies reported the use of DCE-MRI for the assessment of synovitis [192–206].

Composite heuristic parameters of synovial volume and synovial enhancement have been statistically significantly correlated with knee pain [200], and macroscopic and microscopic evidence of synovitis [207]. Loeuille et al. report quantitative measures of SMV where each voxel in the segmented tissue volume is classified as either low-speed enhancement (SMVL), intermediate-speed enhancement (SMVI), or high-speed enhancement (SMVH) based on the increase in tissue signal intensity 186 s after injection of contrast agent. The ratio of rapidly enhancing (highly perfused) synovium to total synovial volume SMVH/SMW was highly variable, ranging from 1 % to 66 % in their sample of 15 patients with knee OA. SMVL was significantly associated with knee pain ($r = 0.61$), but not associated with macroscopic or microscopic synovitis scores. SMVH was highly correlated with synovial vascular congestion ($r = 0.79$) but not with other markers of inflammation such as cellular infiltrate, lining layer thickness or edema [198].

The pharmacokinetic parameter K^{trans}, known to be associated with capillary permeability, is correlated ($r = 0.62$) with MOAKS effusion-synovitis [208], and demonstrated superior test-retest reliability, discriminatory power, and responsiveness in a sample of 14 knee OA participants and 6 age-matched healthy controls [194]. Gait et al. compared static CE-MRI measures of STV to DCE-MRI measures including K^{trans} in a sample of 93 knee OA patients undergoing IACS. While STV demonstrated a mean −0.30 change in standardized score at the 10-day follow-up, DCE-MRI derived measures of synovial enhancement were more sensitive to change (K^{trans} −0.51) [199]. Wenham et al. found that volumetric measures of synovial enhancement demonstrated a greater effect size and standardized response mean than either DCE-MRI parameters or STV alone in knee OA patients two weeks after IACS [209].

3.2.4. Diffusion-weighted Imaging

DWI is based on the measurement of Brownian motion of water molecules within tissue; because water diffusivity is restricted by the presence of membranes and other structures that limit molecular diffusion, DWI allows for inference of tissue microstructure. Modelling water diffusivity using diffusion tensor imaging (DTI) allows for the quantification of mean diffusivity (MD), also referred to as the apparent diffusion coefficient, and fractional anisotropy (FA). MD is the average of total molecular motion independent of directionality, and FA is a measure of diffusion anisotropy, measured from zero (completely isotropic diffusion) to one (infinite anisotropic diffusion).

Two articles investigated the use of DWI/DTI for the assessment of synovitis in knee OA [208,210]. Agarwal et al. performed CE-MRI and DWI/DTI in 18 patients with synovitis and 6 healthy controls, followed by aspiration of synovial fluid for quantification of tumour necrosis factor alpha (TNF-α) and interleukin-1 beta (IL1-β). STV and FA, but not MD, were statistically significantly increased in patients relative to healthy controls, while FA demonstrated moderate to strong positive correlations with TNF-α ($r = 0.68$) and IL1-β ($r = 0.48$); MD demonstrated moderate negative correlations ($r = -0.54$ and $r = -0.46$, respectively) [210]. Sandford et al. compared FA and MD values against K^{trans} derived from DCE-MRI in a sample of 11 subjects with a clinical diagnosis of knee OA, and also measured their relationship with knee OA radiographic severity and MOAKS effusion-synovitis. MD and FA were both statistically significantly correlated with K^{trans} and MOAKS effusion-synovitis: MD demonstrated a positive correlation ($r = 0.79$) with K^{trans} and with MOAKS ($r = 0.60$) and FA demonstrated a negative correlation (−0.72) with K^{trans} and with MOAKS ($r = -0.53$). MD and FA levels did not differ significantly across levels of radiographic severity [208].

3.2.5. Advanced pulse sequences

Given the disadvantages associated with the use of gadolinium-based contrast agents, several advanced non-CE pulse sequences have been applied to OA knee synovium in an effort to improve the contrast resolution between synovitis and adjacent joint effusion.

Gradient echo-type sequences, which use gradient fields to generate transverse magnetization and flip angles of less than 90°, have acceptable reproducibility [75] but remain untested against gold-standard CE-MRI, and may be susceptible to chemical shift artefacts [211].

Double-inversion recovery (DIR) [212,213], quantitative double echo steady-state (qDESS) [214,215], and fluid-attenuated inversion-recovery (FLAIR) [216] sequences have been compared against CE-MRI for the measurement of synovitis separate from effusion. DIR and qDESS both demonstrate moderate correlation with CE-MRI, but DIR tends to overestimate synovial thickness by as much as 17.5 % [213], whereas qDESS tends to underestimate synovial thickness by as much as 28 % [214]. Fat-suppressed FLAIR sequences demonstrated very good reproducibility and agreement with CE-MRI in one study [216], but its applicability to synovitis assessment in OA is questionable, given that only six of the 33 patients consecutively assessed with FLAIR and CE-MRI in this study were participants who met diagnostic criteria for knee OA.

3.3. Ultrasound-based measures of synovitis

US is a cost-effective modality capable of imaging soft tissues with superior spatial resolution. US is particularly well-suited for the assessment of synovitis in knee OA, as it can be used at the point of care and can discriminate between effusion and synovial thickening without administration of IV contrast.

3.3.1. Grayscale ultrasound imaging

The synovium of the suprapatellar recess is accessible with US using an axial (transverse) or sagittal (longitudinal) scanning technique on the semi-flexed anterior knee (Fig. 3). Scanning protocols for the knee joint are based on the European League Against Rheumatism working group protocol [8,217–259].

Joint effusion is identified as intra-articular anechoic signal which is compressible and does not demonstrate flow on Doppler imaging. Definitions for synovitis on US vary considerably between studies; the European League Against Rheumatism definition for synovial hypertrophy includes only hypoechoic abnormal intra-articular tissue, requiring at least 4 mm in AP dimension and taking on a diffuse or nodular appearance. On the other hand, the Outcome Measures in Rheumatology (OMERACT) working group definition includes hypoechoic, isoechoic (relative to subdermal fat) and hyperechoic intra-articular tissue and does not require a measurement to qualify its presence. The OMERACT group also provides a SQ scoring system for “global synovitis”, which

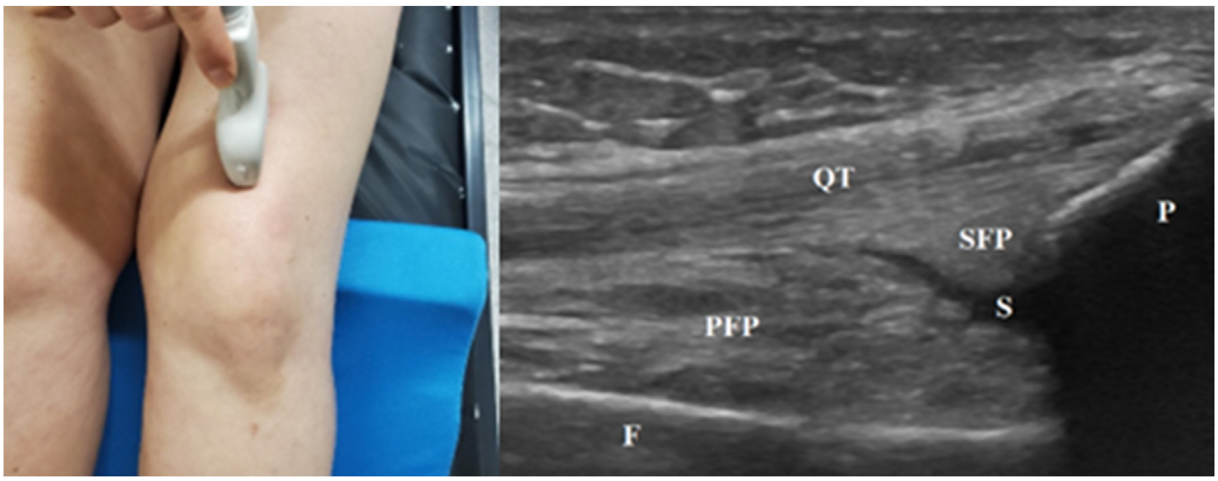

Fig. 3. Longitudinal (midline) US scanning approach for evaluation of the suprapatellar recess. For optimal visualization, the knee is flexed to approximately 30° with the use of a triangular pillow. B) Midline longitudinal US image of the suprapatellar recess QT: quadriceps tendon P: patella SFP: suprapatellar fat pad PFP: pre-femoral fat pad F: femur S: synovial cavity.

represents the degree of maximal joint distension by both effusion and synovial hyperplasia across the midline, lateral, and medial suprapatellar knee compartments from zero to three.

OMERACT measures, which are commonly used in the OA literature, demonstrate positive moderate correlations with pain severity [222], joint damage [8], and MR-based measures of synovitis [220]. One study in this review did not find any association between OMERACT-defined synovial hypertrophy or joint effusion with knee pain measured by PROMs in a sample of 180 patients fulfilling clinical criteria for knee OA [256]. Synovitis and effusion depth can also be measured on the US unit with electronic calipers or segmented with the use of image processing software [232].

Though the IPFP is easily accessible using an anterior sonographic scanning approach, there was a lack of studies describing US-synovitis findings within the IPFP.

3.3.2. *Doppler ultrasound imaging*

As an adjunct modality onboard contemporary US machines, Doppler imaging of hypertrophied synovium is performed to assess the presence/degree of blood flow within synovial tissue (Fig. 4). Doppler-shifted echoes are produced by ultrasonically reflective blood components as they accelerate past the probe. Colour Doppler imaging displays these echoes according to their velocity and direction, while Power Doppler (PD) displays the amplitude of the Doppler-shifted echoes in an angle-independent manner, resulting in increased sensitivity to low-velocity flow [260].

Synovial vascularity is graded with PD as present/absent in the suprapatellar recess according to the OMERACT guidelines, but others have used expanded grading schemes based on the number or concentration of Doppler signals [261]. The reported prevalence rates of Doppler findings in OA knee synovium are highly variable, ranging from 3 % to 73 % in this review [10,11,262].

Advanced Doppler technologies like microvascular imaging can improve sensitivity over PD [263] through the use of adaptive algorithms that suppress clutter artefact as opposed to suppressing low-velocity signals. While the degree of sonographically-detected synovial vascularity has been used as a proxy measure of "active inflammation" in studies of inflammatory arthritis, the underlying construct of this feature in a chronic condition like OA remains poorly understood. As technology becomes more sensitive for the detection of blood vessels, it's important to recognize that these vessels may represent neo-vascularization linked to active-state OA, but could also reflect physiologic or healing processes.

3.3.3. *Contrast-enhanced ultrasound imaging*

CE-US imaging involves the IV administration of 1–11 μm (μm) gas microbubbles stabilized in a phospholipid membrane. Following injection, enhancement of perfused tissue is achieved by the oscillation of microbubbles in response to the US beam, and the large acoustic impedance mismatch between soft tissue and gas. SonoVue™ contrast agent was used in both studies of CE-US imaging of synovium in this review. Due to their size, SonoVue™ microbubbles cannot leave the

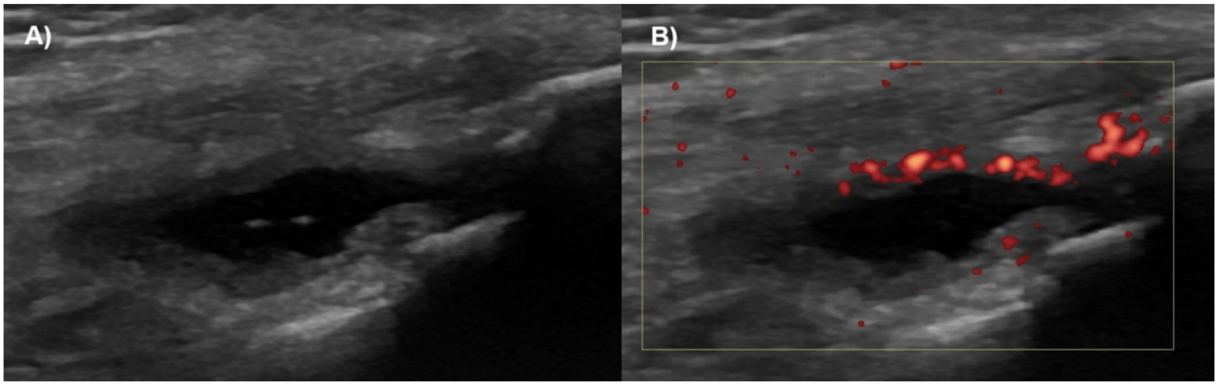

Fig. 4. A) Greyscale suprapatellar US image of knee synovitis. B) Corresponding greyscale image with PD box overlaid- orange Doppler pixels within hypertrophic synovium indicate the presence of blood flow.

vascular system to enhance the interstitium, and thus are classified as blood pool contrast agents. CE-US images can be analyzed in a similar fashion to CE-MRI images, either through SQ methods or through the derivation of quantitative TICs.

In the first study, Song et al. evaluated the TICs of enhancing suprapatellar synovium on CE-US and compared these results to greyscale US, PDUS, and time intensity curves analysis of suprapatellar synovitis on CE-MRI. While correlation between time/intensity results on CE-US and CE-MRI was moderate ($r = 0.63$ $p < 0.01$), agreement between the methods was not greater than what would be expected by chance [264]. In their sample, knee pain correlated moderately with CE-US measures of synovitis ($r = 0.39$ $p = 0.02$) but was not statistically significantly related to CE-MRI measures of synovitis nor synovial hypertrophy on US. A more recent study by de Vries et al. also compared CE-US findings to greyscale US, PDUS, and CE-MRI, though the authors chose to quantify and compare their findings using SQ scoring, as opposed to time/intensity analysis. Synovial thickness on CE-US was scored based on the maximal thickness on any image, and graded as follows: grade zero if less than two mm, grade one if two to four mm, grade two if five to 10 mm, grade three if $>$ 10 mm [261]. The authors only found a moderate statistically significant ($r = 0.39$ $p < 0.03$) correlation between CE-US and CE-MRI sum scores [261].

4. Discussion

The term "synovitis" has been used to describe various imaging features thought to be related to inflammation, including thickening and hyper-perfusion of the synovial membrane, regions of increased signal intensity in the IPFP, and distension of the joint with fluid and/or synovial thickening. A variety of SQ and quantitative methods have been developed to analyze these features, most of which employ the use of either MR or US imaging. Their validity is assessed by measuring linear correlation with structural joint damage, knee pain, anti-inflammatory therapies, and other validated image features.

4.1. Conventional and contrast-enhanced MRI

MRI measures of synovitis are a mainstay in knee OA research due to their ability to assess the entire synovial membrane, and to provide morphologic and physiologic imaging through advanced pulse sequences and techniques. CE-MRI provides excellent contrast resolution for the morphological assessment of synovitis and effusion in knee OA and demonstrates superior correlation with OA outcomes relative to non-enhanced sequences [15,186]. However, the requirement to intravenously administer gadolinium-based contrast is a major drawback of this approach. Gradient echo-type sequences have been used to measure synovitis separate from effusion without CE in some studies but were not validated against CE-MRI. DIR and qDESS sequences have also been investigated as alternatives to contrast administration but tend to either overestimate or underestimate synovial thickness compared to CE-MRI, respectively.

4.2. Dynamic contrast-enhanced MRI

DCE-MRI provides information on the physiology of the synovium and not just its morphology, and therefore may be a key modality in mechanistic studies investigating the response of the synovium to therapeutic agents in future clinical trials. Composite measures of STV and synovial enhancement have the advantage of quantifying both the extent and degree of synovial inflammation in a single variable, and there is evidence for their construct validity through correlation with knee pain and microscopic synovitis [200,207]. Because synovial thickening in the OA knee represents a continuum of both inflammatory and structural changes [12], physiologic measures of synovial perfusion and morphological measures of STV may be measuring slightly divergent constructs; the former may provide a measure of active inflammation whereas the latter likely measures a combination of active inflammation and synovial remodeling, which occurs in highly variables amounts between individuals [198].

4.3. Diffusion-weighted MRI

DWI/DTI can be used for quantitative assessment of synovitis physiology without the need for contrast agent, but data on its use in knee OA is sparse and limited to studies with small sample sizes. It has been theorized that increased FA may correspond to the aggregation of inflammatory cells within synovium [210], but this is not supported by findings from Sandford et al., who found a strong negative correlation between FA and K^{trans}, and no difference in FA levels between knees with low and high radiographic severity [208]. Future, large-scale studies with validation of FA and MD against histological measures of synovitis are needed to better understand the role of this modality in the assessment of synovitis in knee OA.

4.4. Greyscale ultrasound imaging

US imaging of the synovium addresses several drawbacks of MR-based imaging methods, with the caveat of being highly operator-dependent and having a reduced field of view. Most US techniques target the suprapatellar recess of the knee, as it is accessible and likely most representative of whole-knee synovitis [45]. There was a lack of literature regarding the sonographic appearance of the IPFP in the context of knee OA. While most studies reviewed in this paper included a description of US operator background and training in their methods section, we found many descriptions to be insufficient. Terms like "sonographer", or "ultrasonographer" should be fully described in the methods, given that these terms have varying legal and professional implications across jurisdictions. While the use of standardized US scanning protocols (OMERACT/EULAR) appears to be growing in this space, this review revealed significant variability in the reporting practices and definitions of US pathologies in OA.

4.5. Doppler ultrasound imaging

A major advantage to the use of US imaging for evaluating synovitis is the ability to sample blood flow within the synovial membrane at the point of care. However, reported prevalence rates of Doppler findings in OA knee synovium vary widely from 3 % to 73 %, which may be a function of heterogeneity in imaging approach. Doppler sensitivity is dependent on the modality/US machine used, scanning technique, patient body habitus, the presence of synovial hyperplasia, and the anatomical area sampled. In this review, the highest Doppler rates occurred adjacent to the lateral joint margin [241], but this may be an overestimation of true synovial perfusion due to the presence of adjacent vessels, such as the inferior lateral genicular artery.

4.6. Contrast-enhanced ultrasound imaging

Despite its growing use in abdominal and gynecologic imaging, CE-US has seen little implementation in the evaluation of knee joint synovitis. This is likely due to the added effort and risk associated with contrast administration, and its low correlation with CE-MRI. However, because SonoVue™ microbubble contrast agents and gadolinium-based contrast agents work to enhance tissues through different mechanisms, comparisons between the two should be interpreted with caution. While gadolinium-based agents will diffuse into the intercellular space causing interstitial enhancement, SonoVue™ will not leave the vascular system, thereby only enhancing perfused tissues. Whereas CE-MRI enhances all synovial thickening attributable to both inflammatory and remodeling processes, CE-US of OA synovium may preferentially enhance synovial areas undergoing active inflammation. Further studies including correlation with synovial histology and knee pain are needed to better understand the role of this modality in assessing OA synovium.

5. Conclusion

There is no clear consensus on the optimal modality or measurement technique for assessing synovitis in knee OA, though measures of synovial tissue characteristics appear to have superior construct validity compared to morphologic measures of effusion-synovitis. This review revealed conflicting associations in the literature between synovitis and knee OA outcomes, and poor correlation between morphologic and physiologic synovitis features between imaging modalities, including CE-MRI, DCE-MRI, and CE-US. This highlights the fact that measures based on different imaging features thought to be related to inflammation, including synovial perfusion, may be targeting divergent constructs, given that OA synovitis represents a mix of inflammatory and remodeling changes. In addition to the clinical heterogeneity of OA as a disease, this may contribute to heterogeneity in the literature concerning the association of synovitis with radiographic severity and knee pain. Future work may benefit from the evaluation of synovitis separate from joint effusion, and their associations with histologic findings to discriminate between features of synovial remodeling and synovial inflammation.

Author contributions

Robert Dima: Conceptualization, Methodology, Software, Data curation, Writing - original draft, Investigation **Mary-Ellen Empey**: Data curation, Writing - review and editing. **Trevor Birmingham**: Supervision, Methodology, Writing - review and editing. **C. Tom Appleton**: Supervision, Resources, Writing - review and editing.

Other contributors

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Declaration of competing interest

None to report.

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Appendix A. Supplementary data

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