The preferred technique for knee synovium biopsy and synovial fluid arthrocentesis

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REVIEW

The preferred technique for knee synovium biopsy and synovial fluid arthrocentesis

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Abstract

For knee osteoarthritis and related conditions, analysis of biomarkers hold promise to improve early diagnosis and/or offer patient-specific treatment. To compare biomarker analyses, reliable, high-quality biopsies are needed. The aim of this work is to summarize the literature on the current best practices of biopsy of the synovium and synovial fluid arthrocentesis. Therefore, PubMed, Embase and Web of Science were systematically searched for articles that applied, demonstrated, or evaluated synovial biopsies or arthrocentesis. Expert recommendations and applications were summarized, and evidence for superiority of techniques was evaluated. Thirty-one studies were identified for inclusion. For arthrocentesis, the superolateral approach in a supine position, with a 0°-30° knee flexion was generally recommended. 18-gage needles, mechanical compression and ultrasound-guidance were found to give superior results. For blind and image-guided synovial biopsy techniques, superolateral and infrapatellar approaches were recommended. Single-handed tools were preconized, including Parker-Pearson needles and forceps. Sample quantity ranged approximately from 2 to 20. Suggestions were compiled for arthrocentesis regarding approach portal and patient position. Further evidence regarding needle size, ultrasound-guidance and mechanical compression were found. More comparative studies are needed before evidence-based protocols can be developed.

Keywords Arthrocentesis · Synovial biopsy · Knee · Technique

Introduction

Biopsy analysis of the joints aids clinical decision-making in rheumatology, orthopaedics, and sports medicine. With the increasing scientific insight in the complex chain of mechanisms that influence prevalent joint diseases, such as osteoarthritis and rheumatoid arthritis [1–5], more complex analysis of biopsies can be expected in the near future potentially enabling further insights in e.g., the chronic disease of Osteoarthritis (OA) which, in contrast to other chronic diseases, currently lacks a good measurement-control system. The field of research of biomarkers for disease diagnosis [6, 7], progression [3, 8], and personalized treatment [9] has rapidly evolved into one of the main topics in the field of research [10]. In the knee, synovial fluid (SF) and the synovium [7, 11, 12] have been the most studied biomarker sources, due to their important role in various diseases [13, 14], and the ability to collect them with minimal harm to the patient. The implementation of routine biopsy analysis in the clinic is a balance between reliability for clinical decision-making of the provider versus feasibility/safety for the patient. The synovium is the main source of inflammation in the knee, mediated through the release of synovial fluid [3, 13, 15]. To create reliable individualized prediction patterns, large datasets for identification of biologic markers are needed. This requires tissue sampling from large patient cohorts. To be able to compare results between multiple clinicians and centers, a standardized biopsy protocol is needed to ensure a reliable quality of the samples. However, despite rising numbers of clinicians who take samples in daily practice, there is no standardized protocol, leading to a wide variety of approaches reported in surveys [16, 17]. Furthermore, only 11–22% of the senior internal medicine residents reportedly

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felt comfortable with performing knee arthrocentesis [18]. As a starting point for inexperienced clinicians, and to aid the development of standardized protocols, our aim was to summarize the recommended and used techniques throughout the literature, as well as the available evidence.

Materials and methods

Search strategy

Pilot free searches on Google Scholar and Pubmed were conducted to construct the search based on the terminology in the identified relevant papers. After this, PubMed, Embase and World of Science databases were searched on the 31st of May 2022 for studies that evaluated SF aspiration and synovial biopsy techniques. Six categories of terms were used in the final search for articles. In short, the search algorithm consisted of the constructs: “knee”, “arthrocentesis”, “technique”, “collect”, and “synovial fluid” or “synovium”, including appropriate synonyms identified during the pilot phase and using PubMed MeSH (for the complete search, see Appendix A).

Inclusion and exclusion criteria

Articles were included based on the following criteria: (1) the focus was on aspects of either arthrocentesis or synovial biopsies, (2) the study was in the knee joint, and (3) the technique was evaluated by: technique comparison, accuracy report, technique investigation and optimization, technical guidelines, as well as practical tips and tricks. Articles were excluded if (1) the subject population consisted of animals or children, (2) the papers were NOT written in English, (3) the papers were inaccessible, (4) the papers were not focusing on the techniques under scrutiny and/or (5) the techniques were not investigated.

Data collection

For arthrocentesis and synovial biopsy, the following variables were extracted: subject population, knee effusion, technique, tool, approach portal, patient position, knee angle, needle placement, needle gage and length, use of compression, use of imaging, sample information, pain and possible side effects and advantages.

Analysis

For each variable, all approaches and techniques were extracted from the literature prior to being compared and contrasted. The evidence and recommendations by the authors considering all aspects of technique were summarized in tables and text.

Results

1390 unique hits were retrieved from the databases (Fig. 1). At last, 31 articles were included of which 24 articles studied arthrocentesis techniques, while 8 studied synovial biopsy techniques. 1 article focused on both techniques.

Arthrocentesis technique

Approach portal and patient position (Table 1, third, fourth and fifth columns)

Overall, ten different approach portals were identified, among which six were more prominent (Fig. 2). Both suprapatellar portals (superolateral approach (SL)/superomedial (SM)) were found to offer the most direct access to the SF when arthrocentesis was performed on patients in supine position with fully extended or slightly flexed knees (0°–30°). However, only five studies recommended using the SM approach.

While mid-patellar approaches (Lateral mid-patellar portal (LMP)/Medial mid-patellar portal (MMP)) were found to be preferred in cases of relatively little SF in the knee and asymptomatic knees [31], infrapatellar approaches (Anterolateral approach AL/Anteromedial approach AM) were found to be less commonly used for various reasons, including difficulty in obtaining fluid [22, 43] (Fig. 2).

Arthrocentesis using LMP and MMP were performed with patients in supine positions with either full knee extension or a slight flexion of 0°–20° [20, 22, 24, 30, 31, 35, 38, 43], while AL and AN were predominantly performed on patients in seated positions with flexed knees (90°) [20, 22, 28, 30, 35, 37–39, 43].

Seventeen studies on arthrocentesis used the SL approach. Yaqub et al. demonstrated that SL was superior to an AL approach regarding successful diagnostic arthrocentesis [28].

Needle placement

Needle placement depends on the chosen approach. For the suprapatellar approaches, needles were aimed into the suprapatellar bursa, toward the intercondylar notch [20, 23, 27, 28, 30–32, 43]. For the mid-patellar approaches, the needles were aimed into the mid-pole, toward either the intercondylar notch or the opposite mid-pole. Pulling the patella seemingly simplified needle placement [43].

Capacity to aspirate SF and low resistance to injection were reported to confirm proper needle placement [31]. In

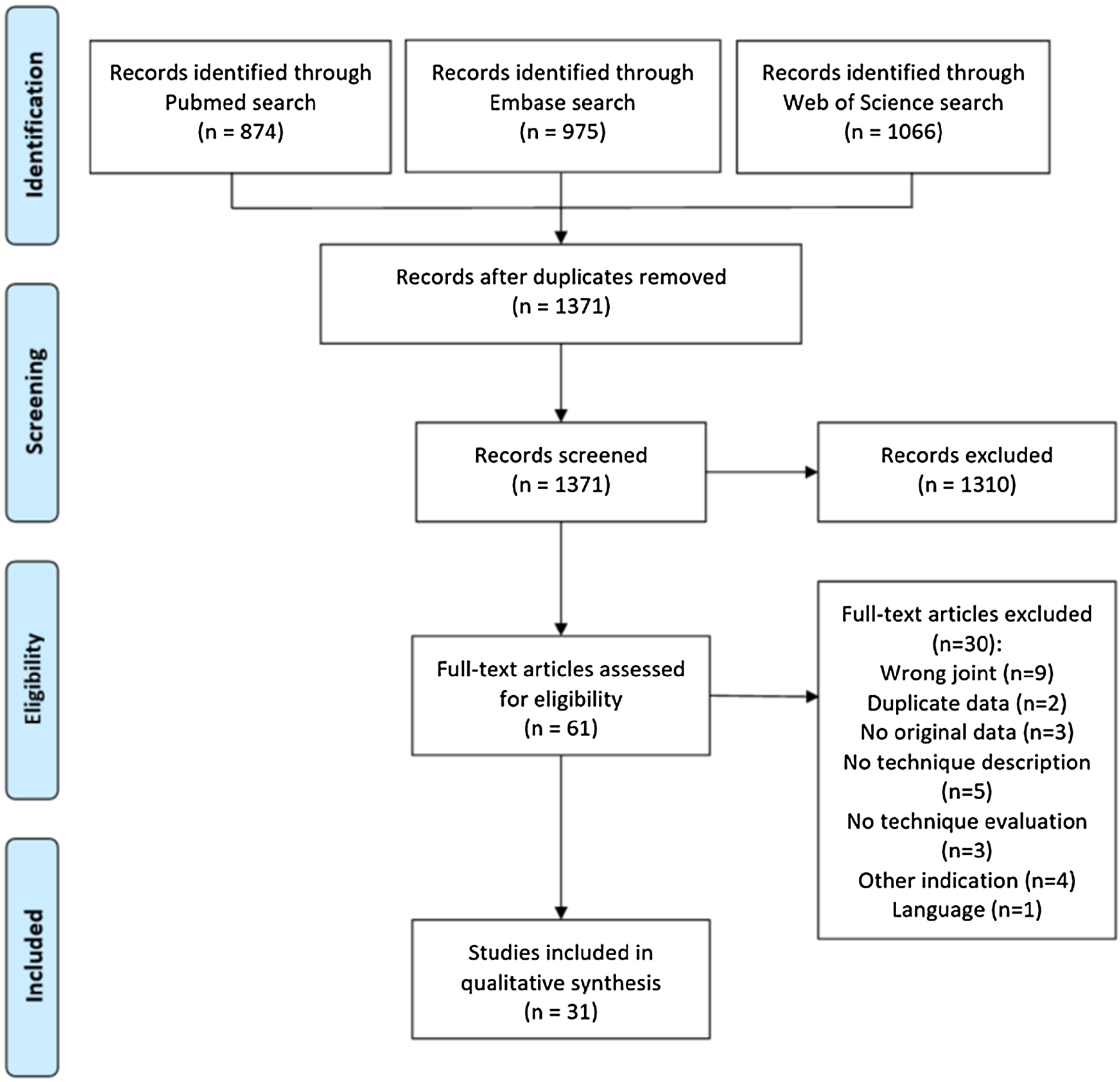

Fig. 1 PRISMA [69] flow diagram

case examiners faced difficulty advancing the needle or in case of unexpected flow resistance, recommendations were to slightly withdraw and reintroduce the needle [26, 31, 37].

Needle size (Table 1, sixth column) & sample collection

Gage size recommendations ranged from 16-gage (1.29 mm) to 25-gage (0.644 mm), with 18-gage (1.02 mm) being recommended (11 out of 19 recommendations). Needle length recommendations ranged from 2.54 cm (1-in.) to 5.08 cm (2-in.), with 3.18 cm being recommended (5 out of 8 recommendations).

In case SF is found to be very purulent, the use of larger needles is an option [31]. Patients with obesity may require longer needles and by experience, authors also preconized using larger needles for larger effusions [26, 35].

Compression (Table 1, seventh column)

Manual, pneumatic and brace compression have been described to displace SF toward an accessible portal. Bhavsar et al. found it impossible to manually displace all SF from the different synovial compartments [27]. However, it was demonstrated using US analysis that pneumatic compression increased fluid area and depth by around 2–3.5-fold [24]. The authors argue that cuffs as used in their study cannot be used to compress extended knees for it covers suprapatellar and infrapatellar portals. Yaqub et al. demonstrated that compressive knee braces increased SF yield of an AL portal aspiration, making it as efficient as the SL approach (SL: 16.9 ± 15.7 mL; AL + compression, 16.7 ± 11.3 mL; $p = 0.073$) [28]. The same brace was used in another study, which also demonstrated an increase of 72.1% in absolute

Table 1 Results of 24 articles on arthrocentesis with regards to approach portal, patient position, knee angle, needle size, use of compression, and assistive imaging

Study	Population sample	Approach portal	Patient position	Knee angle	Needle size	Compression	Imaging technique
Kondo et al. (2019) [19]	44 patients with rheumatoid arthritis	SL		150°			US
Chiodo et al. (2018) [20]		SL/SM LMP/MMP AL/AM	Supine Supine Seated	180° 180° 90°	18–21-g		US, fluoroscopy, CT & MRI
Douglas et al. (2014) [21]		SL/SM LMP/MMP AL/AM Waddell approach (WA) modified Waddell approach (MWA)	Supine Supine Seated - -	180° 180° 90° 150°–140° 150°			US
Monseau et al. (2013) [22]		SL MMP AL/AM	Supine Supine Seated	180° 180° 90°			US
Sibbitt et al. (2012) [23]	64 palpably effusive knees	SL		180°	18-g, 3.81 cm		Landmark & US
Meehan et al. (2019) [24]	37 patients with rheumatoid arthritis/ osteoarthritis/ and more	LMP MMP	Supine	170°–165°	18–20-g	Pneumatic compression	US
Wiler et al. (2010) [25]	66 patients requiring arthrocentesis	Lateral & medial approach			18-g		Landmark & US
Lockman et al. (2006) [26]		"Triangle technique" (similar to LMP)		90°	22-g, 2.54 or 3.81 cm		Imaging, air injection, contrast material injection
Bhavsar et al. (2018) [27]	210 patients with osteoarthritis 158 non-effusive knees 52 effusive knees	SL	Supine	180°–155°	22-g, 5.08 cm	Manual compression Compressive by brace	
Yaqub et al. (2018) [28]	55 clinically effusive knees	SL AL	Supine Seated	180°–160° 90°	22-g, 5.08 cm	SL: Manual compression/ milking AL: Compressive by brace	
Driban et al. (2014) [29]	26 patients with osteoarthritis 15 effused knees 11 non-effused knees	SL			18–21-g, 3.81 cm	Manual compression/ milking + saline assistance	
Akbarnia et al. (2022) [30]		SL/SM LMP/MMP AL/AM	Supine Supine Seated	180°–160° 180°–160° 90°	18-g	Manual compression/ milking	
Courtney et al. (2013) [31]		SL MMP	Supine -	180° mild flexion	21-g	MMP: manual compression/ milking	

Table 1 (continued)

Study	Population sample	Approach portal	Patient position	Knee angle	Needle size	Compression	Imaging technique
Moorjani et al. (2008) [32]	44 patients requiring arthrocentesis 47 palpable effusive knees	SL			22-g, 3.81 cm	Manual compression/milking	
Zuber et al. (2003) [33]		SL	Supine	180° or 90°	21-g, 2.54 cm	Manual compression	
Goldman et al. (1998) [34]	143 patients with clinical effusions	Lateral OR medial approaches		Slight flexion for compression			
Cardone et al. (2003) [35]		SL/SM LMP/MMP AL/AM	Supine Supine Seated	slight flexion slight flexion 120°–90° –	18, 20 or 22-g, 3.81 cm	Manual compression/milking	
Li et al. (2019) [36]	21 "dry taps" knees 119 "wet taps" knees	SL	Supine			+ saline solution injection	
Roberts et al. (1998) [37]		AL/AM	Seated	90°	16–18-g		
Boss et al. (2013) [38]		SL/SM LMP/MMP AL/AM	Supine Supine Seated	Extension Extension 90°	18–22-g		US optional
Brahmbatt et al. (2022) [39]	50 effusive knees	AL	Seated	90°	22-g	Pneumatic compression	
Pascual et al. (2009) [40]	Non-effusive knees	SM MMP			23–25-g	Gentle massage of medial and lateral dimples	
Tieng et al. (2022) [41]		SL	Supine		18–22-g	Gentle manual compression	
Voll et al. (2013) [42]		SL	Semi-Fowler's	15°–20° flexion	18-g	Manual pressure on opposite side	

SL superolateral, *SM* superomedial, *LMP* lateral mid-patellar, *MMP* medial mid-patellar, *AL* anterolateral, *AM* anteromedial, *US* ultrasound, *CT* computer tomography, *MRI* magnetic resonance imaging. If items remain blank, no information was given in the study

volume of aspirate [27]. Brahmbatt et al. used pneumatic compression in a comparative trial and found significant increase in synovial fluid uptake [39] compared to no compression while seated in 90° flexion. As opposed to the other studies, the authors made use of an inexpensive and commonly owned cuff, such as a thigh blood pressure leg cuff.

Imaging (Table 1, eighth column)

Two studies compared conventional landmark-guided and US-guided arthrocentesis. Wiler et al. found no significant difference in success rate (US-guided, 37/39 vs. landmark-guided, 25/27; $p=1.0$), nor in the amount of fluid obtained (US-guided, 45.33 mL (95% CI 35.45–55.21) vs. landmark-guided, 34.7 mL (95% CI 26.09–43.32; $p=0.17$) [25]. Sibbitt et al. demonstrated that US-guidance improved outcomes of arthrocentesis. The volume of aspirated fluid was larger (US-guided, 34 mL ± 25; landmark, 12 mL ± 10; 95% CI 110–276; $p=0.0001$) and the percentage of successful diagnostic arthrocentesis was larger [23]. Boss et al. [38] argue that US guidance is patient-friendly due to reported lower pain scores [23].

Non-effusive knees

Non-effusive knees were reported to be difficult to aspirate [27, 29, 36]. Various indications of approach portal efficacy were given. While studies have preconized infrapatellar approaches for knees containing minimal fluid to aspirate, others recommended using any but these ones, as they are notorious for dry taps [22, 35, 43]. Moreover, the use of a compressive brace was found to also increase aspirate volume in non-effusive knees [27].

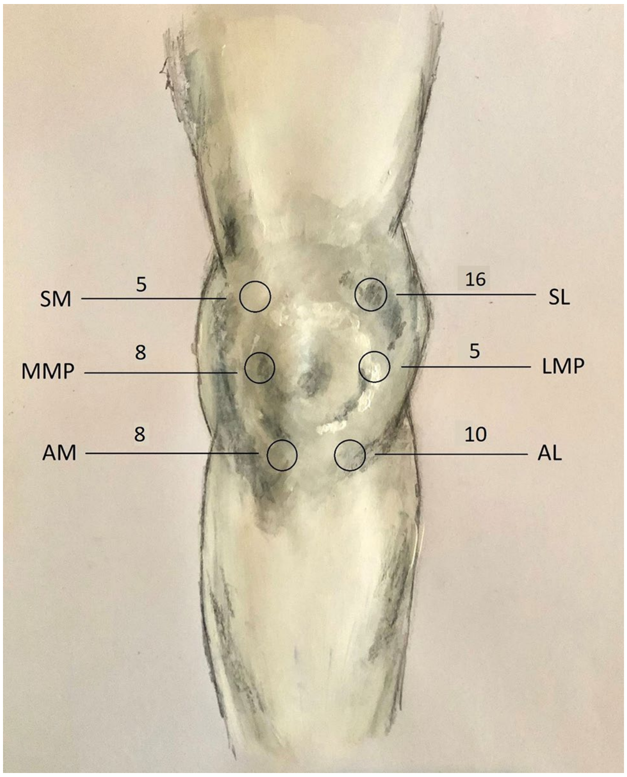

Fig. 2 Location of conventional approach portals. Noted are the number of studies on arthrocentesis and synovial biopsy which are recommending them. *SL* superolateral, *SM* superomedial, *LMP* lateral mid-patellar, *MMP* medial mid-patellar, *AL* anterolateral, and *AM* anteromedial

The study by Bhavsar et al. reported that the use of a compressive brace increased the absolute volume of fluid to be aspirated by 293% [27]. In addition, several studies investigated saline-solution injections to retrieve enough synovial, by comparing it to conventional landmark-guided arthrocentesis. One study reported the sensitivity and specificity of saline solution lavage and reaspiration were 0.851 (95% CI 0.717–0.938) and 0.857 (95% CI 0.697–0.952). It was concluded that for "dry taps" (≤ 1.0 mL), saline solution lavage before reaspirating was an appropriate technique. By injecting up to 15 mL of saline solution, researchers of a second study were able to recover synovial fluid samples. However, saline-solution injections may overly dilute SF, which may explain why the study observed that concentrations in retrieved fluid were not all associated with concentrations of conventionally retrieved fluid, and why it may not recover a similar cell count (mean total protein content = 20.4% of that of traditional aspirate, $p < 0.0001$) [29].

Biopsy techniques

The preferred biopsy technique for synovium was found to vary in image guiding, approach portals, needle placement, device specifications, patient handling, and sample volume (Table 2).

Approach portal and patient position (Table 2, third, fourth and fifth columns)

Similarly to arthrocentesis, the SL was widely recommended to obtain biopsies (4 out of 8 studies). Studies focusing on blind synovial biopsies [48, 49], recommended the biopsy tool to be introduced through the lateral suprapatellar recess or the suprapatellar pouch. Infrapatellar approaches were especially recommended for arthroscopy [47, 51].

Information regarding patient position and knee angle for synovial biopsies was rare, but a supine patient position was recommended in three studies [48–50].

Biopsy device (Table 2, sixth column)

Five types of needles were identified: Parker-Pearson needle, Tru-cut needle, a semi-automatic biopsy system, an automatic Achieve needle, and a Quick-Core biopsy needle. Needle sizes were mainly 14-gage (1.63 mm) or 16-gage (1.29 mm).

Forceps were widely recommended for arthrocentesis, including grasping, semi-rigid, rigid, and retrograde forceps. Forceps diameters ranged from 1.8 to 2.7 mm [51]. Please note that Baeten et al. reported that using 1.8 and 2.1 mm forceps may result in samples which may too small for certain histological analysis technique [51].

Sample number, size, and quality (Table 2, seventh column)

Consensus regarding the number of synovial samples to be collected for tissue analysis is scarce. Recommendations for sample number varied from 3 and up to 20 [45, 50, 51]. Regarding sample size, Hügle et al. reported tissue samples ranging from 2.0 to 4.3 mm in length and 1.4–2.6 mm in width, using their own designed 1-piece prototype [48]. Moreland et al. reported large amounts of approximately 10 g using a microshaver [47]. To prevent sampling error, it was suggested to take sampling biopsy cores from different locations in the synovial [45].

Image-guided techniques (Table 2, eighth column)

Four studies recommended the use of an image-guided synovial biopsy technique [19, 44, 45]. US examination using grayscale and power Doppler can be used to assess synovial hypertrophy and synovial vascularity, respectively. US-guided biopsy as a diagnostic tool was found superior to CT-guided biopsy with a positive yield in 94% of patients against 86% [44].

Table 2 Results of 8 articles on synovial biopsy technique, approach portal, patient position, knee angle, biopsy devices used, sample, and imaging

Study	Population sample	Approach portal	Patient position	Knee angle	Biopsy device	Sample	Imaging technique
Kondo et al. (2019) [19]	44 patients with rheumatoid arthritis	SL		150°	16-g semi-automatic biopsy system		US
McKee et al. (2020) [44]	35 knees	Defined using image-guidance			14-g Achieve needle		US CT
Sitt et al. (2015) [45]		Defined using image-guidance		180°	16-g tru-cut needle 15-g coaxial needle	Around 3 biopsy cores obtained	US
Baeten et al. (1999) [46]	150 patients with synovitis	AL AM			Semi-flexible biopsy forceps (diameter 1.8 mm)	12–20 biopsy cores	Needle arthroscopy
					Rigid biopsy forceps (diameter: 2.1 mm OR 2.7 mm)		Needle arthroscopy
Moreland et al. (1995) [47]	47 patients (51 procedures)	AL AM			Stryker microshaver (2.5–3.5 mm)	Around 10 g	Needle arthroscopy
Hügle et al. (2015) [48]	8 cadavers	SL			New device with a convex trocar and internal plunger with a cutting blade at the distal end	Mean length: 2.4 mm Mean width: 2.0 mm	Pre-procedural: US/MRI
Hügle et al. (2014) [49]		SL	Supine		Retrograde biopsy forceps		Preprocedural: US/MRI
Kondo et al., 2021 [50]	4 inflammatory knees	SL	Supine		16–18-g aspiration-type semi-automatic cutting needle	Minimal 5 samples if tolerated	US

SL superolateral, *SM* superomedial, *LMP* lateral mid-patellar, *MMP* medial mid-patellar, *AL* anterolateral, *AM* anteromedial, *US* ultrasound, *CT* computer tomography, *MRI* magnetic resonance imaging. If items remain blank, no information was given in the study

Two studies performed arthroscopic synovial biopsy [47, 51]. Although arthroscopic biopsy is more invasive and expensive, this technique ensures collection of adequate and high-quality samples. The use of needle arthroscopes was preconized ranging from 1.8 mm diameter (2.4 mm portal diameter) to a 2.7 mm diameter (4.0 mm portal diameter).

Two studies reported a blind biopsy technique [48, 49]. Results indicated lack of visualization and localization of synovial lesions and difficulty to retrieve sufficient synovial tissue samples from a non-swollen joint [48, 49]. Preprocedural imaging helped to locate synovial lesions and/or thickening [48, 49]. Ultrasonography was predominantly used to locate biopsy cores before sampling, but also yielded the best results when compared to computer tomography [44, 45].

Discussion

This review summarized the evidence and recommendations for the preferred techniques in SF arthrocentesis and synovial biopsy. Evidence for superiority was found for use of imaging, particularly US, and the use of a compressive device. However, comparative studies were lacking for other aspects of the technique of arthrocentesis and synovial biopsy (Fig. 3).

Arthrocentesis

Evidence was found in favor of mechanical compression and ultrasound-guidance (Table 1). Recurring recommendations were found on the use of the SL approach, the use of an 18-gage (3.81 cm) needle. For non-effusive

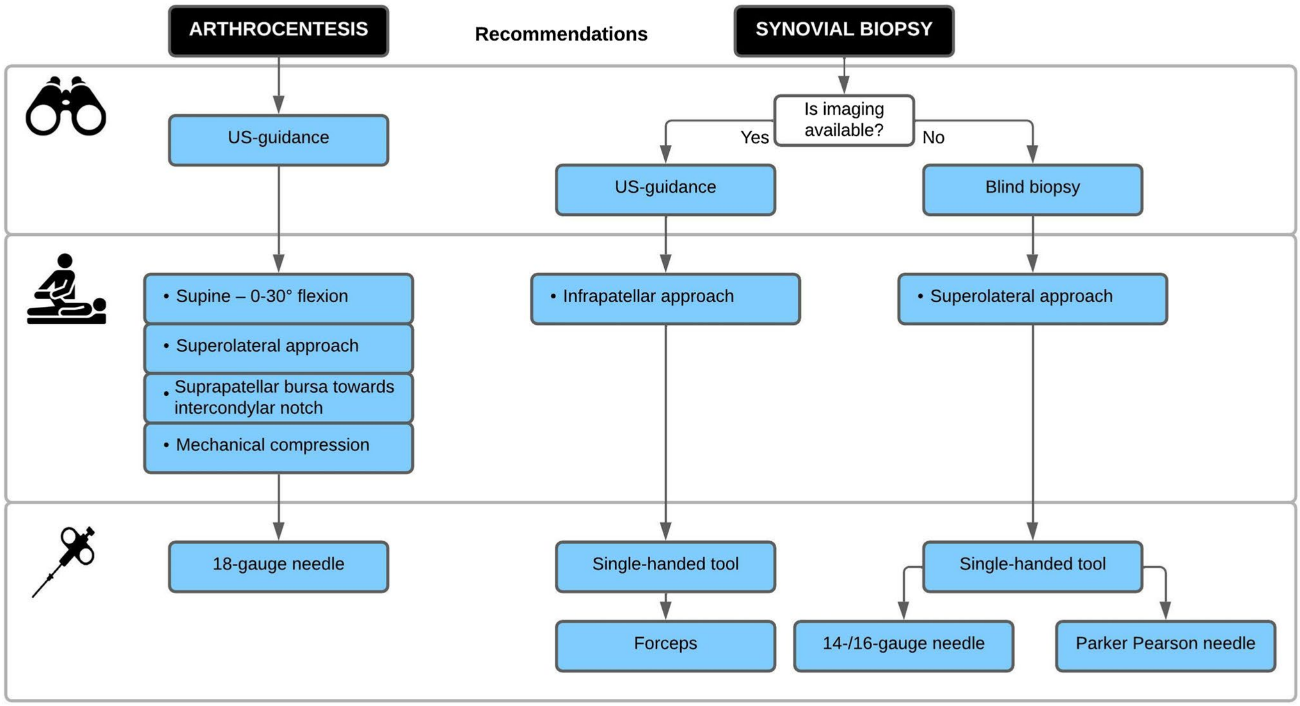

Fig. 3 Summary of the findings on the best practices of arthrocentesis & synovial biopsy. The top box includes recommendations concerning observation and imaging. The middle box includes the findings related to patient position and needle placement. The bottom box includes recommendations regarding tools and their use

knees, mechanical compression is recommended. Successful saline-solution injections were found to retrieve fluid. While authors expressed their concerns, there is no evidence regarding hampered biomarker analysis.

The SL approach was found to be frequently applied through the literature. While no comparative studies were found, a review by Hermans et al. concluded in 2011 that the SL approach has the highest pooled accuracy rate of 91% (95% CI 84–99%) [52]. However, accuracy rates vary throughout the literature with as low as 55% reported [53, 54]. Differences in success rates may be explained by various factors, including practitioners' experience and preferences, needle length and volume of the effusion [43, 52]. Recommendations regarding suprapatellar approaches are in adequacy with past research. Studies using imaging techniques have demonstrated that SF distributes maximally and most frequently into the suprapatellar bursa [55, 56]. It was further demonstrated that effusions were more notably observed in the lateral part of the pouch [57]. This could explain the preference for the SL approach and its needle placement recommendations. The most used needle size was 18-gage (1.02 mm) needle with a length of a 3.81 cm, however, needle size may vary depending on patients and their effusions.

Mechanical compression was found superior to manual or no compression in terms of facilitating the procedure and allowing a more thorough aspiration [27, 28]. Although useful to displace SF, manual compression does not allow proper compression of all synovial compartments simultaneously. Braces and cuffs allow for the fluid located in the medial and inferior knee compartments to be displaced toward the suprapatellar bursa where it can be aspirated [27]. Other literature have attested the efficacy of routine mechanical compression, demonstrating that mechanical compression was associated with a 231% increase in mean aspirate volume, as well as increased the time before a future intervention is necessary [58]. No comparative studies were found on which is the most efficient technique: pneumatic compression or compressive braces.

Ultrasonography (US) was the most recommended imaging technique used to locate areas where the most fluid is contained before the procedure. Conclusions of the included studies diverged for comparing landmark-guided and US-guided aspirations. However, several recent systematic reviews demonstrated that US-guidance improves needle placement accuracy [59, 60].

For non-effusive knees, compression and saline-solution injections were used successfully in retrieving SF [29, 36]. However, pitfalls of the latter technique were noted. As stated in the literature, saline-solution injections may overly dilute SF, rendering analysis and cell counts of the retrieved fluid inaccurate if not adjusted for the dilution [29]. At last, a study developed a modified AL approach aiming for the synovial membrane of the medial femoral condyle, which they found highly accurate and effective for non-effusive knees [61].

Synovial biopsy

For synovial tissue sampling, most commonly issued recommendations were the use of suprapatellar and infrapatellar approaches, the use of 14 to 16-gage single-hand-operated needles (e.g., Parker-Pearson needle), as well as the use of ultrasonography and arthroscopy as effective imaging tools (Table 2).

With regards to synovial biopsies, three techniques were highlighted: blind biopsy, image-guided biopsy, and arthroscopic or needle arthroscopy biopsy. Each technique has their advantages and disadvantages. While minimally invasive and well-tolerated, blind synovial biopsies were found to possibly fail to collect sufficient tissue samples and does not allow visualization [48, 49]. Image-guided biopsies were also described as minimally invasive and well-tolerated, but in contrast, offered visualization for collection of good quality tissue [19, 44, 45]. Finally, while offering the best visuals, arthroscopic biopsy was found to be much more invasive and technically demanding [47, 51]. Unfortunately, there is no study comparing the efficacy of these techniques. Nonetheless, a recent retrospective study in patients with inflammatory arthritis demonstrated that blind biopsies were significantly less reliable than US-guided procedures or arthroscopy in retrieving synovial tissue, and that US-guided procedures were as successful as arthroscopic biopsies in large joints [62]. However, in case imagery is unavailable, blind biopsies remain an efficient alternative for sampling.

Similarly, to the findings on arthrocentesis, the SL approach was more often used if opted for blind biopsy [63]. Regarding biopsy devices, recommendations diverged, and as none of the included studies compared tools' efficacy, it impossible to draw a conclusion with most recommended tool. Worth mentioning is the following. The advantage of the Retroforceps is that its fluid channel linked to a suction portal, allowing examiners to collect SF and synovial tissue samples simultaneously [49]. The Parker-Pearson needle, being the most used one for this technique, allows for the collection of multiple samples, while being a technically simple, single-hand-operated tool [64, 65].

Studies on image-guided biopsies also had varying recommendations. Most authors recommended using imaging tools to locate biopsy cores exists, which in turn define the entry point and patient placement [44, 45]. The most frequent portal identified in the literature remains the lateral entrance of the suprapatellar bursa [65]. Once again, a variety of single-hand-operated biopsy tools were used without comparison to recommend the most efficient. However, considering the results it seems that 14 to 16-gage is an appropriate diameter size. Literature further suggests the effectiveness of US-guidance with features such as power Doppler and grayscale to locate hypertrophy and highly vascularized areas [19, 65].

When performing arthroscopic biopsies, the combination of portals is supported by another study aiming to standardize the procedure of arthroscopic biopsy [65]. Different biopsy devices were used, but the results seem to indicate an incline for forceps larger than 2.1 mm. Likewise for the potential standardized protocol, the author recommends using a 2.3 mm rigid grasping forceps [65]. Unfortunately, no comparison was drawn on the efficacy of the different types of tools. Arthroscopy, seen as the current gold standard, allows examiners to have direct vision to sample adequate tissue [47, 51, 65, 66]. It provides a way for examiner to evaluate the state of the hyperemia and/or hypertrophy of the tissue before sampling [51].

Findings on sample numbers are indicating that the ideal amount would be between 3 and 20 samples. Not enough information is given on sample size, which is why no conclusion can be drawn on the appropriate size for sampling. More studies are advising to obtain and evaluate samples from at least six to eight different sites within the joint to prevent sampling errors and over- or underestimation of inflammation [65, 67].

Regarding the prospect of collecting SF and synovial tissue simultaneously, evidence is absent. But, as can be seen in the results of Tables 1 and 2, one can identify three entry portals (the SL, AL and AM) that have been recommended for successful application of both techniques. Moreover, aside from the Retroforceps being able to collect both SF and synovial tissue, the literature also indicated the possibility to retrieve SF while performing arthroscopic or needle arthroscopy biopsies [51]. More studies resorting to the use of arthroscopy, reported extracting SF before lavage and sampling of synovial biopsy cores [68].

The main limitation of this study resides in the nature of the included studies. Twenty-one out of thirty-three papers were either qualitative guidelines and/or observational studies. The lack of quantitative comparative studies results in experience-based best practice recommendations, rather than evidence-based guidelines. Therefore, more quantitative comparative studies are needed, especially regarding synovial biopsy techniques, biopsy device efficacy and simultaneous collection of SF and synovial tissue. Ideally, standardization and ease of application of these techniques will contribute to retrieval of large amounts of quality tissue samples for biomarker analysis. It would be important to test the application of these recommendations altogether on patients and evaluate their outcomes. More limitations of this review include the lack of analysis of the risk of bias and heterogeneity. Standard risk of bias checklists are designed to identify bias in the inclusion procedure and execution of clinical studies. The variables assessed are not applicable to the majority of the included studies, as e.g., a technique description paper does not rely on the included patients or blinding. Furthermore, preregistration of reviews is preferable.

Conclusion

Not enough comparative studies exist to date to allow generation of evidence-based protocols for biopsy techniques. However, based on few comparative studies combined with the reported clinician's preference throughout the literature, we extracted the following suggestions: for synovial fluid aspiration, we suggest a SL approach, performed with the subject in a supine position with the knee either fully extended or slightly flexed, while aiming the needle into the suprapatellar bursa toward the intercondylar notch. An 18-gage (3.81 cm) can be used to start with, as well as mechanical compression and ultrasound-guidance. For synovial biopsies, image-guided and arthroscopic biopsy techniques are superior to blind biopsies, which may still be an alternative for when imagery is unavailable. US can be used in combination with a single-handed operated biopsy tool. Arthroscopic biopsy can be conducted using rigid biopsy forceps in combination with small-bores arthroscopes, performed using either both infrapatellar or AL and SL approaches. At last, simultaneous collection may be considered through either SL or infrapatellar portals, using a 14 to 18-gage single-handed needle or Retroforceps, as well as under arthroscopic biopsy. Clinical implementation of these recommendations is depended on clinical experience, clinical goal and added value for clinical decision-making, and patient's consent.

Appendix

See Tables 3, 4, 5

Table 3 Search query used to collect scientific literature from the PubMed database on 31-05-2022

Search	Query	Items found
#1	Search (knee*[tiab] OR patellofemoral[tiab])	173 128
#2	Search (aspirat*[tiab] OR arthrocentesis[tiab])	121 260
#3	Search (techni*[tiab] OR approach*[tiab] OR procedur*[tiab] OR practic*[tiab] OR maneuver*[tiab] OR portal*[tiab])	5 671 694
#4	Search (drain*[tiab] OR collect*[tiab] OR obtain*[tiab])	2 773 611
#5	Search synovial fluid[tiab]	13 413
#6	Search (#1 AND #3 AND (#2 OR (#4 AND #5)))	691
#7	Search (collect*[tiab] OR obtain*[tiab] OR biops*[tiab] OR extract*[tiab] OR sampl*[tiab] OR retriev*[tiab] OR resect*[tiab] OR dissect*[tiab] OR forceps[tiab] OR trocar*[tiab])	5 849 859
#8	Search (synovium[tiab] OR fat pad*[tiab] OR Hoffa*[tiab])	16 310
#9	Search (#1 AND #3 AND #7 AND #8)	199
#10	Search (#6 OR #9)	874

Table 4 Search query used to collect scientific literature from the Embase databaseon 31-05-2022

Search	Query	Items found
1	(Knee* or patellofemoral).ti,ab,kw	224 210
2	(Aspirat* or arthrocentesis).ti,ab,kw	174 910
3	(Techni* or approach* or procedur* or practic* or maneuver* or portal*).ti,ab,kw	7 065 889
4	(Drain* or collect* or obtain*).ti,ab,kw	4 722 356
5	Synovial fluid.ti,ab,kw	17 540
6	1 and 3 and (2 or (4 and 5))	1 340
7	(Collect* or obtain* or biops* or extract* or sampl* or Retriev* or resect* or dissect* or forceps or trocar*).ti,ab,kw	8 495 090
8	(Synovium or {fat pad} or Hoffa*).ti,ab,kw	20 649
9	1 and 3 and 7 and 8	463
10	6 or 9	1 784
11	Limit 10 to conference abstract status	784
12	10 not 11	975

Table 5 Search query used to collect scientific literature from the web of science database on 31-05-2022

Search	Query	Items found
1	TS = (knee* OR patellofemoral)	196 332
2	TS = (aspirat* OR arthrocentesis)	140 016
3	TS = (techni* OR approach* OR procedur* OR practic* OR maneuver* OR portal*)	12 054 257
4	TS = (drain* or collect* or obtain*)	7 923 501
5	TS = (synovial fluid)	19 631
6	#1 AND #3 AND (#2 OR (#4 AND #5))	885
7	TS = (collect* or obtain* or biops* or extract* or sampl* or retriev* or resect* or dissect* or forceps or trocar*)	12 817 476
8	TS = (synovium or "fat pad" or Hoffa*)	13 866
9	#1 and #3 and #8 and #9	247
10	#6 or #9	1 100
11	Exclude conference proceedings	1 066

Total 2915 hits

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Author contributions Conception and design: KSE, GJMT, PJE. Data collection: MF-B and KSE. Writing: original draft: MF-B and KSE. Writing: Review and editing: GJMT, PJE. Final approval: MF-B, GJMT, PJE, KSE. To have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and have drafted the work or revising it critically for important intellectual content; and gave final approval of the version to be published; and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest No conflict of interest related to this study was reported by the authors.

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