Micro-Fragmented Adipose Tissue Has No Advantage Over Platelet-Rich Plasma and Bone Marrow Aspirate Injections For Symptomatic Knee Osteoarthritis. A systematic review and meta-analysis.

Running Title: Meta-Analysis MFAT

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Abstract

Background:

Micro-fragmented adipose tissue (MFAT) has been proposed for intra-articular treatment of knee osteoarthritis. There is little data comparing the outcomes of treatment between MFAT and other biologic treatments.

Purpose

To perform a systematic review and meta-analysis comparing micro-fragmented aspirated fat injections to other orthobiologics, hyaluronic acid and corticosteroid injections for symptomatic knee osteoarthritis.

Study Design

Systematic review and meta-analysis

Methods:

Systematic review of Medline, Embase, Scopus, and Google Scholar, including all level 1-3 from 2000 to 2023. Validated knee scores (VAS, KOOS, Lysholm, IKDC) were included as outcome measures. Risk of bias was assessed using the Cochrane

Collaboration's tools. The GRADE system was used to assess the quality of the body of evidence and the modified Coleman Methodology score (CMS) was used to assess study quality. Heterogeneity was assessed using χ^2 and I^2 statistics.

Results:

Five studies were included in the analysis. One study had a high risk of bias; four studies had some risk of bias. The overall study quality was fair, and the certainty of evidence was low. The pooled estimate for VAS did not demonstrate significant differences at 3, 6 and 12 months. The pooled estimate for KOOS sub-scores pain, other symptoms, activities of daily living, sports and quality of life did not demonstrate significant differences at 3, 6 and 12 months.

Conclusion:

The results of this systematic review and meta-analysis demonstrated that there were no statistically significant differences for both the clinical outcomes and pain between MFAT and other orthobiologics [PRP, BMAC] for the treatment of knee osteoarthritis. However, modest study quality, some risk of bias and low certainty of evidence reduce external validity, and these results must be viewed with some caution.

Key Terms:

adipose lipoaspirate; micro fragmented adipose tissue; knee osteoarthritis; biologics; platelet-rich plasma; bone marrow aspirate

What is known about the subject

There is an increased interest in the use of orthobiologic treatments for patients with knee osteoarthritis. The safe and effective use of platelet-rich plasma has been

demonstrated by numerous randomized controlled trials and case series. Recently, the intra-articular application of MFAT has also been proposed to be a feasible option. Numerous studies have shown significant clinical improvement. MFAT has the potential advantage of providing growth factors and possibly a certain number of progenitor cells without the need to manipulate cells or use other expansion techniques. However, there is little comparative outcomes data for various orthobiologic treatment modalities and the sample size of published studies is rather low.

What this study adds to existing knowledge

Osteoarthritis (OA) is a condition caused by the degeneration of cartilage, and when occurring in the knee, can lead to significant morphological and functional changes in the knee joint [Mikkelsen RK, et al. Treatment of osteoarthritis with autologous, micro-fragmented adipose tissue: a study protocol for a randomized controlled trial. Trials 2021; 22 (1):748. [PMID 34706757]. Unfortunately, no current medical treatment available can reverse these changes and ultimately, total knee arthroplasty (TKA) is the only reasonable surgical option. Orthobiologics and minimally manipulated cellular-based treatments have created interest for the treatment of mild to moderate knee osteoarthritis but continues to be controversial [Jones IA, et al. A randomized, controlled study to evaluate the efficacy of intra-articular, autologous adipose tissue injections for the treatment of mild-to-moderate knee osteoarthritis compared to hyaluronic acid: a study protocol. BMC Musculoskelet Disord 2018; 19 (1): 383. [PMID 30355323]. A PubMed search by the authors showed that 31 clinical studies were published within the last five years; five of which were designed as controlled randomized trials. [3,13,41,25,22] Dallo et al demonstrated statistically

significant superior results in patients treated with MFAT at 6 and 12 months. [41] Zaffagnini et al could not show any significant between group differences but reported that a higher percentage of patients reached MCID in the MFAT group. [17] Three studies did not observe significant differences between group outcomes. [3,22,25] Unfortunately, the sample size of these studies is low with less than 55 patients per group. This could have resulted in Type II errors and the obvious lack of power may have invalidated their results. When using the MCID values for VAS (δ2), [Katz NP, et al. Determining the clinical importance of treatment benefits for interventions for painful orthopaedic conditions. J Orthop Surg Res 2015; 10:24. [PMID 25645576] an alpha of 0.5, power of 0.9, medium effect size of 0.5, a total number of 172 patients are required. The benefit of pooling using meta-analysis tools not only affords the inclusion of small or inconclusive studies but also allows for obtaining higher quality evidence and analysis of sources of bias [Ioannidis JP & Lau J. Pooling research results: benefits and limitations of meta-analysis. Jt Comm J Qual Improv 1999; 25 (9):462-469. [PMID 10481815]. This meta-analysis has increased the total sample size to 346 patients and confirms that there is no clinical benefit of MFAT injections when compared to other orthobiologics, specifically PRP or BMAC.

Introduction

OA is an increasingly prevalent condition with worldwide impacts on many health outcomes. [1] The cumulative 5-year incidence of grade 1-3 knee osteoarthritis has been reported to be nearly 18% in individuals aged over 45 years and the weighted prevalence of radiographic knee osteoarthritis ranged from 13-35%. [1] The condition is typically caused by irreversible cartilage damage and often requires eventual surgical treatment. [3] The 2019 OARSI guidelines for non-surgical management of knee

osteoarthritis include weight management, exercise programs, topical and systemic anti-inflammatory drugs and intra-articular injections with hyaluronic acid and corticosteroids. [36]

The use of orthobiologics is a relatively new concept and includes stromal cells, platelet-rich plasma (PRP), bone-marrow aspirate concentrate (BMAC), and micro-fragmented adipose tissue (MFAT) injections. [43] Some studies have shown clinical superiority of PRP and BMAC injections over hyaluronic acid injections. [5,22] Recently, intraarticular injections with mesenchymal stromal cells have been proposed as a feasible option. [37] However, clinical studies with mesenchymal stromal cells could not demonstrate any functional improvement or pain relief when compared to other orthobiologics and placebo. [13,41,42] Therefore, the application of mesenchymal stromal cells lacks support, and its use should be approached cautiously until stronger evidence is available. [38,41] On the contrary, Kim et al. demonstrated that autologous adipose-derived mesenchymal stromal cells resulted in significant pain relief and functional improvements at 6 months placebo. [28]

MFAT contains collagen, microvascular networks, and cell clusters including pericytes, adipocytes and mesenchymal stromal cells. [47] MFAT can be harvested by lipoaspirate and does not require isolation or activation of cells. [35] In theory, intra-articular injections with MFAT to treat patients with knee osteoarthritis could be an innovative approach [35] and clinical studies have shown short-term improvements in pain, function, and quality of life. [19,39,47] In a prospective level 2 therapeutic study Dallo et al. have shown that MFAT resulted in significantly better improvements for the KOOS symptoms, KOOS ADL and Tegner scores at 6 months when compared to

a combined injection of PRP and hyaluronic acid. [14] Zaffagnini et al. reported no differences in clinical outcomes between MFAT and PRP in a randomized controlled trial. [48] However, the authors noted that MFAT had lower failure rates [15%] compared to 25% noted with PRP. [48] Moreover, MCID was reached in 75% the MFAT group compared to only 35% in the PRP group. [48]

The purpose of this study was therefore to perform a systematic review and meta-analysis of both randomized controlled and observational studies comparing MFAT to other available orthobiological injections for patients with knee osteoarthritis.

Methods

The preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, [33] and the updated guidelines described in the Cochrane Handbook [12] were followed when conducting this study.

Eligibility criteria

Studies that compared micro-fragmented adipose tissue (MFAT) injections to other orthobiologic injections such as platelet-rich plasma (PRP) and bone marrow aspirate concentrate (BMAC), synthetics agents (hyaluronic acid), and corticosteroid injections were included if they fulfilled the inclusion and exclusion criteria. Level I-III evidence studies were included if they were published between January 2000 and August 2023. Level III evidence studies were included to increase sample size and increase the generalizability of the results. [4] Two previous studies have shown that the inclusion of level III evidence studies does not cause any differences in the risk estimate of the treatment effect of an intervention that was derived from meta-analysis

of either randomized controlled trials, observational studies, or a combination of these two study types. [8,18] Studies were also included if they compared more than two interventions.

For analysis, each intervention was then compared to the MFAT treatment arm. Other inclusion criteria included: symptomatic knee osteoarthritis (Kellgren Grade I-IV), mean age of older than 40 years, minimum follow-up of 6 months, and inclusion of at least one validated outcome score (KOOS, VAS, IKDC, Lysholm). Studies that included patients who had received knee injections with any of the above agents prior to study commencement or injected these agents as adjuvant treatment with knee surgery in the past 3 months were excluded. Clinical case level of evidence (LOE) IV studies, case series, abstracts, and conference proceedings were also excluded. If the LOE was not mentioned in the study, the level of evidence was determined as per standard research guidelines. [21]

Literature search

A systematic review of the literature was performed to identify all publications in English and German, screening the databases Medline, Embase, Scopus, and Google Scholar. These databases were screened using the following terms and Boolean operators: "orthobiologics" AND/OR "platelet-rich plasma" AND/OR "PRP" AND/OR "bone marrow aspirate concentrate"; AND/OR "BMAC" AND/OR "hyaluronic acid" AND/OR "adipose stem cells injections" AND/OR "micro-aspirated fat tissue" AND/OR "MFAT"; AND/OR "knee osteoarthritis"; AND/OR "degenerative knee". For the Medline search the MeSH term "osteoarthritis, knee" was used with the following qualifiers: drug therapy and therapy. One reviewer

conducted independent title and abstract screening. Disagreements between reviewers were resolved by consensus, and if no consensus was reached, they were carried forward to the full-text review. All eligible articles were manually cross-referenced to ensure that other potential studies were identified.

Data extraction and quality assessment

An electronic data extraction form was used to obtain the following data from each article: level of evidence, country, age, gender, length of follow-up, sample size, clinical outcome scores, range of motion, and complications. Risk of bias was assessed using the Cochrane Collaboration's Risk of Bias Tool. [12] The GRADE system was used by three reviewers to assess the quality of the body of evidence for each outcome measure. [12] The recommendations from the Cochrane Handbook were followed, and an initial level of certainty was assigned. Studies were downgraded if there was a high risk of bias, inconsistency and imprecision of the results, and indirectness of evidence. Studies were upgraded if there were large treatment effects, a dose-response, or reasons to oppose plausible residual bias and confounding effects. Any disagreement between reviewers was resolved by consensus and/or by arbitration between the two senior authors. The modified Coleman Methodology Score was used as a second validated instrument to assess the quality of the included surgical studies. The score ranges from 0-100 and the final score was categorized as excellent (85-100 points), good (70-84 points), fair (55-60 points), and poor (<55 points). [29]

Statistical analysis

Inter-observer differences for study eligibility and risk of bias were measured using Cohen's kappa coefficient. Heterogeneity of the data was assessed using χ^2 and I^2

statistics. Outcomes were pooled using a random effects model if the I^2 statistic was >25%, and a fixed model was used if the statistic was <25%. Pooling of data for clinical outcomes was only performed if a minimum of three studies were available. If standard deviations were not reported the standard deviation was calculated using the following formula: SD = max-min/4. [23] If the included studies did not include tables describing their outcome measures of central tendency and variations, the first author was contacted, and results were requested. All tests of significance were two-tailed, and an α of less than 0.05 was considered significant. If more than ten studies were included, publication bias was assessed in accordance with the guidelines outlined in the Cochrane Handbook. In such instances, funnel plots and Egger's test were subsequently employed. [12] Funnel and forest plots, and all statistical analyses, were performed using STATA SE (Version 13.0; StataCorp, College Station, Texas, USA) for Windows, and the comprehensive meta-analysis software package (CMA), version 3 (Biostat Inc, Englewood, NJ, USA).

Results

Study selection and characteristics

The initial literature search identified 129 studies for consideration. Of those, 42 studies were excluded for duplication, and the titles and abstracts of the remaining 87 publications were checked for eligibility. Fifty-two (n = 52) studies were excluded after inspection of the abstracts. These studies were either published study protocols, basic science studies or narrative reviews. Of the remaining 35 studies, the full text manuscripts were examined. Nine (n = 9) studies were systematic reviews and/or meta-analysis, fifteen (n = 15) studies did not include MFAT, used a combination of various mixed biologics or investigated multiple injections. Six (n = 6) studies were

LOE IV evidence case series. After all exclusions, five (n = 5) studies met all the eligibility criteria and were included in the analysis (Figure 1). [3,14,25,30,48] All 5 studies were published in English between 2019 and 2022 with a cumulative total of 346 cases. A total of 167 were treated with MFAT and 179 cases were treated with other biologics. The study characteristics are summarized in Table 1.

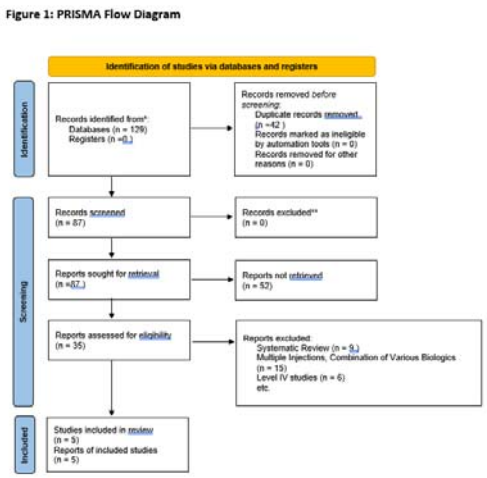

Figure 1: PRISMA Flow Diagram. From the initial 129 records, 5 studies were included in the quantitative synthesis.

Table 1: Summary of all included studies

Authors	LOE	Country	MFAT	Patients (n)	Control	Patients (n)	Follow-Up (months)	Outcomes MFAT-Control
Mautner 2019	II	USA	30 ml lipoaspirate Lipogems® 9 ml MFAT Injection	N=35 F=23, M=12 Mean age 63+11	60 cc BMAC 8cc BMAC Injection	N=41 F=17 M=24 Mean Age 5911	6	VAS 6/12: 2.8+0.38 – 2.5+0.35 KOOS Pain 6/12: 70.4+3.69 – 70.6+3.13 KOOS Symptoms 6/12: 67.6+4.12 – 69.4+3.7 KOOS ADL 6/12: 75.6+3.4 – 79.2+3.05 KOOS Sport 6/12: 46.3+6.33 – 56.1+5.83 KOOS QOL 6/12: 48.0+4.3 – 52.0+3.85
Dallo 2021	II	Italy	60 ml lipoaspirate Lipomas® ? ml MFAT Injection	N=25 F=16, M=9 Mean age 61.5+9.5	LP-PRP + HA Regenlab® 3ml PRP/2ml HA	N=25 F=11, M=14 Mean age 62.5+11.3	12	VAS 6/12: 3.44+1.66 – 3.2+2.09 12/12: 3.4+2.24 – 2.64+2.0 KOOS Pain 6/12: 81.78+17.48 – 77.4+18.63 12/12: 78.63+21.62 – 73.78+17.49 KOOS Symptoms 6/12: 80.97+15.76 – 74.62+15.62 12/12: 77.97+17.47 – 77.3+13.41 KOOS ADL 6/12: 83.62+14.73 – 76.45+18.82 12/12: 82.38+17.49 – 78.15+17.19 KOOS Sport 6/12: 50.0+27.36 – 40.95+26.01 12/12: 52.13+32.06 – 48.87+29.29

								KOOS QOL 6/12: 60.43+18.7 – 55.98+19.76 12/12: 61.8+24.4 – 57.0+23.25
Baria 2022	I	USA	30 ml lipoaspirate Lipogems® 8 ml MFAT Injection	N=28 F=20, M=20 Mean age MFAT 56.1+1.7	156 ml blood Angel PRP Arthrex ® 8 ml PRP injection	N=30 F=10, M=20 Mean age 51.9+2.4	6	VAS 3/12: 16.0+18.8 – 20.57+21.29 6/12: 14.59+19.8 – 19.74+21.65 KOOS Pain 3/12: 81.48+15.24 – 77.32+17.99 6/12: 81.61+16.37 – 80.38+16.07 KOOS Symptoms 3/12: 74.05+17.49 – 76.19+17.78 6/12: 75.37+19.45 – 76.38+17.78 KOOS ADL 3/12: 88.19+12.52 – 83.63+16.86 6/12: 88.85+15.05 – 88.19+12.52 KOOS Sport 3/12: 63.67+22.05 – 64.17+23.05 6/12: 65.86+25.6 – 64.52+27.67 KOOS QOL 3/12: 65.0+18.76 – 59.17+23.14 6/12: 68.1+24.41 – 63.71+21.97
Kaszynski 2022	I	Poland	100 ml lipoaspirate Lipogems® 10 ml MFAT Injection	N=26 F=?, M=? Mean age 55+8	40 ml blood Centrifuge: 7min@2320g 3 ml PRP injection	N=28 F=?, M=? Mean age 57+8	12	VAS 3/12: 3.7+2.5 – 3.2+2.4 6/12: 3.1+2.2 – 3.2+2.4 12/12: 2.8+2.2 – 3.0+2.2 KOOS Pain 3/12: 75.8+12.6 – 76.2+21.8 6/12: 75.1+13.2 – 79.3+17.2 12/12: 78.9+13.2 – 81.5+17.1 KOOS Symptoms 3/12: 75.0+11.8 – 76.3+19.7 6/12: 75.4+16.2 – 75.7+16.9

								12/12: 78.9+16.9 – 79.3+16.3 KOOS ADL 3/12: 79.1+11.3 – 78.7+20.3 6/12: 79.3+15.8 – 83.4+15.0 12/12: 84.0+11.6 – 83.6+18.0 KOOS Sports 3/12: 53.1+18.2 – 55.8+30.4 6/12: 54.8+23.7 – 60.8+25.3 12/12: 66.1+21.2 – 61.5+28.8 KOOS QOL 3/12: 51.3+9.1 – 57.8+23.5 6/12: 55.9+17.0 – 54.1+18.6 12/12: 62.2+18.2 – 59.2+20.5
Zaffagnini 2022	I	Italy	60 ml lipoaspirate Lipogems® 5 ml MFAT Injection	N=53 F=25, M=28 Mean age 54.5+12.1	150 ml blood Centrifuge: 6 min@1480 rpm 15 min@3400 rpm ?ml PRP	N=55 F=19, M=36 Mean age 54.1+10.6	24	VAS 3/12: 5.0+2.5 – 4.3+2.7 6/12: 4.2+2.6 – 4.0+2.6 12/12: 5.3+2.4 – 4.3+2.8 KOOS Pain 3/12: 48.9+18.7 – 54.9+15.7 6/12: 41.6+16.4 – 51.2+17.9 12/12: 47.0+16.4 – 40.9+18.7 KOOS Symptoms 3/12: 52.8+16.6 – 63.2+15.5 6/12: 49.8+16.8 – 51.7+17.5 12/12: 49.4+16.4 – 48.9+18.7 KOOS ADL 3/12: 57.5+17.7 – 58.3+19 6/12: 55.7+16.8 – 55.7+17.5 12/12: 57.4+20.1 – 55.2+21.2 KOOS Sport 3/12: 19.7+27.8 – 19.5+23.7 6/12: 14.9+28.8 – 16.5+24.4 12/12: 18.0+29.6 – 16.1+24.9

								KOOS QOL 3/12: 15.2+20.1 – 32.0+17.1 6/12: 11.0+21.2 – 19.3+19.2 12/12: 14.2+20.5 – 18+22.5

Risk of bias and quality assessment

The findings of the risk of bias assessment are summarized in Table 2.

Table 2.1: Risk of Bias Cochrane Risk of Bias Assessment Within Studies Tool Version 2

Authors	LOE	Bias from Randomization	Bias from Deviations from Intended Interventions	Bias due to Missing Outcome Data	Bias in Measurement of the Outcome	Bias in Selection of the Reported Results	Overall Risk of Bias
Mautner 2019		High	Some	Low	Low	Low	High
Dallo 2021		Some	Some	Low	Low	Low	Some
Baria 2022		Low	Some	Some	Low	Low	Some
Kaszynski 2022		Low	Some	Low	Low	Low	Some
Zaffagnini 2022		Low	Some	Low	Low	Low	Some

Table 2.2: Risk of Bias Cochrane Across Studies Tool Version 2

Risk of bias Cochrane Assessment Tool Version 2

One study [30] was assessed as having a high risk because of the retrospective study design and the lack of randomization. The other four studies [3,14,25,48] were assessed to have some risk of bias. These studies had either bias from randomization or bias from deviations from the intended interventions. The risk of bias across studies was some bias in 80% and high risk of bias in 20%.

Quality Assessment

The Grade quality assessment is summarized in Table 3. All included studies were initially categorized as high level of certainty. Due to the high risk of bias, the study by Mautner [30] was downgraded to a very low level of certainty. The studies by Baria, Dallo and Kaszynkski [3,14,25] were downgraded to a low final level of certainty due to some risk of bias and imprecision of results. The study by Zaffagnini [48] was downgraded to a moderate final level of certainty due to some imprecision of reporting their results. All five studies demonstrated imprecision of results. One study [30] reported wide 95% confidence intervals and the other four studies [3,14,25,48] failed to report the 95% confidence intervals. Given the overall low final level of certainty, the confidence in the effect estimate is therefore low and the true effect may be substantially different from the estimate of the effect.

Table 3: Quality Assessment of the Included Studies using the Cochrane GRADE system

Authors	LOE	Initial Level of Certainty	**Final Level of Certainty**	Risk of Bias	Inconsistency of Results	Indirectness of evidence	Imprecision of Results	Large Effects (Upgrading)	Dose Response (Upgrading)	Opposing Plausible Residual Bias and Confounding (Upgrading)
Mautner 2019	II	High	**Very Low**	High	Some	Low	Some	-	-	Low
Baria 2020	II	High	**Low**	Some	Low	Low	Some	-	-	Low
Dallo 2021	II	High	**Low**	Some	Low	Low	Some	-	-	Low
Kaszynski 2022	I	High	**Low**	Low	Low	Low	Some	-	-	Low
Zaffagnini 2022	I	High	**Moderate**	Low	Low	Low	Some	-	-	Low

The mean modified Coleman score was 54 indicating overall fair study quality. The study by Mautner [30] scored 42 points (poor study quality); the other four studies [3,14,25,48] were scored between 49 to 69 (fair study quality). (Table 4).

Table 4: Quality Assessment of the Included Studies with the Modified Coleman Methodology Score

Authors	**Total Points**	**Study Size**	**Mean Follow-Up**	**Percent of patients with follow-up**	**Number of Interventions**	**Type of Study**	**Diagnostic Certainty**	**Description Surgical Technique**	**Description Post Op Rehabilitation**	**Outcome Criteria**	**Procedures for Assessing Outcomes**	**Description of Subject Selection**
Mautner 2019	**42**	**10**	**2**			**7**	**5**	**5**	**0**	**5**	**3**	**5**
Baria 2020	**49**	**4**	**0**			**7**	**5**	**5**	**0**	**5**	**8**	**15**
Dallo 2021	**59**	**7**	**2**			**7**	**5**	**5**	**0**	**10**	**8**	**15**
Kaszynski 2022	**53**	**4**	**0**			**10**	**5**	**5**	**0**	**10**	**8**	**15**
Zaffagnini 2022	**69**	**10**	**2**			**10**	**5**	**5**	**0**	**10**	**12**	**15**
Total (Mean)	**54**											

Outcome scores: VAS

The clinical outcomes for VAS for all studies are summarized in Table 1. Three studies were included to analyze VAS at 3 months. [3,25,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD 0.120, 95% CI: -0.145 to 0.385, p=0.375, I^2= 16%; Figure 2).

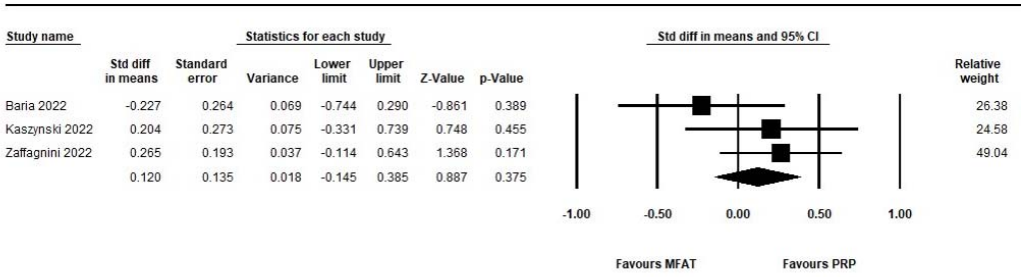

Figure 2: Forest Plot comparing VAS at 3 months could not demonstrate significant differences (p=0.375).

Although the SMD favored other biologicals, the magnitude of effect was small, strongly suggesting that the differences between groups were negligible. [11] All five studies were included to analyze VAS at 6 months. [3,14,25,30,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD 0.153, 95% CI: -0.186 to 0.492, p=0.376, I^2= 62%; Figure 3).

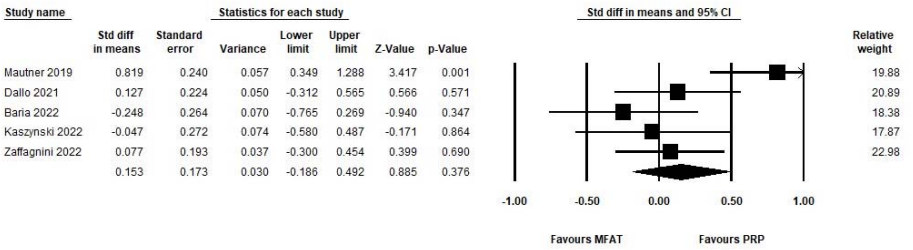

Figure 3: Forest Plot comparing VAS at 6 months could not demonstrate significant differences (p=0.376).

Although the SMD favored other biologicals, the magnitude of effect was small, strongly suggesting that the differences between groups were negligible. [11] Three studies were included to analyze VAS at 12 months. [3,14,25] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD 0.081, 95% CI: -0.172 to 0.334, p=0.529, I^2= 12%; Figure 4).

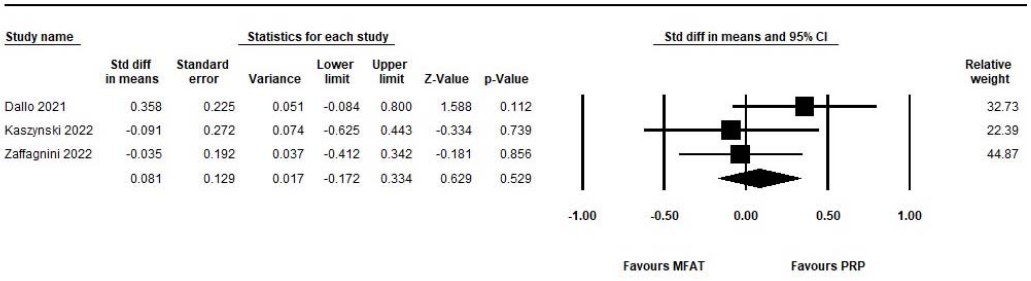

Figure 4: Forest Plot comparing VAS at 12 months could not demonstrate significant differences (p=0.529).

Although the SMD favored other biologicals, the magnitude of effect was very small, strongly suggesting that the differences between groups were negligible. [11]

Outcome scores: KOOS

The clinical outcomes for the KOOS sub-scores for all studies are summarized in Table 1. For the KOOS pain sub-score, three studies were included for analysis at 3 months. [18,27,29] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD -0.064, 95% CI:
-0.329 to 0.201, p=0.638, I^2= 7%; Figure 5).

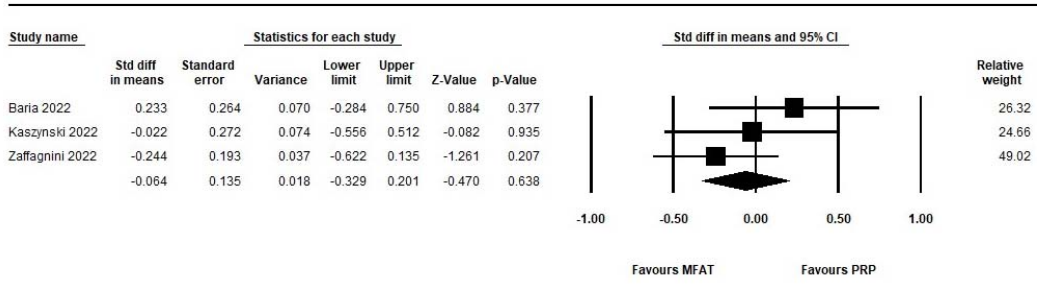

Figure 5: Forest Plot comparing the KOOS sub-score pain at 3 months could not demonstrate significant differences (p=0.375).

For the KOOS pain sub-score, all five studies were included for analysis at 6 months. [3,14,25,30,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD -0.003, 95% CI: -0.200 to 0.205, p=0.979, I^2=0%; (Figure 6).

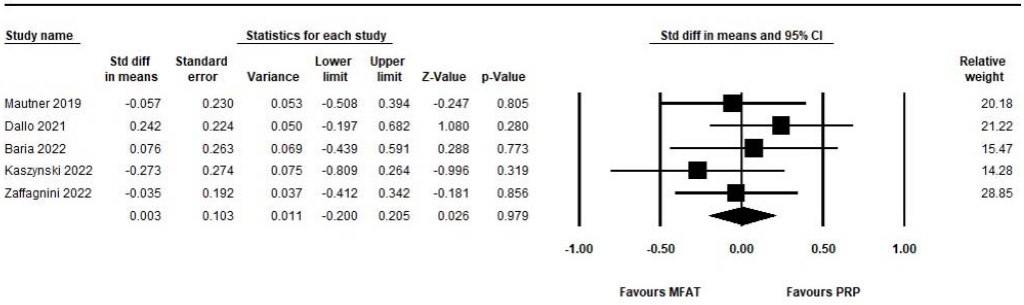

Figure 6: Forest Plot comparing the KOOS sub-score pain at 6 months could not demonstrate significant differences (p=0.376).

For the KOOS pain score, three studies were included for analysis at 12 months. [14,25,48] The pooled estimate did not demonstrate significant differences between FAT and other biologicals (SMD -0.099, 95% CI: -0.470 to 0.272, p=0.602, I^2= 51%; Figure 7). Although the SMD favored MFAT at all follow-up intervals (3-, 6-, and 12-

months), the magnitude of effect was very small, strongly suggesting that the differences between groups were negligible. [11]

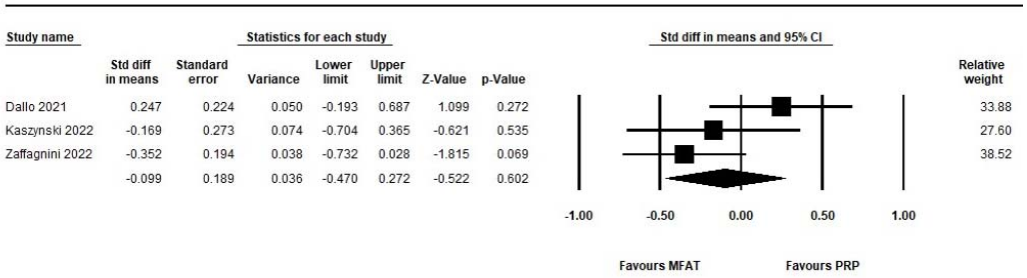

Figure 7: Forest Plot comparing the KOOS sub-score pain at 12 months could not demonstrate significant differences (p=0.52).

For the KOOS sub-score other symptoms, three studies were included to analyze at 3 months. [3,25,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD -0.003, 95% CI: -0.268 to 0.262, p=0.983, I^2= 0%; Figure 8).

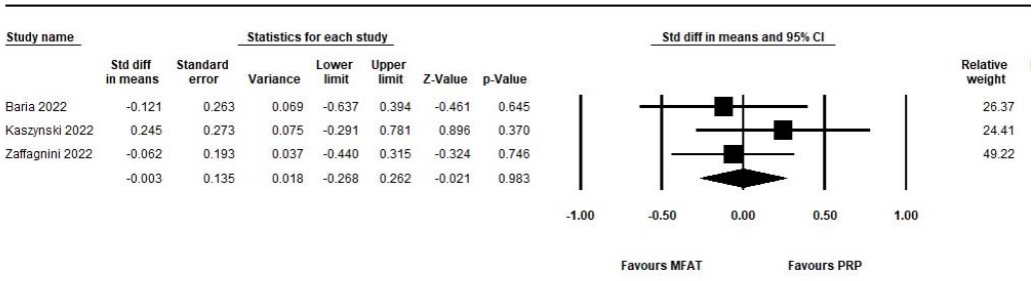

Figure 8: Forest Plot comparing the KOOS other symptoms at 3 months could not demonstrate significant differences (p=0.983).

For the KOOS sub-score other symptoms, all five studies were included for analysis at 6 months. [3,14,25,30,48] The pooled estimate did not demonstrate significant differences

between MFAT and other biologicals (SMD -0.077, 95% CI: -0.281 to 0.128, p=0.461, I^2= 71%; Figure 9).

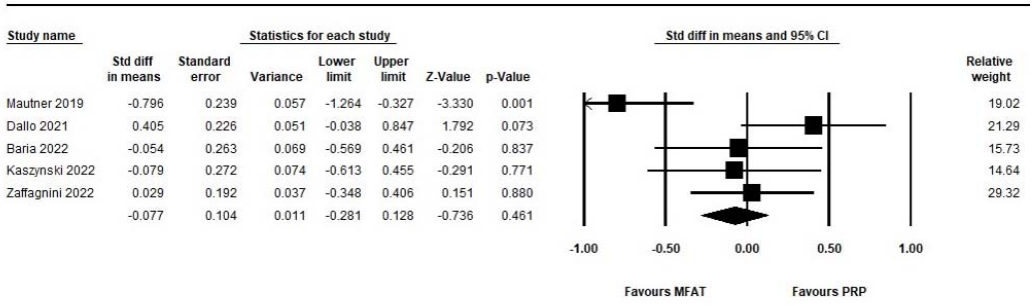

Figure 9: Forest Plot comparing the KOOS sub-score other symptoms at 6 months could not demonstrate significant differences (p=0.461).

For the KOOS sub-score other symptoms, three studies were included for analysis at 12 months. [3,25,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD -0.146, 95% CI: -0.398 to 0.107, p=0.259, I^2=3%; Figure 10). Although the SMD favored MFAT at 6 and 12 months, the magnitude effect was very small, strongly suggesting that the differences between groups were negligible. [11]

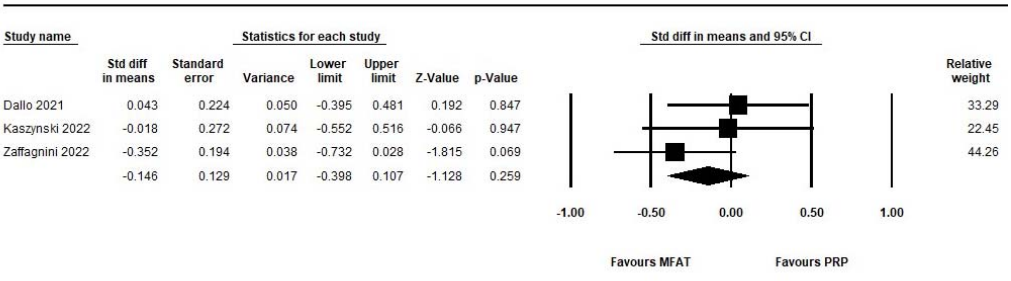

Figure 10: Forest Plot comparing the KOOS other symptoms at 12 months could not demonstrate significant differences (p=0.259).

For the KOOS sub-score ADL, three studies were included for analysis at 3 months. [3,25,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD 0.055, 95% CI: -0.210 to 0.320, p=0.683, I^2= 0%; Figure 11).

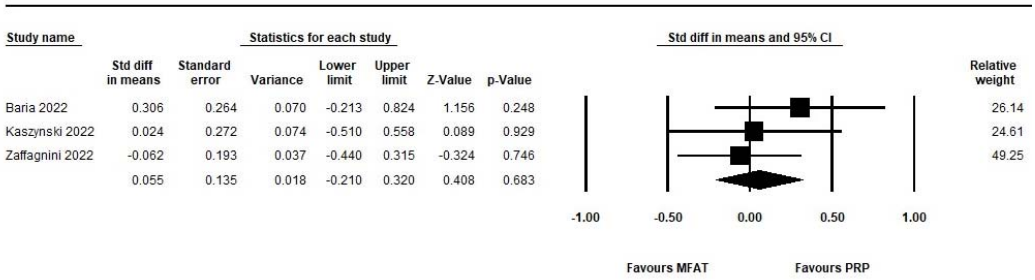

Figure 11: Forest Plot comparing the KOOS ADL at 3 months could not demonstrate significant differences (p=0.683).

For the KOOS sub-score ADL, all five studies were included for analysis at 6 months. [3,14,25,30,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD -0.172, 95% CI: -668 to 0.324, p=0.496, I^2= 82%; Figure 12).

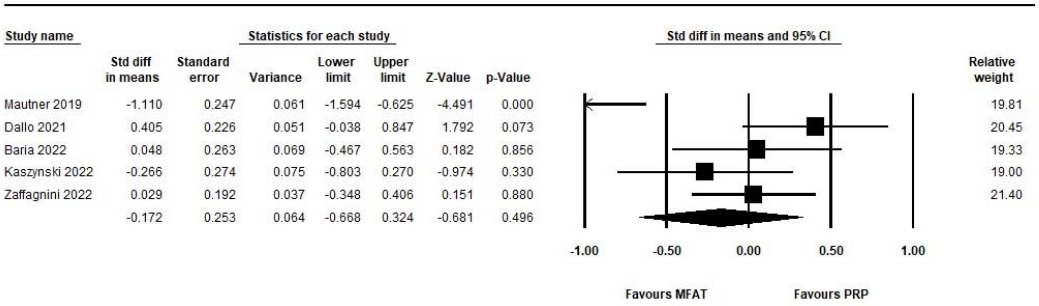

Figure 12: Forest Plot comparing the KOOS ADL at 6 months could not demonstrate significant differences (p=0.496).

Although the SMD favored MFAT, the magnitude effect was very small, strongly suggesting that the differences between groups were negligible. [11] For the KOOS sub-score ADL, three studies were included to analyze at 12 months. [14,25,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD 0.062, 95% CI: -0.190 to 0.315, p=0.629, I^2= 0%; Figure 13).

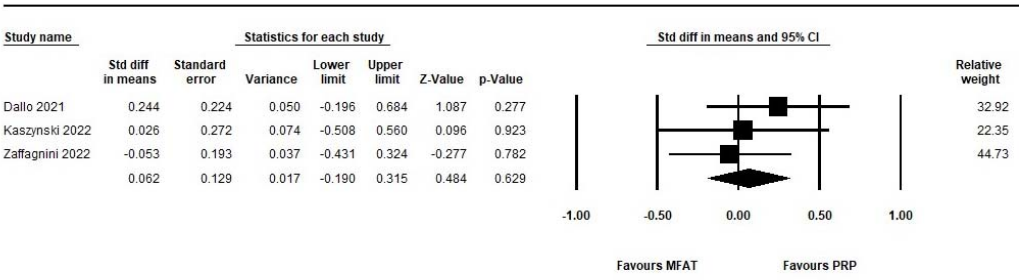

Figure 13: Forest Plot comparing the KOOS ADL at 12 months could not demonstrate significant differences (p=0.629).

For the KOOS sub-score sport, three studies were included to analyse at 3 months. [3,25,48] The pooled estimate did not demonstrate significant differences between FAT and other biologicals (SMD -0.181, 95% CI: -0.446 to 0.0845, p=0.180, I^2= 0%; Figure 14).

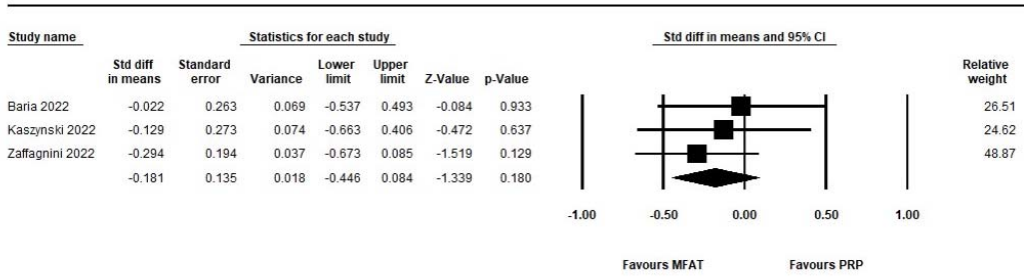

Figure 14: Forest Plot comparing the KOOS Sports at 3 months could not demonstrate significant differences (p=0.18).

For the KOOS sub-score sport, all five studies were included for analysis at 6 months. [3,14,25,30,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD -0.287, 95% CI: -0.926 to 0.352, p=0.379, I^2= 89%; Figure 15).

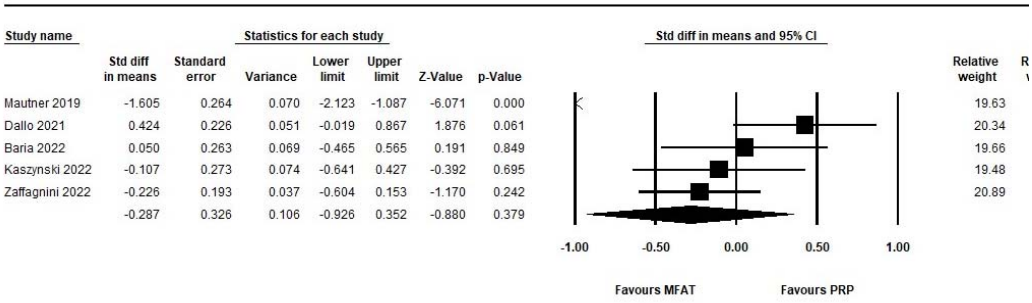

Figure 15: Forest Plot comparing the KOOS Sports at 6 months could not demonstrate significant differences (p=0.379).

For the KOOS sub-score sport, three studies were included for analysis at 12 months. [14,25,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD -0.191, 95% CI: -0.507 to 0.125, p=0.237, I^2= 39%; Figure 16).

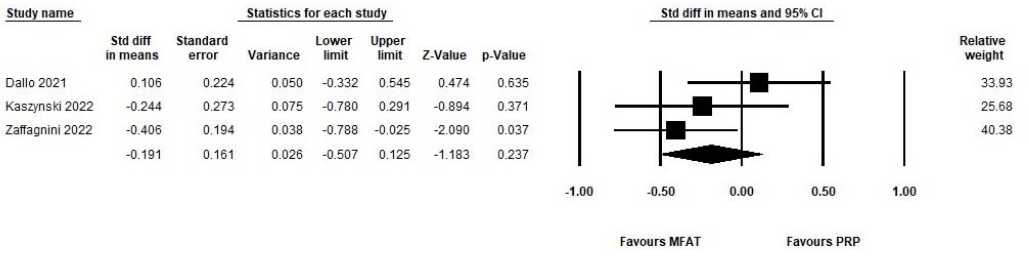

Figure 16: Forest Plot comparing the KOOS Sports at 12 months could not demonstrate significant differences (p=0.18).

Although the SMD favored MFAT at all follow-up intervals (3-, 6-, and 12-months), the magnitude effect was very small, strongly suggesting that the differences between groups were negligible. [11]

For the KOOS sub-score QOL, three studies were included to analyze at 3 months. [3,25,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD -0.024, 95% CI: -0.289 to 0.241, p=0.860, I^2= 0%; Figure 17).

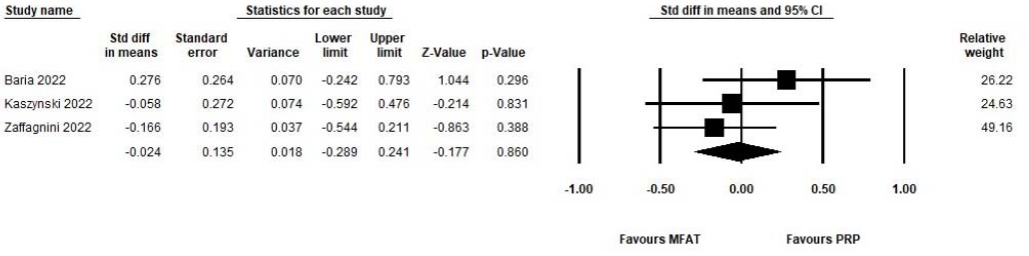

Figure 17: Forest Plot comparing the KOOS QOL at 3 months could not demonstrate significant differences (p=0.86).

For the KOOS sub-score QOL, all five studies were included to analyze at 6 months. [3,14,25,30,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD -0.101, 95% CI: -0.537 to 0.335, p=0.651, I^2=73%; Figure 18).

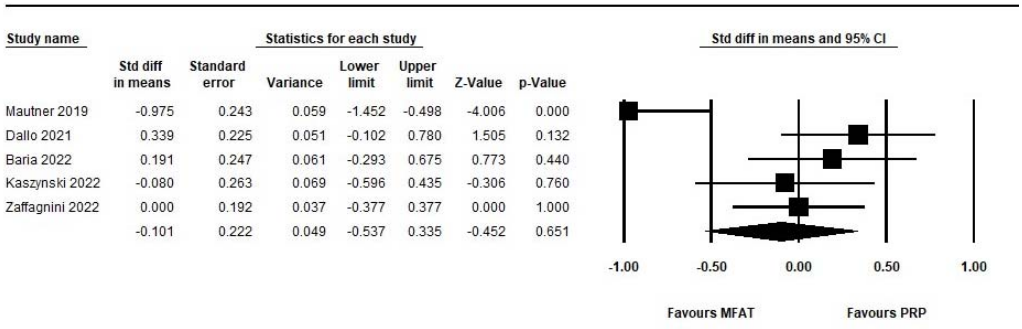

Figure 18: Forest Plot comparing the KOOS QOL at 6 months could not demonstrate significant differences (p=0.651).

For the KOOS sub-score QOL, three studies were included to analyze at 12 months. [14,25,48] The pooled estimate did not demonstrate significant differences between MFAT and other biologicals (SMD -0.006, 95% CI: -0.336 to 0.324, p=0.971, I^2= 39%; Figure 19).

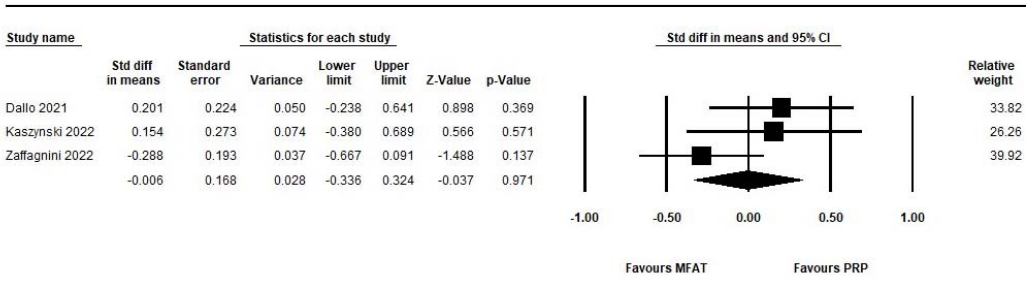

Figure 19: Forest Plot comparing the KOOS QOL at 12 months could not demonstrate significant differences (p=0.971).

Discussion

The results of this meta-analysis demonstrated that there is no difference for pain and clinical outcomes measured by the KOOS sub-scores when comparing MFAT injections to PRP or BMAC for osteoarthritis of the knee. Five recent studies were included in this meta-analysis, and of these only Dallo et al. [14] were able to demonstrate statistically significant differences in favor of MFAT injections. However, when calculating the statistics for each study, the conclusions by Dallo et al. [14] were invalidated and no statistically significant differences were observed between MFAT and PRP for all time intervals and measures. It is possible that the authors have committed a Type I error despite having performed a priori sample size calculation. The authors have used an effect size of 0.8, significance level of p=0.05 and power of 0.8. When recalculating the sample size using a smaller and more acceptable effect size of 0.5, numbers needed to treat increased to 64 patients per group and when applying power settings of 0.9, the numbers needed to treat increased to 86 patients per group. These calculations would indicate that the authors have also committed a Type II error. The conclusions by Dallo et al. therefore must be viewed with caution.

In contrast, Mautner et al. concluded that there was no difference between a group of patients treated with BMAC and MFAT. [28] However, statistical analysis revealed that there was a significant difference in favor of MFAT at six months for VAS, KOOS ADL, QOL, Sports and Symptoms sub-scores. The authors also analyzed the pre- and post-injection differences and were able to show that MFAT had statistically significant better outcomes, explaining the findings in this study. [30]

Risk of bias across studies was high in one study and assessment of "some" bias was found for the other four studies. The Cochrane Handbook states that some concerns in the overall risk of bias judgement indicates that the potential limitations are unlikely to lower the confidence in the estimate of the effect. [12] The quality assessment using the GRADE system determined that the final level of certainty for all studies was low suggesting that there is limited confidence in the estimated effect and that the true effect might be substantially different from the estimated effect. [12] Despite the favorable assessment with regards to risk of bias, the Grade Recommendations for clinicians are consequently considered to be weak. These recommendations are supported by the fair study quality assessment with a mean score of 54 using the modified Coleman methodology score. The main reasons for the low score were the low ratings for study size, mean follow-up, description of post-injection protocols, outcome criteria, procedures for assessing outcomes, and description of subject selection.

Clinical studies have suggested that the effects of PRP can last up to six months. [34] Given these short-term effects, shorter follow-up periods seem appropriate but even with the highest possible score for follow-up, the overall score only increased by four points. Obviously, the weaknesses of the included studies are clearly related to the above points and are areas for improvement in future studies. The current meta-analysis has pooled the available data and provides the most recent and comprehensive analysis substantially increasing the number of patients and outcomes for analysis. The results confirm the conclusions of the individual included studies demonstrating no clinical advantage of MFAT injections over other orthobiologics.

The use of PRP for the treatment of knee osteoarthritis is supported by clinical evidence and the most recent meta-analysis concluded that PRP is effective and safe. [46] The effect is also independent of age, gender and body mass index but is more effective in the early stages of the disease; less than 12 months. [40] In a prospective RCT comparing PRP to sham saline injections, PRP was superior to sham saline and was effective for 24 months. [10] The exact mechanism of PRP is currently debated but the proposed actions are inhibition of catabolic cytokines such as IL-1β and TNF-α, and the recruitment of cytokines such as fibroblast growth factor (FGF) and transforming growth factor-β (TGF-β). [7,27,44] Van Buul suggested that PRP may also influence the regulation of matrix degradation and decrease NFκB activation, a major pathway involved in the pathogenesis of OA. [44]

MFAT analysis showed that the aspirate contains pericytes, VEGF, endothelial-like cells, and immunostaining showed markers that indicated the presence of various growth factors and chemokines. [9] The mechanism of action is not yet fully understood, but clinical studies have shown improvements in pain, function, and quality of life. [19,39,47] The current understanding is that various "orthobiologic" formulations provide symptom improvement via anti-inflammatory and immuno-modulatory factors. Although there have been some positive clinical outcomes in terms of MFAT use with some studies showing improved clinical, functional, and QOL at 2 years, [17] there are also contradicting studies that demonstrate that treatment may only show early clinical improvement in mild to moderate OA, with only average results after 12 months. [45] It has also been reported that in some cases there is an inflammatory response/flare initiated within 2-4 weeks following MFAT injection, which resolved within 1 month, but in those individuals, there appeared to be a higher

therapeutic response rate (TRR) when compared to individuals that did not have an inflammatory reaction. [45] The literature is generally sparse in terms of reporting inflammatory reactions following various injectable biologics, but as van Genechten et al. [45] suggest, this may be an important early indicator of the efficacy of available orthobiologic treatments. Another interesting and contradicting outcome in terms of MFAT treatment is that age (>60 years) and the presence of synovitis have been proposed as possible factors that reduce positive clinical outcomes after 12 months; [16] however, studies have also shown positive clinical, functional, and QOL outcomes in elderly patients (>60 years). [17] The same study by Ferracini et al. 2022 [16] demonstrated that gender and BMI did not negatively influence the efficacy of MFAT treatment; however, other studies (2021) found that gender, age, and BMI do influence the outcome of MFAT treatment. [20] Betzler et al. conducted a systematic review of intra-articular knee injections of orthobiologics, encompassing a total of 585 patients. [6] The study incorporated PRP, BMAC and MSCs with no observed complications or severe adverse reactions. The authors concluded that these treatment options are deemed safe. The autologous nature of these formulations supports their safety. Based on the literature, there is still a large research potential in determining the effectiveness of MFAT treatment and additionally, basic science evidence needs to establish mechanisms of action, safety profile, and optimal processing techniques prior to the widespread use of MFAT injections for the treatment of knee osteoarthritis.

Osteoarthritis is caused by irreversible degeneration of articular cartilage and commonly leads to substantial reduction in function. [32] Ultimately total knee arthroplasty is the only reasonable surgical option. [24] Orthobiologics are a relatively

new option that can reduce pain, increase function and potentially repair and regenerate tissues. [43] These therapies include micro-fragmented fat and recent studies have demonstrated a decrease in symptoms and improvement in both functional capacity and overall quality of life. [19,35,39,47] In contrast, Mautner et al. have a randomized controlled trial which compared cell-based therapies including autologous bone marrow aspirate, autologous adipose stromal vascular fraction and allogenic human umbilical cord tissue-derived mesenchymal stroma cells against corticosteroid injections and failed to demonstrate any superiority at 12 months. [31] In the face of rising numbers of published studies demonstrating clinical efficacy of orthobiologics, there is ongoing uncertainty whether orthobiologics are more effective than established therapies. [47]

Regrettably, the majority of published clinical studies reporting the application of orthobiologics for knee osteoarthritis suffer from low sample sizes likely introducing type II errors and the obvious lack of power may have invalidated their results. Katz et al. have shown that a minimum number of 172 patients are required to achieve a power of 0.9. [26] Through this meta-analysis, the overall sample size has been increased to 346 patients and confirmed that there is no clinical benefit of MFAT injections when compared to orthobiologics, specifically PRP or BMAC.

The results of this meta-analysis should be interpreted in light of the following limitations. The combination of some risk of bias, only modest study quality, study heterogeneity, and weak GRADE recommendations decrease external validity. The final level of certainty was low and suggests that the addition of newly published studies may change the directions in the estimate of the treatment effect in both

directions. The results may have also been influenced by missed studies. However, the search strategies were extensive but limited to English and German language publications only. It is possible that high quality evidence was published in other languages and publication bias cannot be entirely excluded. Publication bias was not assessed as this project was only able to include five studies and the assessment of publication bias requires at least ten studies. [12] Publication bias is associated with an inflated treatment effect and can lower the certainty of evidence. Theoretically, conflict of interest of authors and source of funding may have also influenced the results of the individual studies. In two studies [14,25] the authors declared no conflict of interest; in two studies [3,48] conflict of interest statements were not published and in one study [30] one author declared royalties that he received form a publishing house and also declared investments in shares. It is therefore unlikely that conflict of interest could have influenced the overall conclusions.

Conclusions

The results of this systematic review and meta-analysis demonstrated that there are no statistically significant differences for both clinical outcomes and pain between MFAT and other orthobiologics [PRP, BMAC] for the treatment of knee osteoarthritis. However, fair study quality, some risk of bias, and low certainty of evidence reduce external validity and these results must be viewed with some caution.

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