Meta-analysis

Surgical Techniques for Knee Cartilage Repair: An Updated Large-Scale Systematic Review and Network Meta-analysis of Randomized Controlled Trials

Radoslav Zamborsky, M.P.H., Ph.D., and Lubos Danisovic, M.Sc., Ph.D.

Purpose: The aim of this study was to investigate the most appropriate surgical interventions for patients with knee articular cartilage defects from the level I randomized clinical trials. **Methods:** We searched five databases for level I randomized clinical trials. Treatments were compared if reported in more than one study using network meta-analysis to boost the number of included studies per comparison. **Results:** We studied 21 articles that included 891 patients. Traumatic lesion was the most common cause in the included patients. There were significantly higher failure rates in the microfracture (MF) group compared to autologous chondrocyte implantation (ACI) group at 10-year follow-up. Moreover, osteochondral autograft transplantation (OAT) showed significantly more excellent or good results at > 3-year follow-up compared to MF, whereas MF showed significantly more poor results versus ACI and matrix-induced autologous chondrocyte implantation (MACI). Furthermore, OAT showed significantly more poor results than MACI at 1-year follow-up. Similarly, patients who underwent OAT had higher return-to-activity rates than those with MF. It is noteworthy that the Knee injury and Osteoarthritis Outcome Score was higher in patients who underwent characterized chondrocyte implantation or MACI compared to MF. Finally, there were no significant differences among the various interventions regarding reintervention, biopsy types or adverse events. According to the *P* scores for interventions ranking, there was a disagreement concerning the best intervention; however, MF was always ranked as the last. **Conclusions:** Cartilage repair techniques, rather than MF, provide higher quality repair of tissue and have lower failure and higher return-to-activity rates. Moreover, OAT had significantly more excellent or good results compared to MF, whereas MF had significantly more poor results than ACI and MACI. Future studies need to have longer follow-up periods and more representative populations to investigate the efficacy and safety of these interventions. **Level of evidence:** Level I: meta-analysis of Level I studies.

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Knee cartilage lesions remain a challenging clinical practice due to the limited intrinsic healing capacity of the knee cartilage tissue.[1] Indeed, the full-thickness lesions in > 60% of adults can significantly affect the knee-associated quality of life. Additionally, patients with full-thickness cartilage defects of the knee experience considerable pain and impairment of activity. Articular cartilage is prone to damage from traumas, repetitive shear and torsional forces applied to the surface.[2] Although the majority of these lesions are asymptomatic, cartilage defects of the knee still represent a large source of pain and disability.[3,4] Furthermore, focal chondral lesions left untreated may progress to clinically relevant joint pain with dysfunction, osteoarthritis and detrimental influences on the quality of life.[5,6] The lack of a successful endogenous repair mechanism has been attributed to the poor recruitment of regenerative cells into the cartilage defect area.[7]

After the theory of marrow stimulation by subchondral drilling, the concept was popularized by introducing the microfracture (MF) intervention, whereby the migration of mesenchymal stem cells and growth factors from subchondral bone facilitates the restoration of hyaline-like fibrocartilage.[8] The use of

From the Department of Orthopaedics, Comenius University Bratislava and the National Institute of Children's Diseases (R.Z.); Expert Medical Services s.r.o. (R.Z.); and Institute of Medical Biology, Genetics and Clinical Genetics, Comenius University (L.D.), Bratislava, Slovakia.

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Address correspondence to: Radoslav Zamborsky, M.P.H., Ph.D., Department of Orthopaedics, Comenius University Bratislava and the National Institute of Children's Diseases, Limbova 1. 833 40 Bratislava, Slovakia. E-mail: radozamborsky@gmail.com

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articular resurfacing interventions has become increasingly widespread. A biologic approach to articular cartilage lesions is a new challenge, because it has inherent limited healing potential. Between 30,000 and 100,000 knee cartilage procedures are performed annually.[3,9] MF and debridement form more than 98% of these procedures, due largely to their simplicity, low cost and established clinical track records.[3,10,11] Moreover, MF is still considered to be the first-line treatment for the chondral defects of the knee joint, and it shows good short-term results.[12] However, there is evidence that the results of MF deteriorate over time, may compromise the results of cell-based therapies and have a limited ability to regenerate the hyaline cartilage.[10,11] Moreover, there are concerns surrounding suboptimal repair with fibrocartilage infill[13] and long-term clinical outcomes compared with other available cartilage-restoration procedures, such as autologous chondrocyte implantation (ACI), mosaicplasty/osteoarticular transfer system (OATS) and osteochondral allograft transplantation (OAT).[14-18]

There is no uniform approach to managing hyaline cartilage defects in the knee. Treatment options, intended primarily to achieve symptomatic relief, include knee washout (lavage) with debridement.[19] Interventions that also attempt to reestablish the articular surface include marrow stimulation techniques, such as abrasion arthroplasty, drilling and MF, and mosaicplasty (or OAT).[20] Lesions treated with these procedures, especially larger lesions (> 2 cm^2), commonly require subsequent operative intervention.[21] A study by Brittberg et al. described the stimulation of hyaline-like repair tissue and resulting successful repair of femoral condyle defects of the knee using implantation of autologous cultured chondrocytes, and this generated significant interest.[22] A number of studies have subsequently suggested that ACI is an effective procedure for cartilage defects of the knee.[23] So far, various techniques have been suggested to be effective for treating articular cartilage defect of the knee joint, yet knowledge regarding which method is best still remains uncertain. Hence, the aim of this systematic review and network meta-analysis was to investigate the most appropriate surgical interventions for patients with knee articular cartilage defects from the level I randomized clinical trials (RCTs). We hypothesized that the patients would have better clinical improvements through using the more advanced cartilage tissue-repair techniques rather than MF.

Methods

Search Strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[24] and the PRISMA Network Meta-analysis Extension Statement[25] (Appendix 1). The study protocol was registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42019125604). In December 2018, we performed searches to identify pertinent studies in the following databases: PubMed, Institute of Science Index, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Embase. Prespecified search terms were used and adapted to each database to yield the most accurate results (Appendix 2). A manual search, using references of the included RCTs and the previous systematic reviews, was conducted to retrieve additional articles.[26-29] Both authors (RZ, LD) independently screened titles and abstracts according to our inclusion and exclusion criteria.

Selection Criteria

The inclusion criteria were level I RCTs comparing different surgical interventions for patients with articular cartilage defects of the knee. No restrictions regarding language, race, sex, country, year, or age were applied. Our exclusion criteria were articles comparing alternative medical treatments, such as rehabilitation, anti-inflammatory medications and physical therapy, enrolling patients with diseases other than those in the knee, and animal studies or other study designs. All full texts were reviewed carefully by both authors independently to reach the final decision.

Data Extraction

We developed and pilot-tested a data-extraction sheet against the included papers and modified it accordingly (Appendix 3). Both authors extracted independently each paper's data, and any disagreements were resolved through discussion. Potentially duplicated data from the same research group studying the same factors were verified using year and place of recruitment, and the largest dataset was chosen for final analysis to prevent overlapping of patients. In order to be comprehensive, all data from texts, tables, graphs, and supplementary materials were extracted. Data from figures or error bars were extracted using WebPlotDigitizer software, version 3.8 (http://arohatgi.info/WebPlotDigitizer/index.html).[26,30,31]

Appraisal of Bias

The quality of randomized studies was evaluated in accordance with the methods of the Cochrane Collaboration tool.[32] It includes sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential threats to validity. For each of the 7 items, each author prepared a review of the empirical evidence, a discussion of specific issues and uncertainties and a proposed set of criteria for assessing protection

from bias as low risk, high risk or unclear. The level of evidence was determined based on the criteria established by the Oxford Centre for Evidence-Based Medicine.[33] Moreover, appraisal of bias was conducted carefully by both authors independently, and if any discrepancies in ratings or disagreements happened, both authors discussed them to reach the final decision.

Outcomes and Extracted Data

We extracted data, such as age, sex, length of follow-up, previous knee surgery, duration of symptoms, articular cartilage defect characteristics, surgical technique, clinical outcome measures, histology and treatment failures, lesion size, frequency of postoperative complications, and all reported pre- and postoperative clinical outcome scores (such as International Knee Documentation Committee Subjective Knee Form, visual analog scale—pain, Lysholm score, Cincinnati, Western Ontario and McMaster Universities Osteoarthritis Index, magnetic resonance observation of cartilage repair tissue score, Tegner activity scale, Knee injury and Osteoarthritis Outcome Score [KOOS]), if reported (Table 1) (Table 2). Different treatments were compared if reported in more than 1 study by using network meta-analysis to boost the number of included studies per comparison and to take all evidence (both direct and indirect comparisons) into account simultaneously.

Statistical Analysis

We performed the network meta-analysis using RStudio software version 1.0.44 (https://www.rstudio.com/) by the *netmeta* package to generate risk ratios for categorical outcomes, mean difference for continuous outcomes and 95% confidence intervals (CI). A fixed-effect model[34] was used when there was no evidence of heterogeneity between studies; otherwise, a random-effects model was chosen.[35] The heterogeneity among studies was evaluated using the Q statistic and the I^2 test, which describes the percentage of variability in the effect estimates that occur because of heterogeneity beyond sampling error.[27,31,35-37] For heterogeneity across studies, we utilized χ^2 and I^2 tests, where the P value $= 0.10$ and/or $I^2 > 50\%$, indicating significant heterogeneity.[26,31,37-40]

Forest plots were presented to give a visual overview of the findings. Most trials compared MF to other treatments, so we generated the forest plots for MF, as the control, against other treatments, yet all other direct and indirect comparisons were already conducted as well (Table 3).

Furthermore, we demonstrated the network meta-analysis ranking of all surgical interventions according to the methods of Rücker and Schwarzer using P rank scores.[41] The P score of a certain treatment can be interpreted as the mean extent of certainty where that treatment is better than another treatment. The statistical significance was considered if the P value was < 0.05.

Results

Search Results

Our search retrieved 3,697 articles, among which 1,142 duplicates were removed (Fig 1). The rest underwent abstract screening to yield 100 articles for full-text review. Ultimately, a total of 21 articles[18,42-61] (from 12 RCTs) that met our eligibility criteria were included in our study.

Studies' and Patients' Characteristics

Table 1 describes the characteristics of included studies, which enrolled a population of 891 patients. The follow-up periods ranged from 12 months[42,56,58] to 15 years.[48]

Our study population contained more male than female patients (479 (53.76%) and 412 (46.24%), respectively). The patients' mean age ranged from 14.4 years to 40.4 years; the mean defect size ranged from 2.1 to 6.1 cm^2; the mean duration of symptoms ranged from 21.24 to 103.2 months, and the mean prior surgeries ranged from 1.1 to 2.2 (Table 1). Of note, traumatic lesion was the most common cause in the included patients (ranging from 42.9% to 100% in some studies). There were 3 studies that were conducted multicentrically.[18,50-56] There were 2 articles[51,62] that were conducted on a subset of patients reported in another article.[18,50,52]

In addition to that, failure of the intervention was defined differently by the included studies; some studies defined it as failure of graft, due to the lack of healing of the defect or reintervention affection of $> 20\%$ of the index lesion (Table 2).

Appraisal of Bias

All of our included studies are of level I, so most of them had low risk regarding selection, attrition, reporting, and other biases (Appendix 4). It is noteworthy that performance bias was nearly present in all included articles, because it was not possible to blind the surgeon performing the various surgical techniques. Further, it was not possible to blind the patients to their interventions if it involved the use of a 2-stage intervention such as matrix-induced autologous chondrocyte implantation (MACI), ACI, bioscaffold technology-cartilage gel (BST)-CarGel, or characterized chondrocyte implantation (CCI).[46,47,51,53,63]

Quantitative Synthesis

Moreover, MF was used alone in most of the studies or in combination with other treatments such as BST-CarGel.[55] There were significantly higher failure rates

Table 1. Characteristics of the Included Studies

Author, country, year	Treatment groups	Patients (n)	Mean follow-up (months)	Mean age (years)	Sex, male	Mean defect size (cm^2)	Traumatic cause No., %	Mean duration of symptoms (months)	Mean prior surgeries (n)
Bartlett, UK, 2005[42]	ACI or MACI	91	12	33.6	54	6.1	39 (42.9)	103.2	2.2
Basad, Germany, 2010[43]	MACI or MF	60	24	34.2	42	4	60 (100)	27.6	-
Bentley, UK, 2003[44]	ACI or Mosaicplasty	100	19 (12 to 26)	31.3 (16-49)	57	4.66 (1-12.2)	46 (46)	86.4 (9 months -20 years)	1.5
Bentley, UK, 2012[45]	ACI or Mosaicplasty	100	120	31.3 (16-49)	57	4.2 (1-15.25)	46 (46)	86.4 (9 months -20 years)	1.5 (0-4)
Crawford, USA, 2012[46]	MACI or MF	30	26	40.4 ± 9	25	2.69	-	36 ± 60	-
Knutsen, Norway, 2004[49]	ACI or MF	80	24	32.2	48	4.8	52 (65)	36	1.5
Knutsen, Norway, 2007[47]	ACI or MF	80	60	32.2	48	4.8	52 (65)	36	1.5
Knutsen, Norway, 2016[48]	ACI or MF	80	180	32.2	48	4.8	52 (65)	36	1.5
Saris, MC, 2008[18]	CCI or MF	118	18	33.9	41	2.4 ± 1.2 (1-5)	-	21.24	1.1
Saris, MC, 2009[50]	CCI or MF	118	36	33.9	41	2.4 ± 1.2 (1-5)	-	21.24	1.1
Vanassche, MC, 2010[51]	CCI or MF	67	24	31	46	2.4	-	-	-
Vanlauwe, MC, 2011[52]	CCI or MF	112	60	33.4	76	2.4 ± 1.2 (1-5)	-	21.24	1.1
Saris, MC, 2014[89]	MACI or MF	144	24	33.85	93	5.55	-	57	-
Brittberg, MC, 2018[54]	MACI or MF	128	60	34 and 38*	82	5	-	57	-
Stanish, MC, 2013[56]	MF or MF + BST-CarGel	80	12	36.2	48	2.1	-	20.52	-
Shive, MC, 2015[55]	MF or MF + BST-CarGel	80	60	36.1 (18-55)	36	2.25	-	26.4*	-
Gudas, Lithuania, 2005[59]	MF or MOCT	57	37.1 (36-38)	24.3 (15-40)	-	2.8 (1-4)	32 (56.1)	21.32 ± 5.57	-
Gudas, Lithuania, 2012[60]	MF or MOCT	57	124.8 (86-132)	24.3 (15-40)	36	2.8 (1-4)	32 (56.1)	21.3	-
Gudas, Lithuania, 2009[61]	MF or MOCT	47	50.4	14.4	-	3.2	-	23.54	-
Volz, Germany, 2017[57]	MF, AMIC glued or AMIC sutured	34	60	27-47	37	3.6	-	-	-
Visna, Czech Republic, 2004[90]	ACT or abrasive techniques	50	12	30.84	34	3.72 (2-9.4)	43 (86)	-	-

ACI, autologous chondrocyte implantation; ACT, autologous chondrograft transplantation; AMIC, autologous matrix-induced chondrogenesis; CCI, characterized chondrocyte implantation; MACI, matrix-induced autologous chondrocyte implantation; MC, multicenter; MF, microfracture; MOCT, mosaic osteochondral autologous transplantation; OAT, osteochondral autograft transplantation.

*The numbers are median.

Table 2. Failure Rates and Their Definitions in Various Cartilage Repair Interventions in the Included Studies

Author, country, year	Follow-up	Treatment groups	Failure	Definition of failure	Significant difference
Bartlett, UK, 2005[42]	1 year	ACI	0	Failure of the graft	NS
		MACI	2		
Basad, Germany, 2010[43]	2 years	MF	1	Not stated	NS
		ACI	0		
Bentley, UK, 2012[45]	10 years	ACI	10	Clinically poor results with arthroscopic	$P < 0.001$
		OAT	23	evidence of the graft or revision surgery to a defect of any kind	
Crawford, USA, 2012[46]	2 years	MACI	Not stated	-	-
		MF			
Knutsen, Norway, 2004[12]	2 years	ACI	2	If the patient needed a reoperation because of symptoms due to a lack of healing of	NS
		MF	1	the primary treated defect; the need for shaving or trimming a lesion was not defined as a failure	
Knutsen, Norway, 2007[47]	5 years	ACI	9	Reoperation because of symptoms due to lack of healing of the defect	NS
		MF	9		$P = 0.101$
Knutsen, Norway, 2016[48]	15 years	ACI	17	The operation was considered to have failed if a reoperation was performed because of	$P = 0.35$
		MF	13	symptoms resulting from a lack of healing of the treated defect.	
Saris, MC, 2014[92]	2 years	MACI	0	If, at any time after week 24, they had a patient and physician global assessment result	NS
		MF	2	that was the same as or worse than at baseline, a < 10% improvement in the KOOS pain subscale, physician-diagnosed failure ruling out all other potential causes, and the physician deciding that surgical retreatment was needed	
Brittberg, MC, 2018[54]	5 years	MF	3	If, at any time after week 24, they had a patient and physician global assessment result	$P = 0.361$
		MACI	1	that was the same as or worse than at baseline, a < 10% improvement in the KOOS pain subscale, physician-diagnosed failure ruling out all other potential causes, and the physician deciding that surgical retreatment was needed	
Stanish, MC, 2013[56]	1 year	BST-CarGel	Not stated	-	-
		MF			
Vanlauwe, MC, 2011[52]	5 years	CCI	7	Reintervention affecting > 20% of the index lesion	NS
		MF	10		$P = 0.561$
Gudas, Lithuania, 2005[91]	37.1 months	OAT	1	If the patient needed reoperation because of a lack of healing symptoms of the	$P = 0.012$
		MF	9	primary treated defect	
Gudas, Lithuania, 2012[92]	10 years	OAT	4	Reoperation because of symptoms to primary defect	$P < 0.05$
		MF	11		

ACI, autologous chondrocyte implantation; ACT, autologous chondrograft transplantation; AMIC, autologous matrix-induced chondrogenesis; CCI, characterized chondrocyte implantation; KOOS, knee injury and osteoarthritis outcome score; MACI, matrix-induced autologous chondrocyte implantation; MC, multicenter; MF, microfracture; MOCT, mosaic osteochondral autologous transplantation; OAT, osteochondral autograft transplantation.

Table 3. Network Meta-analysis Showing the Direct and Indirect Comparisons Among the Available Treatments

Comparisons				
Treatment failure				
2 years				
Intervention	MF	ACI	MACI	
MF	-	0.5 (0.05; 5.3)	5.4 (0.61; 48.05)	
ACI	2 (0.18; 21.18)	-	10.85 (0.44; 269.83)	
MACI	0.18 (0.02; 1.63)	0.09 (0.004; 2.29)	-	
5 years				
Intervention	MF	ACI	MACI	CCI
MF	-	1 (0.44; 2.26)	0.32 (0.04; 3.02)	0.73 (0.32; 1.75)
ACI	1 (0.44; 2.26)	-	3.1 (0.29; 33.44)	1.37 (0.42; 4.5)
MACI	0.32 (0.04; 3.02)	0.32 (0.03; 3.5)	-	0.44 (0.4; 4.86)
CCI	0.73 (0.32; 1.75)	0.73 (0.22; 2.4)	2.27 (0.21; 24.99)	-
10 years				
Intervention	MF	ACI	OAT	
MF	-	1.65 (0.18; 14.88)	1.14 (0.12; 10.77)	
ACI	0.61 (0.07; 5.44)	-	0.69 (0.08; 6.22)	
OAT	0.88 (0.09; 8.36)	1.46 (0.16; 13.19)	-	
Rate of excellent or good results				
1 year				
Intervention	MF	ACI	MACI	OAT
MF	-	0.73 (0.28; 1.9)	0.6 (0.28; 1.27)	0.79 (0.5; 1.25)
ACI	1.37 (0.52; 3.63)	-	0.82 (0.44; 1.52)	1.08 (0.46; 2.54)
MACI	1.67 (0.79; 3.55)	1.22 (0.66; 2.28)	-	1.32 (0.73; 2.38)
OAT	1.27 (0.8; 2.02)	0.93 (0.39; 2.2)	0.76 (0.42; 1.38)	-
More than 3 years				
Intervention	MF	OAT		
MF	-	**0.64 (0.45; 0.9)**		
OAT	**1.59 (1.22; 2.07)**	-		
Rate of poor results				
1 year				
Intervention	MF	ACI	MACI	OAT
MF	-	**119.29 (1.95; 7287.18)**	**169.89 (3.13; 9229.53)**	7.78 (0.47; 129.99)
ACI	**0.01 (0.0001; 0.51)**	**-**	1.42 (0.54; 3.78)	0.07 (0.003; 1.31)
MACI	**0.01 (0.0001; 0.32)**	0.7 (0.27; 1.86)	-	**0.05 (0.003; 0.78)**
OAT	0.13 (0.01; 2.15)	15.33 (0.77; 307.04)	**21.84 (1.28; 371.46)**	**-**
Biopsy				
Intervention	MF	ACI	MACI	OAT
MF	-	0.57 (0.31; 1.07)	0.57 (0.31; 1.07)	1 (0.86; 1.17)
ACI	1.75 (0.93;3.28)	-	1.22 (0.48; 3.09)	1.75 (0.92; 3.34)
MACI	1.43 (0.47; 4.39)	0.82 (0.32; 2.07)	-	1.43 (0.46; 4.44)
OAT	1 (0.86; 1.17)	0.57 (0.3; 1.09)	0.7 (0.23; 2.16)	-
Reintervention				
Intervention	MF	MACI	CCI	AMIC-g
MF	-	1.2 (0.43; 3.39)	1.19 (0.6; 2.36)	1.15 (0.07; 17.97)
MACI	0.83 (0.3; 2.34)	-	0.98 (0.28; 3.41)	1.13 (0.07; 19.67)
CCI	0.84 (0.42; 1.68)	1.02 (0.29; 3.52)	-	1.36 (0.09; 19.5)
AMIC-g	0.73 (0.05; 10.49)	0.88 (0.05; 15.33)	0.87 (0.06; 13.57)	-
Return to activity				
Not more than 1 year				
Intervention	MF	OAT		
MF	-	**0.54 (0.42; 0.69)**		
OAT	**1.86 (1.46; 2.37)**	**-**		
3-5 years				
Intervention	MF	OAT		
MF	-	**0.36 (0.2; 0.56)**		
OAT	**2.98 (1.79; 4.96)**	-		
10 years				
Intervention	MF	OAT		
MF	-	0.28 (0.13; 0.59)		
OAT	**3.57 (1.7; 7.47)**	-		
Adverse events				
Intervention	MF	MACI	CCI	OAT
MF	-	1.09 (0.93; 1.29)	1.04 (0.8; 1.34)	0.19 (0.01; 3.85)

(continued)

Table 3. Continued

		Comparisons		
MACI	0.92 (0.78; 1.08)	-	0.95 (0.7; 1.29)	0.18 (0.01; 3.55)
CCI	0.97 (0.74; 1.25)	1.05 (0.78; 1.43)	-	0.19 (0.01; 3.76)
OAT	5.18 (0.26; 103.17)	5.64 (0.28; 113.06)	5.36 (0.27; 108.03)	-
KOOS				
Intervention	MF	MACI	CCI	
MF	-	**−8.45 (−15.28; -1.62)**	**−7.1 (−8.12; −6.09)**	
MACI	**8.45 (1.62; 15.28)**	-	1.35 (−5.55; 8.26)	
CCI	**7.1 (6.09; 8.12)**	−1.35 (−8.26; 5.55)	-	

NOTE. Significant values are in boldface type.

ACI, autologous chondrocyte implantation; ACT, autologous chondrograft transplantation; CCI, characterized chondrocyte implantation; KOOS, knee injury and osteoarthritis outcome score; MACI, matrix-induced autologous chondrocyte implantation; MC, multicenter; MF, microfracture; MOCT, mosaic osteochondral autologous transplantation; OAT, osteochondral autograft transplantation.

in the MF group compared to the ACI group at the 10-year follow-up period (RR, 95% CI 0.12 (0.04; 0.39)); however, there was no significant difference among MF and OAT, CCI or MACI at the same follow-up period nor at the 2- and 5-year follow-up periods (Table 2). Moreover, OAT had significantly more excellent or good results at the > 3-year follow-up period than MF, whereas MF had significantly more poor results versus ACI and MACI. Furthermore, OAT had significantly more poor results over MACI at the 1-year follow-up period (RR, 95% CI 0.05, (0.003; 0.7791)). Notwithstanding this, patients who had undergone OAT had higher rates of return to activity than those having undergone MF at 1-, 3- to 5-, as well as 10-year follow-up periods (Fig 2) (Fig 3).

It is noteworthy that the KOOS score was higher in patients who underwent CCI or MACI than in those who underwent MF (mean difference 95% CI 7.10 (6.08; 8.12) and 8.45 (1.62; 15.28), respectively.

Finally, there was no significant difference among the various interventions regarding reintervention, biopsy types or adverse events (Fig 4).

According to the *P* scores for interventions ranking, arranged according to their efficacy and safety, ACI was the best intervention, followed by OAT, then MF for the failure outcome at 10-year follow-up. OAT ranked as the best for the excellent or good results, then MF, whereas for poor results, MACI was followed by ACI and OAT, then MF. Additionally, OAT was better than MF for the return-to-activity outcome. Finally, MACI

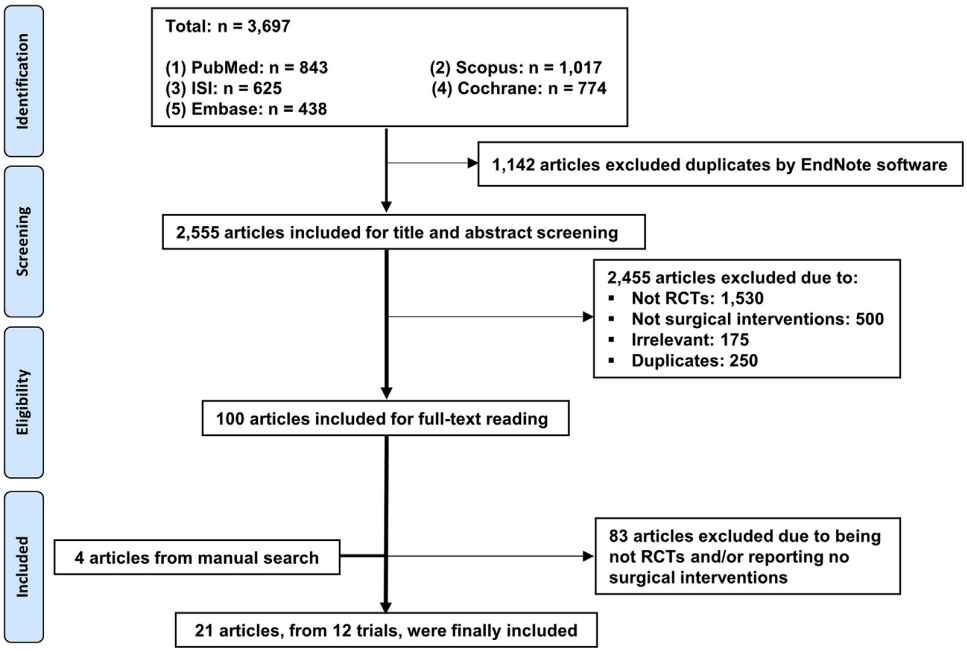

Fig 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart showing the flow of publications throughout the review process.

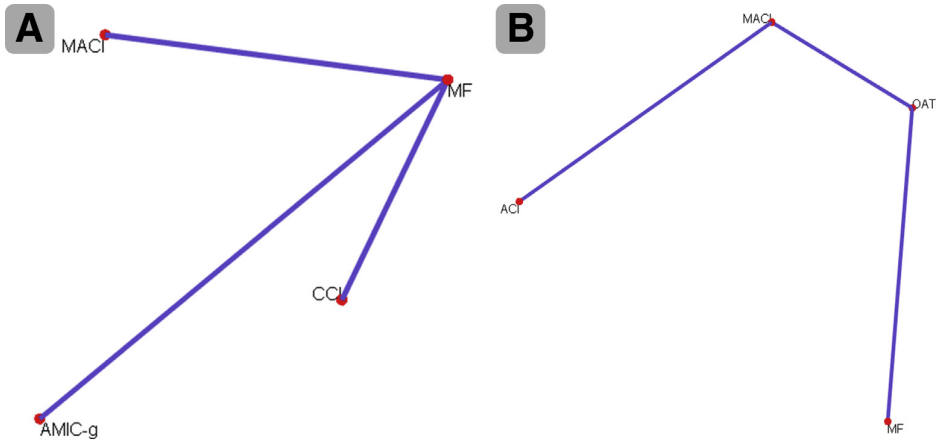

Fig 2. Network plots representing direct and indirect comparisons. (A) reoperation or reintervention rates among different techniques; (B) rate of poor results among different techniques at 1-year follow-up period. Connections (purple line) between 2 nodes (red circles) indicate that those interventions have been compared directly in at least 1 head-to-head study. ACI, autologous chondrocyte implantation; ACT, autologous chondrograft transplantation; AMIC-g, glued autologous matrix-induced chondrogenesis; CCI, characterized chondrocyte implantation; MACI, matrix-induced autologous chondrocyte implantation; MF, microfracture; OAT, osteochondral autograft transplantation.

came in at first place, followed by CCI, then MF, when evaluating the KOOS outcome (Appendix 5).

Other Individual Studies

Stanish et al. conducted an international multicenter RCT to evaluate BST-CarGel as an MF adjunct compared with MF alone in the repair of cartilage lesions in the knee in 80 patients. After 12-month follow-up, BST-CarGel treatment resulted in a greater lesion filling and superior repair of tissue quality than MF. However, the clinical benefits and safety levels were similar in both groups.[56] Subsequently, at 5-year follow-up, the BST-CarGel treatment lead to sustained and significantly superior repair of tissue quantity and quality compared to MF alone.[55]

Moreover, Van Assche et al. demonstrated the functional performance across a 2-year period after ACI against MF and concluded that after ACI, patients had similar overall functional outcome compared to patients with MF.[51]

Discussion

We found that there were significantly higher failure rates in the MF group compared to the ACI group at 10-year follow-up. Second, OAT showed significantly more excellent or good results at the > 3-year follow-up period as compared to MF, whereas MF had significantly more poor results versus ACI and MACI. Furthermore, OAT had significantly more poor results over MACI at the 1-year follow-up period. Similarly, patients who had undergone OAT had higher return-to-activity rates at 1-, 3- to 5- and 10-year follow-up periods than those after MF. It is noteworthy that the KOOS scores were higher in patients who had undergone CCI or MACI compared to MF. Hence, advanced cartilage repair techniques perform better than MF, with lower failure and higher return-to-activity rates. These findings are similar to those of previously published studies.[64]

MF, a bone marrow stimulating procedure,[65] is frequently used to repair specific cartilage injuries. Although MF provides good clinical outcomes, they are not always sustained.[10,47,66,67] This has been attributed largely to the questionable durability of fibrocartilage tissue, which lacks the nascent hyaline articular structure.[68] Previous studies show that patients with smaller lesions have better clinical outcomes with MF than patients with larger lesions,[69] whereas lesions on the trochlea do not improve as well as those on the femoral condyle.[70] Repair tissue with MF has been shown to be fibrous in nature[18] compared to the more hyaline-like repair tissue reported with MACI.[71] In addition, intralesional osteophytes may result from MF and could compromise any successful clinical outcomes after the procedure.[72,73] Also, MF may negatively affect outcomes of subsequent cell-based cartilage-repair treatment.[72]

Given that previous literature demonstrates inferior long-term outcomes following MF, many surgeons are giving stronger consideration to alternative cartilage-restoration procedures such as ACI and OAT, despite the limitations of some of these techniques, including the need for a 2-stage procedure, donor-site morbidity and the increased cost and limited availability of allograft donor tissue. Saris et al. demonstrated superior clinical outcomes with matrix-applied characterized

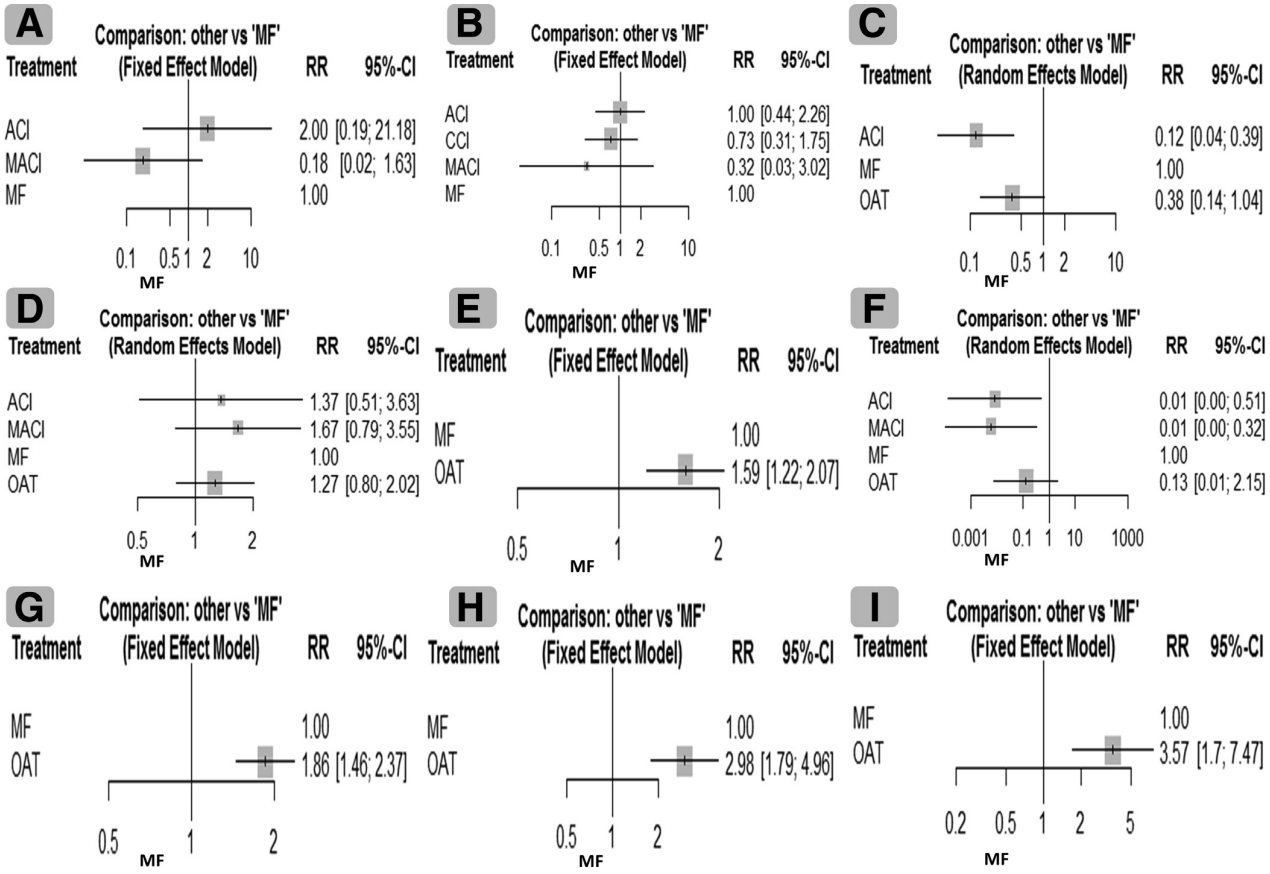

Fig 3. Forest plots that depict all pairwise treatment comparisons. The vertical line represents the null line (line of no effect). The point estimate for each risk ratio, for categorical outcomes, is represented by a gray square, and the 95% CI is represented by a horizontal line. If the 95% CI does not cross the null line, the given pairwise comparison reaches statistical significance. Failure rates at (A) 2-year follow-up period, (B) 5-year follow-up period, (C) 10-year follow-up period. Rates of excellent or good results at (D) 1-year follow-up period, (E) more than 3-year follow-up period, (F) rate of poor results at 1-year follow-up period, (G) rate of return to activity at 1-year follow-up period, (H) 3- to 5-year follow-up period, (I) 10-year follow-up period. ACI, autologous chondrocyte implantation; ACT, autologous chondrograft transplantation; CCI, characterized chondrocyte implantation; MACI, matrix-induced autologous chondrocyte implantation; MF, microfracture; OAT, osteochondral autograft transplantation.

ACI for symptomatic chondral defects $\geq$ 3 cm relative to MF. Akin to that finding, Krych et al. demonstrated that osteochondral autograft/mosaicplasty has superior activity levels as measured by the Marx Activity Rating Scale at 2-year follow-up and beyond when compared with MF.[15] However, future high-quality randomized controlled trials are necessary to compare directly augmented MF with other cartilage-restoration procedures so as to determine differential efficacy and cost-effectiveness.

In comparison with our study, a number of other systematic reviews were conducted, focusing on MF,[10] ACI,[74] OAT,[75] and MACI.[76] However, most of these studies included levels II to IV studies, yet revealed beneficial effects across the available surgical techniques, thus giving little clarity about which articular cartilage intervention to use. For instance, Bekkers and colleagues[77] concluded that smaller lesions should be treated by MF or single-plug OAT, whereas in active patients with large articular lesions, ACI or OAT resulted in improved outcomes as compared to MF. Moreover, another review found that osteoarthritis and clinical failure were the norm with MF beyond the 5-year follow-up, regardless of lesion size.[78] On the contrary, Lynch et al. demonstrated improved clinical outcomes with OAT. These patients were able to return to sport 6 months after the intervention, and they proposed that OAT could be more appropriate for lesions $\leq$ 2 cm^2 with a known risk of treatment failure between 2 and 4 years.[79]

Previous animal and human studies have attributed the poor tissue quality and gradual decline in clinical outcomes following MF to either the instability of marrow-derived blood clots formed during the healing

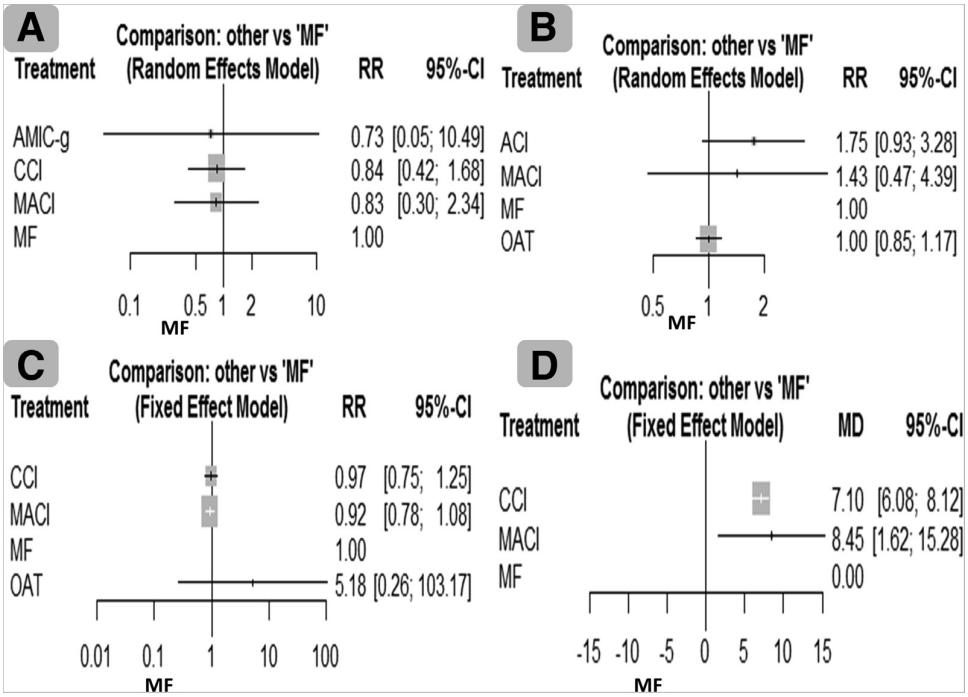

Fig 4. Forest plots that depict all pairwise treatment comparisons. The vertical line represents the null line (line of no effect). The point estimate for each risk ratio for categorical outcomes, or mean difference for continuous outcomes, is represented by a gray square, and the 95% CI is represented by a horizontal line. If the 95% CI does not cross the null line, the given pairwise comparison reaches statistical significance. (A) reoperation, or reintervention rates in different techniques, (B) biopsy types, (C) adverse events, (D) KOOS score. ACI, autologous chondrocyte implantation; ACT, autologous chondrograft transplantation; AMIC-g, glued autologous matrix-induced chondrogenesis; CCI, characterized chondrocyte implantation; MACI, matrix-induced autologous chondrocyte implantation; MF, microfracture; OAT, osteochondral autograft transplantation.

process, which shrink and detach in response to subchondral stimulation,[80,81] or to the insufficient concentration of marrow precursors required to facilitate cartilage repair.[56,82,83] The proposed advantage of MF plus scaffolding and injectable adjuvants is the theoretical ability to increase the concentration of mesenchymal stem cells in the formed clot as well as to facilitate stabilization on clot formation.[84]

It is worth mentioning that the future is now looking to the repair of whole cartilage surfaces beyond the focal defects. In previous studies, small- and large-animal models of MF, supplemented by a wide variety of these adjuvant treatments, have consistently demonstrated superior histologic integration and cartilage restoration, biomechanical properties and repair-tissue durability in vivo[85-87] and may be a viable single-stage alternative for cartilage repair. Among these marrow-stimulation adjuncts, scaffolding supplements that have been investigated include matrices derived from synthetic copolymers, chitosan and collagen.[88] Strauss et al., using a rabbit model, demonstrated that viscosupplementation with intra-articular hyaluronic acid injections promoted more tissue infill and more hyaline-like tissue quality compared with controls.[85]

Limitations

Although our comprehensive study included a large number of RCTs, there are a limited number of studies of each intervention. This review showed that there was a heterogeneity in patient selection, indications, scoring of the defects, scoring of the results, period of follow-up, definition of failure, and technique of surgery. Hence, difficulties occurred in comparing objectively the results of the various studies. Differing surgical approaches were another issue; for example, there is an RCT that reported on the deterioration of results after mosaicplasty performed by arthrotomy but not by arthroscopy.[44] In addition, the scoring system used was different from that used in RCTs by Gudas et al.[59-61]

Conclusions

Cartilage repair techniques, rather than MF, provide higher-quality repair tissue and have lower failure and higher return-to-activity rates. Moreover, OAT had significantly more excellent or good results compared to MF, whereas MF had significantly more poor results than ACI and MACI. Future studies need to have longer follow-up periods and more representative populations

so as to investigate the efficacy and safety of these interventions.

References

1. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: Study of 25,124 knee arthroscopies. *Knee* 2007;14:177-182.
2. Negrin LLV. Do meta-analyses reveal time-dependent differences between the clinical outcomes achieved by microfracture and autologous chondrocyte implantation in the treatment of cartilage defects of the knee? *J Orthop Sci* 2013;18:940-948.
3. Cole BJ, Kercher JS. Special issue on microfracture. *Cartilage* 2010;1:77.
4. Safran MRS. The evidence for surgical repair of articular cartilage in the knee. *J Am Acad Orthop Surg* 2010;18:259-266.
5. Gelber AC, Hochberg MC, Mead LA, Wang N-Y, Wigley FM, Klag MJ. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. *Ann Intern Med* 2000;133:321-328.
6. Buckwalter JA. Articular cartilage: injuries and potential for healing. *J Orthop Sports Phys Ther* 1998;28:192-202.
7. Farr JC, Dhawan A, Kercher J, Sherman S. Clinical cartilage restoration: Evolution and overview. *Clin Orthop Relat Res* 2011;469:2696-2705.
8. Steadman JR, Rodkey WG, Rodrigo JJ. Microfracture: Surgical technique and rehabilitation to treat chondral defects. *Clin Orthopaed Relat Res* 2001;391:S362-S369.
9. Montgomery SR, Foster BD, Ngo SS, et al. Trends in the surgical treatment of articular cartilage defects of the knee in the United States. *Knee Surg Sports Traumatol Arthros* 2014;22:2070-2075.
10. Mithoefer KM, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: An evidence-based systematic analysis. *Am J Sports Med* 2009;37:2053-2063.
11. Moran CJP-G, Chubinskaya S, Potter HG, Warren RF, Cole BJ, Rodeo SA. Restoration of articular cartilage. *J Bone Joint Surg Series A* 2014;96:336-344.
12. Knutsen GI, Johansen O, Engebretsen L, et al. Autologous chondrocyte implantation compared with microfracture in the knee: A randomized trial. *J Bone Joint Surg Series A* 2004;86:455-464.
13. Hoemann CDT, Chevrier A, Chen G, et al. Chondroinduction is the main cartilage repair response to microfracture and microfracture with BST-CarGel: Results as shown by ICRS-II histological scoring and a novel zonal collagen type scoring method of human clinical biopsy specimens. *Am J Sports Med* 2015;43:2469-2480.
14. Bedi AF, Williams RJ. Management of articular cartilage defects of the knee. *J Bone Joint Surg Series A* 2010;92:994-1009.
15. Krych AJ, Harnly HW, Rodeo SA, Williams RJ. Activity levels are higher after osteochondral autograft transfer mosaicplasty than after microfracture for articular cartilage defects of the knee: A retrospective comparative study. *J Bone Joint Surg* 2012;94:971-978.
16. Solheim E, Hegna J, Inderhaug E, Øyen J, Harlem T, Strand T. Results at 10−14 years after microfracture treatment of articular cartilage defects in the knee. *Knee Surg Sports Traumatol Arthros* 2016;24:1587-1593.
17. Gobbi AK, Kumar A. Long-term results after microfracture treatment for full-thickness knee chondral lesions in athletes. *Knee Surg Sports Traumatol Arthros* 2014;22:1986-1996.
18. Saris J, Victor J, Haspl M, et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. *Am J Sports Med* 2008;36:235-246.
19. National Institute for Health and Clinical Excellence. The use of autologous chondrocyte implantation for the treatment of cartilage defects in knee joints. *Technology Appraisal Guidance* 2005;89, http://wwwniceorguk/pageaspx?o=259211.
20. Minas T. Autologous cultured chondrocyte implantation in the repair of focal chondral lesions of the knee: Clinical indications and operative technique. *J Sports Traumatol Relat Res* 1998;20:90-102.
21. Wasiak JC, Villanueva E. Autologous cartilage implantation for full thickness articular cartilage defects of the knee. Cochrane Database of Systematic Reviews *(online)* 2006;3:CD003323.
22. Brittberg ML, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *New Engl J Med* 1994;331:889-895.
23. Erggelet C, Steinwachs MR, Reichelt A. The operative treatment of full thickness cartilage defects in the knee joint with autologous chondrocyte transplantation. *Saudi Med J* 2000;21:715-721.
24. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLOS MED* 2009;6:e1000100.
25. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann Intern Med* 2015;162:777-784.
26. Abdellatif M, Ghozy S, Kamel MG, et al. Association between exposure to macrolides and the development of infantile hypertrophic pyloric stenosis: A systematic review and meta-analysis. *Eur J Pediatr* 2019;178:301-314.
27. Waqas A, Elhady M, Surya Dila KA, et al. Association between maternal depression and risk of infant diarrhea: a systematic review and meta-analysis. *Public Health* 2018;159:78-88.
28. Koziarz A, Sne N, Kegel F, et al. Optic nerve sheath diameter sonography for the diagnosis of increased intracranial pressure: A systematic review and meta-analysis protocol. *BMJ Open* 2017;7:e016194.
29. Doheim MFM, Sara K, Samar M, et al. Efficacy and safety of ethyl-eicosapentaenoic acid as a treatment for Huntington's disease: A systematic review and meta-analysis of randomized clinical trials (P4.049). *Neurology* 2018;90:P4.049.
30. Jelicic Kadic A, Vucic K, Dosenovic S, Sapunar D, Puljak L. Extracting data from figures with software was

faster, with higher interrater reliability than manual extraction. *J Clinl Epidemiol* 2016;74:119-123.
31. Nguyen AV, Thanh LV, Kamel MG, et al. Optimal percutaneous coronary intervention in patients with ST-elevation myocardial infarction and multivessel disease: An updated, large-scale systematic review and meta-analysis. *Int J Cardiol* 2017;244:67-76.
32. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
33. Obremskey WT, Pappas N, Attallah-Wasif E, Tornetta P, Bhandari M. Level of evidence in orthopaedic journals. *J Bone Joint Surg* 2005;87:2632-2638.
34. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-748.
35. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-188.
36. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557.
37. Kamel MGN, Nguyen TH, Nguyen HBao, et al. Post-dengue acute disseminated encephalomyelitis: A case report and meta-analysis. *PLOS Negl Trop Dis* 2017;11: e0005715.
38. Zintzaras E, Lau J. Synthesis of genetic association studies for pertinent gene-disease associations requires appropriate methodological and statistical approaches. *J Clin Epidemiol* 2008;61:634-645.
39. Munafo MR, Flint J. Meta-analysis of genetic association studies. *Trends Genet* 2004;20:439-444.
40. Morra ML, Kamel MG, Ghazy A, et al. Clinical outcomes of current medical approaches for Middle East respiratory syndrome: A systematic review and meta-analysis. Rev Med Virol 2018;28:e1977.
41. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015;15:58.
42. Bartlett W, Skinner J, Gooding C, et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: A prospective, randomised study. *J Bone Joint Surg, Br* 2005;87:640-645.
43. Basad EI, Bachmann G, Sturz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: A 2-year randomised study. *Knee Surg Sports Traumatol Arthros* 2010;18:519-527.
44. Bentley GB, Carrington R, Akmal M, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J Bone Joint Surg Series B* 2003;85:223-230.
45. Bentley G, Biant LC, Vijayan S, Macmull S, Skinner JA, Carrington RWJ. Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. *J Bone Joint Surg Br* 2012;94B:504-509.
46. Crawford DC, DeBerardino TM, Williams RJ Iii. NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: An FDA phase-II prospective, randomized clinical trial after two years. *J Bone Joint Surg Series A* 2012;94: 979-989.
47. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture: Findings at five years. *J Bone Joint Surg Am* 2007;89:2105-2112.
48. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized multicenter trial comparing autologous chondrocyte implantation with microfracture: Long-term follow-up at 14 to 15 years. *J Bone Joint Surg Am* 2016;98:1332-1339.
49. Knutsen G, Engebretsen L, Ludvigsen TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee: A randomized trial. *J Bone Joint Surg* 2004;86:455-464.
50. Saris DB, Vanlauwe J, Victor J, et al. Treatment of symptomatic cartilage defects of the knee: Characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. *Am J Sports Med* 2009;37:10-19 (Suppl 1).
51. van Assche DS, van Caspel D, Vanlauwe J, Bellemans J, Saris DB, Luyten FP. Autologous chondrocyte implantation versus microfracture for knee cartilage injury: A prospective randomized trial, with 2-year follow-up. *Knee Surg Sports Traumatol Arthros* 2010;18:486-495.
52. Vanlauwe JS, Victo J, Almqvist KF, Bellemans J, Luyten FP. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: Early treatment matters. *Am J Sports Med* 2011;39:2566-2574.
53. Saris D, Price A, Widuchowski W, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: Two-year follow-up of a prospective randomized trial. *Am J Sports Med* 2014;42:1384-1394.
54. Brittberg M, Recker D, Ilgenfritz J, Saris DB, Group SES. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: Five-year follow-up of a prospective randomized trial. *Am J Sports Med* 2018;46: 1343-1351.
55. Shive MS, Stanish WD, McCormack R, et al. BST-CarGel treatment maintains cartilage repair superiority over microfracture at 5 years in a multicenter randomized controlled trial. *Cartilage* 2015;6:62-72.
56. Stanish WDM, Forriol F, Mohtadi N, et al. Novel scaffold-based BST-Carel treatment results in superior cartilage repair compared with microfracture in a randomized controlled trial. *J Bone Joint Surg Series A* 2013;95: 1640-1650.
57. Volz MS, Frick H, Grifka J, Anders S. A randomized controlled trial demonstrating sustained benefit of autologous matrix-induced chondrogenesis over microfracture at five years. *Int Orthop* 2017;41:797-804.
58. Visna P, Pasa L, Cizmar I, Hart R, Hoch J. Treatment of deep cartilage defects of the knee using autologous chondrograft transplantation and by abrasive techniques: A randomized controlled study. *Acta Chir Belg* 2004;104: 709-714.
59. Gudas R, Kalesinskas RJ, Kimtys V, et al. A prospective randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the

treatment of osteochondral defects in the knee joint in young athletes. *Arthroscopy* 2005;21:1066-1075.
60. Gudas R, Gudaite A, Pocius A, et al. Ten-year follow-up of a prospective, randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint of athletes. *Am J Sports Med* 2012;40:2499-2508.
61. Gudas R, Simonaityte R, Cekanauskas E, Tamosiūnas R. A prospective, randomized clinical study of osteochondral autologous transplantation versus microfracture for the treatment of osteochondritis dissecans in the knee joint in children. *J Pediatr Orthop* 2009;29:741-748.
62. Van Assche DVC, Vanlauwe J, Bellemans J, Saris DB, Luyten FP, Staes F. Physical activity levels after characterized chondrocyte implantation versus microfracture in the knee and the relationship to objective functional outcome with 2-year follow-up. *Am J Sports Med* 2009;37:42S-49S (Suppl 1).
63. Stanish WDR, McCormack RG, Mohtadi N, et al. An international randomized clinical trial evaluating BST-Cargel, a novel scaffold for cartilage repair, demonstrates superiority of repair when compared with microfracture alone treatment. *Arthroscopy* 2013;29:e137 (Suppl 1).
64. Goyal D, Keyhani S, Goyal A, Lee EH, Hui JHP, Vaziri AS. Evidence-based status of osteochondral cylinder transfer techniques: A systematic review of level I and II studies. *Arthroscopy* 2014;30:497-505.
65. Steadman JR, Rodkey WG, Singleton SB, Briggs KK. Microfracture technique forfull-thickness chondral defects: Technique and clinical results. *Oper Tech Orthop* 1997;7:300-304.
66. Mithoefer K, Williams RJ, Warren RF, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee: A prospective cohort study. *J Bone Joint Surg* 2005;87:1911-1920.
67. Kreuz PCS, Erggelet C, Krause SJ, Konrad G, Uhl M, Sudkamp N. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthrit Cartil* 2006;14:1119-1125.
68. Hoemann CD, Tran-Khanh N, Chevrier A, et al. Chondroinduction is the main cartilage repair response to microfracture and microfracture with BST-CarGel: Results as shown by ICRS-II histological scoring and a novel zonal collagen type scoring method of human clinical biopsy specimens. *Am J Sports Med* 2015;43:2469-2480.
69. Miller BS, Joseph TA, Barry EM, Rich VJ, Sterett WI. Patient satisfaction after medial opening high tibial osteotomy and microfracture. *J Knee Surg* 2007;20:129-133.
70. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthrit Cartil* 2006;14:1119-1125.
71. Brittberg M. Cell carriers as the next generation of cell therapy for cartilage repair: A review of the matrix-induced autologous chondrocyte implantation procedure. *Am J Sports Med* 2010;38:1259-1271.
72. Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. *Am J Sports Med* 2009;37:902-908.
73. Pestka JM, Bode G, Salzmann G, Südkamp NP, Niemeyer P. Clinical outcome of autologous chondrocyte implantation for failed microfracture treatment of full-thickness cartilage defects of the knee joint. *Am J Sports Med* 2012;40:325-331.
74. Harris JD, Siston RA, Pan X, Flanigan DC. Autologous chondrocyte implantation: A systematic review. *J Bone Joint Surg* 2010;92:2220-2233.
75. Chahal J, Gross AE, Gross C, et al. Outcomes of osteochondral allograft transplantation in the knee. *Arthroscopy* 2013;29:575-588.
76. Kon EV, Condello V, Delcogliano M, et al. Matrix-assisted autologous chondrocyte transplantation for the repair of cartilage defects of the knee: Systematic clinical data review and study quality analysis. *Am J Sports Med* 2009;37:156S-166S (Suppl 1).
77. Bekkers JEI, Saris DB. Treatment selection in articular cartilage lesions of the knee: A systematic review. *Am J Sports Med* 2009;37:148s-155s (Suppl 1).
78. Goyal DK, Lee EH, Hui JHP. Evidence-based status of microfracture technique: A systematic review of level i and ii studies. *Arthroscopy* 2013;29:1579-1588.
79. Lynch TSP, Benedick A, Amin NH, Jones MH, Miniaci A. Systematic review of autogenous osteochondral transplant outcomes. *Arthroscopy* 2015;31:746-754.
80. Hoemann CD, Hurtig M, Rossomacha E, et al. Chitosan-glycerol phosphate/blood implants improve hyaline cartilage repair in ovine microfracture defects. *J Bone Joint Surg* 2005;87:2671-2686.
81. Chevrier A, Hoemann C, Sun J, Buschmann M. Chitosan-glycerol phosphate/blood implants increase cell recruitment, transient vascularization and subchondral bone remodeling in drilled cartilage defects. *Osteoarthrit Cartil* 2007;15:316-327.
82. Fortier LA, Potter HG, Rickey EJ, et al. Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. *J Bone Joint Surg* 2010;92:1927-1937.
83. Koh Y-G, Kwon O-R, Kim Y-S, Choi Y-J, Tak D-H. Adipose-derived mesenchymal stem cells with microfracture versus microfracture alone: 2-year follow-up of a prospective randomized trial. *Arthroscopy* 2016;32:97-109.
84. Bark S, Piontek T, Behrens P, Mkalaluh S, Varoga D, Gille J. Enhanced microfracture techniques in cartilage knee surgery: Fact or fiction? *World J Orthoped* 2014;5:444.
85. Strauss E, Schachter A, Frenkel S, Rosen J. The efficacy of intra-articular hyaluronan injection after the microfracture technique for the treatment of articular cartilage lesions. *Am J Sports Med* 2009;37:720-726.
86. Milano G, Deriu L, Passino ES, et al. Repeated platelet concentrate injections enhance reparative response of microfractures in the treatment of chondral defects of the knee: An experimental study in an animal model. *Arthroscopy* 2012;28:688-701.
87. Vaisman A, Figueroa D, Calvo R, et al. Steroids and platelet-rich plasma as coadjuvants to microfracture for the treatment of chondral lesions in an animal model: can the healing be enhanced? *Cartilage* 2012;3:118-127.
88. Case JMS. Treatment of articular cartilage defects of the knee with microfracture and enhanced microfracture techniques. *Sports Med Arth Rev* 2016;24:63-68.

89. Saris D, Price A, Widuchowski W, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture two-year follow-up of a prospective randomized trial. *Am J Sports Med* 2014;42:1384-1394.
90. Visna P, Pasa L, Folvarsky J, Hart R, Adler J, Horky D. Treatment of deep cartilage defects in the knee by mosaicplasty combined with autologous cultivated chondrocytes in Tissucol. *Eur J Trauma* 2002;28:43 (Suppl 1).
91. Gudas RK, Kimtys V, Stankevicius E, Toliusis V, Bernotavicius G, Smailys A. A prospective randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint in young athletes. *Arthroscop* 2005;21:1066-1075.
92. Gudas RG, Pocius A, Gudiene A, Čekanauskas E, Monastyreckiene E, Basevičius A. Ten-year follow-up of a prospective, randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint of athletes. *Am J Sports Med* 2012;40:2499-2508.