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Review

Correlation between histological outcome and surgical cartilage repair technique in the knee: A meta-analysis☆,☆☆

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ABSTRACT

Background: Compare histological outcomes after microfracture (MF), autologous chondrocyte implantation (ACI), and osteochondral autograft transfer (OATS).
Methods: Literature review using PubMed MEDLINE, SCOPUS, Cumulative Index for Nursing and Allied Health Literature (CINAHL), and Cochrane Collaboration Library. Inclusion criteria limited to English language studies International Cartilage Repair Society (ICRS) grading criteria for cartilage analysis after ACI (autologous chondrocyte implantation), MF (microfracture), or OATS (osteochondral autografting) repair techniques.
Results: Thirty-three studies investigating 1511 patients were identified. Thirty evaluated ACI or one of its subtypes, six evaluated MF, and seven evaluated OATS. There was no evidence of publication bias (Begg's $p = 0.48$). No statistically significant correlation was found between percent change in clinical outcome and percent biopsies showing ICRS Excellent scores ($R^2 = 0.05$, $p = 0.38$). Percent change in clinical outcome and percent of biopsies showing only hyaline cartilage were significantly associated ($R^2 = 0.24$, $p = 0.024$). Mean lesion size and histological outcome were not correlated based either on percent ICRS Excellent ($R^2 = 0.03$, $p = 0.50$) or percent hyaline cartilage only ($R^2 = 0.01$, $p = 0.67$). Most common lesion location and histological outcome were not correlated based either on percent ICRS Excellent ($R^2 = 0.03$, $p = 0.50$) or percent hyaline cartilage only ($R^2 = 0.01$, $p = 0.67$).
Conclusions: Microfracture has poorer histologic outcomes than other cartilage repair techniques. OATS repairs primarily are comprised of hyaline cartilage, followed closely by cell-based techniques, but no significant difference was found cartilage quality using ICRS grading criteria among OATS, ACI-C, MACI, and ACI-P.
Level of evidence: IV, meta-analysis

Contents

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1. Introduction

Cartilage defects in the knee can cause substantial patient morbidity and predispose patients to chronic knee problems such as osteoarthritis (OA) [10,40,48,49]. Unfortunately, full thickness cartilage defects of the knee joint are quite common. Over half of patients in a recent retrospective study of knee arthroscopy were confirmed to have cartilage defects, [53] and athletes may be at greater risk [16,50]. Although the natural history of cartilage lesion progression to osteoarthritis is not fully understood, prompt treatment of symptomatic cartilage defects has been shown to have good results. [17] These defects in the knee range in severity from small changes in knee cartilage to larger full-thickness lesions.

Several methods have been proposed for the treatment of cartilage defects in the knee. Microfracture (MF), osteochondral autograft (OATS), osteochondral allografts (OCA), and autologous chondrocyte implantation (ACI) have all been well-described treatments. Treatment algorithms have been created based on size and location of defects, activity level, and whether one is performing a primary or secondary procedure [4,13]. However, tissue regenerated after different cartilage repair techniques can vary in the amount of hyaline cartilage.

For instance, microfracture is traditionally thought to produce fibrocartilage, whereas other techniques such as OATS and ACI are thought to produce more hyaline like tissue. [54] Thus, the histological outcome of each cartilage repair technique is different, and many studies have been performed that analyze these histological outcomes. Importantly, previous studies have not focused on a comparison of histological outcomes among the different techniques. The objective of this study is to compare the histological outcomes among cartilage repair techniques and to evaluate any correlation between histological outcomes and clinical outcomes. We hypothesized that microfracture would have the worst outcomes based on histological scores.

2. Material and methods

2.1. Methods

Using guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and QUORUM (Quality of Reporting of Meta-Analysis) statements for standardized reporting of systematic reviews in the preparation of this manuscript, [33,37] a systematic search of the literature was performed to identify studies that evaluated histological outcomes after surgical cartilage repair in the knee joint (Figure 1). Cartilage repair techniques evaluated were limited to autologous chondrocyte implantation (with a periosteal cover [ACI-P], with a type I/type III collagen-derived cover [ACI-C], or with a matrix-induced cover [MACI]), osteoarticular transfer system (OATS)/mosaicplasty (MO), and microfracture (MF). One study reported on CCI (characterized chondrocyte implantation), in which chondrocytes are grown on a matrix substance (often cartilage or hyaluronan). This CCI was thus included in the MACI analysis group. The PubMed MEDLINE, SCOPUS, Cumulative Index for Nursing and Allied Health Literature (CINAHL), and Cochrane Collaboration Library databases were searched from their earliest entry points to July 27, 2013. The search terms were autologous chondrocyte implantation, ACI, autologous chondrocyte transplantation, microfracture, osteoarticular transfer, osteochondral autograft transfer, OATS, histology, histological, outcome, and knee.

Inclusion criteria

- English-language studies
- Levels 1 to 4 evidence
- Cartilage defects treated with ACI, MACI, ACI-C, OATS, or MF
- Second-look arthroscopy at follow-up
- Use of a biopsy or International Cartilage Repair Society visual grading scale to grade the treated lesion

Exclusion criteria

- Non-English-language studies
- Animal studies
- Level 5 evidence
- Studies investigating joints other than the knee
- Multiple cartilage repair techniques used in combination

In this review, the ICRS visual grading scale (International Cartilage Repair Society) was used to measure outcomes between studies as numerous studies evaluated used this method of assessing cartilage post-operatively [52]. The scale assesses the degree of defect repair, integration to boarder zone, and macroscopic appearance. Each of these three categories is graded on a one to four scale, and then the sum of the three categories is used to grade the repair site. Grades

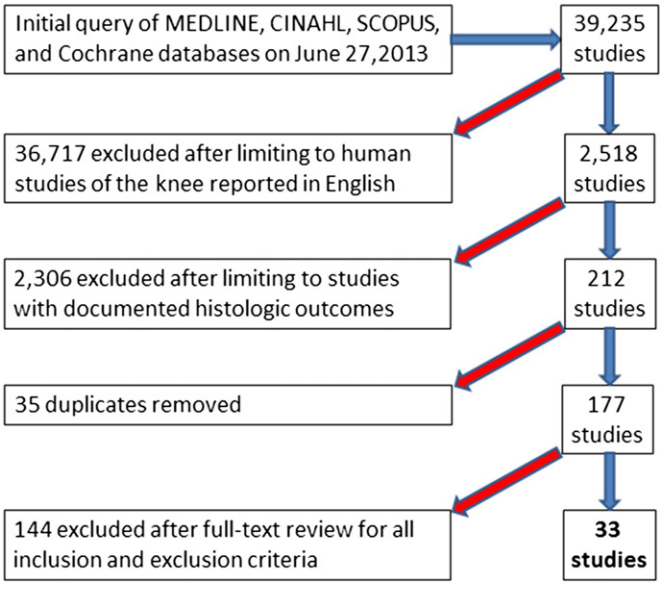

Figure 1. Systematic search process. The initial searches of MEDLINE, CINAHL, SCOPUS, and Cochrane databases identified 39,235 studies. After limiting the searches to human studies reported in English on the knee that included histologic outcomes, duplicates were removed and the full text of the remaining 177 studies was reviewed, resulting in a final total of 33 studies that met all inclusion and exclusion criteria.

include normal/excellent (ICRS score = 12), nearly normal/good (IRCS score = 8 to 11), abnormal/fair (ICRS score = 7–4), or severely abnormal/poor (ICRS score = 1 to 3). Direct histological assessment was also used to measure outcomes between studies as this was also used as an outcome measure by numerous of the included studies. Levels of histological appearance included hyaline-like cartilage, fibrocartilage, fibrous tissue, or mixed fibrocartilage and hyaline-like cartilage.

2.2. Statistical analysis

All statistical tests were performed with a standard software package (STATA 13.0, StataCorp, College Station, TX). Treatment effect size was defined as the mean ICRS histologic grade or biopsy appearance after conversion to numerical scales (ICRS: 4 = excellent; 3 = good; 2 = fair; 1 = poor). Due to a left-skewed distribution in values (most biopsies were graded as a three or four), a squared transformation was applied to the data to achieve a more normal distribution. Studies were weighted by the inverse of the variance of the modified ICRS score. Effect heterogeneity was determined within a given treatment group and between modalities using the I-squared measure as described by Higgins et al. [28] Percentage I-square scores indicate level of inconsistency or heterogeneity across studies assessed, with lower scores indicating lower levels of heterogeneity. ACI-C, MACI, and ACI-P were kept as separate groups, as all have been studied extensively as individual techniques in existing literature.

Due to the potential for publication bias among multiple small studies and relatively new treatment modalities, we performed a graphical assessment of bias among all studies with a funnel plot and a statistical assessment of bias among all studies and within treatment groups using Begg's test [3] and Egger's test [14] for publication bias (Figure 2). The funnel plot and a non-significant Begg's ($p = 0.48$) and Egger's ($p = 0.81$) tests showed no graphical or statistical evidence of reporting bias, respectively. There was also no statistical evidence of publication bias within groups (Begg's and Egger's tests, $p > 0.25$ for all groups). Pearson's correlation coefficient was used to correlate cartilage histology (biopsy histology or ICRS score) with clinical outcome and lesion size. Analysis of variance (ANOVA) was used correlate histological outcome with lesion location.

3. Results

Study specific information is depicted in Table 1 and Tables 2 through 8 (Appendix).

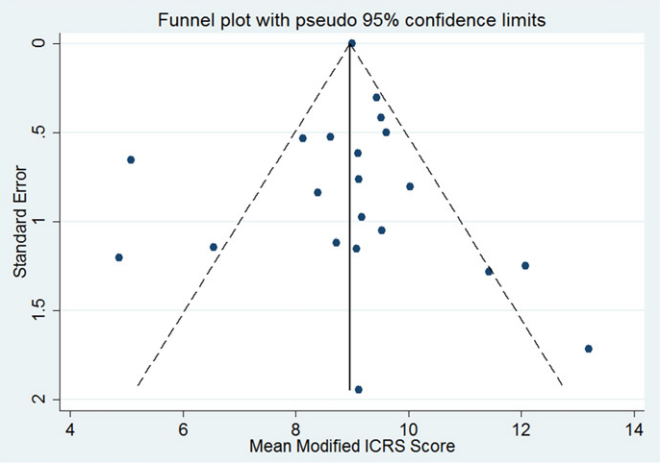

Figure 2. A funnel plot of the mean modified ICRS score versus standard error (95% confidence limits represented by dashed lines) demonstrates a grossly symmetric distribution of points. There is no overt evidence of negative publication bias, which would be represented by a lack of studies in the left portion of the figure.

3.1. Autologous chondrocyte implantation with periosteum cover (ACI-P)

Thirteen studies were identified that reported data on histological outcomes of ACI-P knee cartilage repair (Table 3, Appendix). [6,8,20,25,26,27,30,31,34,38,42,45,51] The 13 studies included data from 489 patients and reported data on 272 biopsy samples. Of the 272 biopsy specimens, 84 (30.9%) showed hyaline cartilage only. Eight of the studies reported data using the International Cartilage Repair Society (ICRS) Histological Visual Scale. [52] Fifty (23.5%) repair sites were rated as excellent according to ICRS criteria. The mean modified ICRS score described above for ACI-P was 9.34 (95% CI; 8.84, 9.84).

3.2. Matrix-induced autologous chondrocyte implantation (MACI)

Twelve studies were identified that reported data on histological outcomes of MACI or CCI (characterized chondrocyte implantation) knee cartilage repair (Table 4, Appendix). [2,5,9,12,15,18,19,29,36,44,46,55] Of the 216 biopsies performed, histological data was reported for 123. Of these, 51 (38.3%) showed hyaline cartilage only. Fourteen (21.5%) repair sites were rated as excellent according to ICRS criteria. The mean modified ICRS score for MACI was 9.59 (95% CI; 5.88, 13.20).

3.3. Autologous chondrocyte implantation with type I/type III collagen cover (ACI-C)

Five studies were identified that reported data on histological outcomes of ACI-C knee cartilage repair (Table 5, Appendix). [2,7,20,23,32] Of the 104 biopsies performed, 31 (29.8%) showed hyaline cartilage only. Eight (9%) repair sites were rated as excellent according to ICRS criteria. The mean modified ICRS score for ACI-C was 8.80 (95% CI; 7.97, 9.63).

3.4. Microfracture

Six studies reported data on histological outcomes of MF knee cartilage repair (Table 6, Appendix). [1,21,22,31,34,44] Of the 150 biopsies in this category, histological data was reported for 49 of them with four (8.2%) showing hyaline cartilage only. Seven (12.5%) repair sites were rated as excellent based on ICRS criteria. The mean modified ICRS score for MF was 6.74 (95% CI; 4.67, 8.82).

3.5. Osteoarticular transfer system (OATS) and mosaicplasty (MO)

Seven of the investigated studies reported data on histological outcomes of OATS or MO knee cartilage repair (Table 7, Appendix) [6,11,21,22,30,34,35]. Only one of these studies investigated MO [6] and the other six investigated OATS. Of the 32 biopsies from OATS procedures, 25 (78.1%) showed hyaline cartilage only. In the OATS category, 13 (36.1%) repair sites were rated as excellent according to ICRS criteria. In addition, the MO study reported 0 repair sites as excellent based on ICRS criteria. The mean modified ICRS score for OATS/MO was 9.54 (95% CI; 5.88, 13.2).

3.6. Magnetic resonance imaging

Eleven studies reported magnetic resonance imaging (MRI) findings. Unfortunately, results were considerably heterogeneous and a formal statistical analysis is not appropriate. Only Tins et al. attempted to correlate histological outcomes with MRI findings [51]. They found no statistically relevant correlation between graft thickness on MRI and histological appearance in their study of 41 patients receiving ACI. Five OATS studies [11,21,22,34,35], three MF studies [21,22,34], four ACI studies [25,27,34,51], and four MACI studies [18,19,47,55] reported varying MRI findings but did not correlate them with histological findings.

3.7. Clinical outcomes and histologic outcomes

Twenty-eight of the 33 studies included clinical outcomes data at varying follow-up periods. Of these 28 studies, 21 reported histological outcomes based on biopsies and second-look arthroscopies from patients receiving second-look arthroscopy as part of the original study protocol (versus receiving second-look arthroscopy due persistent symptoms). Furthermore, six of these 21 studies attempted to correlate clinical outcome results with histological analysis.

For instance, in their study of ACI-C, Briggs et al. found that only one of three patients with excellent clinical outcomes based on the Brittberg rating scale had hyaline cartilage on biopsy, and three of the five patients with a clinical outcome rated as good had hyaline cartilage. In the four with fair outcomes, one had hyaline cartilage, and in the two with poor outcomes, one had hyaline cartilage. Brittberg et al.'s study of ACI found seven of seven biopsies of patients with excellent clinical outcome to show hyaline cartilage, five of eight with good clinical outcome to show hyaline cartilage, and none of the fair or poor clinical outcome patients' biopsies to show hyaline cartilage. In their study of MACI, Brun et al. found that five of six patients asymptomatic at follow-up had hyaline tissue on biopsy, compared to 0 of five having hyaline tissue at follow-up in the symptomatic patient group. In Chow et al.'s study of OATS, seven of nine biopsy specimens had hyaline cartilage and an excellent or good outcome on the Lysholm knee scale, compared to the remaining two showing fibrocartilage at biopsy and having a good and fair clinical outcome.

Only two studies attempted to statistically correlate clinical outcome to histological outcome. Knutsen et al. reported a lack of statistically significant correlation between

Table 1
Study specific information.

Study	Country	No. of surgeons	Study design	No. of patients	Percent male	Average age (years)	Treatment[a]	Avg. follow-up time (m)	Avg. biopsy procurement time (m)	Number of biopsies (n)	Most common lesion site n (%)[d]	Defect size (cm^2)
Bae et al. (2006)	Korea	Multiple	Case series	46	9.1	57	MF	27.6	12	47	44 (89.8%) M	3.9
Bartlett et al. (2005)	UK	Multiple	RCT	44	59.3	33.7	ACI-C	12	12	14	25 (42.4%) MFC	6
Bartlett et al. (2005)	UK	Multiple	RCT	47	59.3	33.4	MACI	12	12	11	25 (47.2) MFC	6.1
Behrens et al. (2006)	Germany	Multiple	Case series	38	50	35	MACI	34.5	12	4	16 (42.1%) MFC	4.08
Bentley et al. (2003)	UK	–[b]	RCT	58	57	20.9	ACI-P	19	12	19	24 (45%) MFC	4.66
Bentley et al. (2003)	UK	–	RCT	42	57	31.6	MO	19	na	na	29 (69%) MFC	4.66
Briggs et al. (2002)	UK	1	Case series	14	71.4	30	ACI-C	33	11	14	8 (51.7%) MFC	2.46
Brittberg et al. (2002)	Sweden	–	Case series	23	47.8	27	ACI-P	20	24	22	16 (100%) FC	3.1
Brun et al. (2008)	Italy	Multiple	Case series	63	65.1	39	MACI	–	14.1	70	62 (88.6%) FC	4.3
Chow et al. (2004)	USA	1	Case series	30	43.3	44.6	OATS	45.1	8.8	9	28 (93.3%) MFC	
D'Anchise et al. (2005)	Italy	–	Case series	35	65.7	33.1	MACI	22	20	3	19 (44.2) MFC	4
Enea et al. (2011)	Italy	Multiple	Case series	30	63.3	40.5	MACI	–	15	33	17 (56.7%) MFC	5
Gobbi et al. (2009)	Italy	3	Case series	34	67.6	31.2	MACI	75.5	14.75	3	21 (61.8%) P	4.45
Gobbi et al. (2006)	Italy	3	Case series	32	65.6	30.5	MACI	–	12.5	6	22 (68.8%) P	4.7
Gooding et al. (2006)	UK	–	RCT	35	48.5	30.55	ACI-C	–	12, 24[c]	20	18 (51%) MFC	4.54
Gooding et al. (2006)	UK	–	RCT	33	48.5	30.52	ACI-P	–	12, 24	17	20 (61%) P	4.54
Gudas et al. (2005)	Lithuania	1	RCT	29	–	24.3	MF	37.1	12.4	14	48 (84%) MFC	2.77
Gudas et al. (2005)	Lithuania	1	RCT	28	–	24.3	OATS	37.1	12.4	11		2.8
Gudas et al. (2009)	Lithuania	1	RCT	22	59.1	14.09	MF	50.4	na	na	20 (90.9%) MFC	3.17
Gudas et al. (2009)	Lithuania	1	RCT	25	60	14.64	OATS	50.4	20.3	5	21 (84.0%) MFC	3.2
Haddo et al. (2003)	UK	1	Case series	30	66.7	31	ACI-C	–	12.6	33	20 (60.6%) MFC	2.86
Henderson et al. (2004)	Australia	1	Case series	22	68.2	40	ACI-P	–	10.5	20	14 (45.2%) MFC	3.3
Henderson et al. (2003)	Australia	1	Case series	57	78.9	40.5	ACI-P	–	11.3	13	34 (42.0%) MFC	3.7
Henderson et al. (2005)	Australia	1	Case series	53	75.5	41	ACI-P	–	13.4	20	32 (44.4%) MFC	3.7
Hollander et al. (2006)	Italy	Multiple	Case series	23	78.3	35.6	MACI	–	16	23	12 (52.2%) MFC	5
Horas et al. (2003)	Germany	–	RCT	20	40	31.4	ACI-P	–	<24	8	17 (85%) MFC	3.86
Horas et al. (2003)	Germany	–	RCT	20	75	35.4	OATS	–	15.8	5	16 (80%) MFC	3.63
Knutsen et al. (2004)	UK	Multiple	RCT	40	60	33.3	ACI-P	–	24	32	36 (90%) MFC	5.1
Knutsen et al. (2004)	UK	Multiple	RCT	40	60	31.1	MF	–	24	35		4.5
Krishnan et al. (2006)	UK	–	Case series	37	62.2	31.9	ACI-C	48.96	12	23	27 (73%) MFC	5.93
Lim et al. (2009)	South Korea	1	RCT	18	55.6	25.1	ACI-P	62.4	na	na	13 (72.2%) MFC	2.84
Lim et al. (2009)	South Korea	1	RCT	30	58.6	32.9	MF	80.4	na	na	23 (76.7%) MFC	2.77
Lim et al. (2009)	South Korea	1	RCT	22	54.5	30.4	OATS	69.6	na	na	19 (86.4%) MFC	2.75
Ma et al. (2004)	Taiwan	–	Case series	18	66.7	29	OATS	42	19.5	2	11 (68.8%) MFC	4.1
Marcacci et al. (2007)	Italy	–	Case series	70	–	29	MACI	–	13.5	2	38 (63.3%) MFC	2.4
Peterson et al. (2002)	Sweden	3	Case series	61	–	–	ACI-P	88.8	54.3	12	30 (63.8%) FC	
Roberts et al. (2009)	UK	–	Case series	58	–	34	ACI-P	–	15.7	65	45 (69.2%) MFC	
Saris et al. (2008)	Belgium, Netherlands, Germany, and Croatia	13	RCT	61	61	33.9	CCI	–	12	47	61 (100%) FC	2.6
Saris et al. (2008)	Belgium, Netherlands, Germany, and Croatia	13	RCT	57	67	33.9	MF	–	12	54	57 (100%) FC	2.4
Scorrano et al. (2004)	Italy	–	Case series	5	–	24.8	ACI-P	–	12	3	3 (60%) MFC	6.89
Selmi et al. (2008)	France	Multiple	Case series	17	70.6	30	MACI	–	24	13	14 (70%) C	4
Tins et al. (2005)	UK	2	Case series	41	73.2	35	ACI-P	–	12	41	29 (70.7%) MFC	4.78
Zhang et al. (2006)	Australia	–	Case series	3	100	24	MACI	12.7	–	1		8

[a] Autologous chondrocyte implantation (periosteum cover (ACI-P), type I/type III collagen derived cover (ACI-C), matrix-induced cover (MACI), characterized chondrocyte implantation (CCI)), osteoarticular transfer system (OATS), mosaicplasty (MO), or microfracture (MF).
[b] Indicates unavailable data.
[c] Indicates two biopsy time points, number of biopsy column includes biopsies from both time points.
[d] Medial (M), medial femoral condyle (MFC), femoral condyle (FC), patella (P), central (C).

histological outcome and clinical outcome in their study of ACI and MF. Similarly, Selmi et al. was also unable to find a statistically significant correlation between clinical and histological outcomes when evaluating ACI.

When analyzing all studies that included clinical outcomes and histological outcomes (ICRS score or biopsy results), no statistically significant correlation was found between percent change in clinical outcome (pre-operative to final follow-up) and percent biopsies showing ICRS Excellent scores ($R^2 = 0.05$, $p = 0.38$). However, there was a significant association between percent change in clinical outcome and percent of biopsies showing only hyaline cartilage ($R^2 = 0.24$, $p = 0.024$). In addition, there was no correlation between mean lesion size and histological outcome based on either percent ICRS Excellent ($R^2 = 0.03$, $p = 0.50$) or percent hyaline cartilage only ($R^2 = 0.01$, $p = 0.67$). There was no correlation between most common lesion location and histological outcome based on either percent ICRS Excellent ($R^2 = 0.03$, $p = 0.50$) or percent hyaline cartilage only ($R^2 = 0.01$, $p = 0.67$).

As it relates to lesion site, there was no difference in mean percent biopsies with hyaline cartilage between studies with patellofemoral lesions or femoral condylar lesions being the most common site (mean = 53%, SD = 24% patellofemoral most common site; mean = 43%, SD = 33% femoral condyle most common site; $p = 0.58$). A trend toward higher average percent biopsies with Excellent ICRS histological scores among studies with femoral condylar lesions as the most common site compared to patellofemoral lesions as the most common site did exist (femoral condyle lesions mean = 24%, SD 21%; patellofemoral mean = 2.5%, SD = 4.3%; $p = 0.11$). Interestingly, having an ICRS score of excellent did not correlate with percent biopsies showing only hyaline cartilage ($R^2 = 0.04$, $p = 0.51$).

Average length of follow-up was evaluated for a potential cause of heterogeneity; though this was non-significant among all groups ($p = 0.22$), after stratifying by repair type there was an association between better histologic scores and increased length of follow-up among chondrocyte implantation techniques (ACI-P, MACI, and ACI-C; $p = 0.028$) and no association among microfracture or OATS/mosaicplasty ($p = 0.40$). No other potential causes of heterogeneity were identified in our analysis, as there was no association between the mean modified ICRS score and case series vs. randomized controlled trial design ($p = 0.16$), average defect size ($p = 0.81$), average patient age ($p = 0.64$) or percent male patients ($p = 0.57$).

4. Discussion

The present meta-analysis investigated various cartilage repair techniques and found that repair tissue after the OATS procedure contained a larger amount of hyaline cartilage than was achieved with the other investigated techniques. Similarly, microfracture tissue was found to be primarily fibrocartilage. For cell-based techniques (ACI-P, MACI, and ACI-C), repair tissue was predominantly fibrocartilage to mixed hyaline and fibrocartilage.

Interestingly, repair tissue varies not only by technique but also by time. In our review of ICRS scores we found that with increasing time from surgery, repairs from chondrocyte implantation techniques become more hyaline-like, demonstrating maturation of the tissue. The amount of fibrocartilage formed in MF is even greater, with more than half of the biopsy specimens in this group indicating fibrocartilage only with no maturation to improved tissue quality over time. In contrast to OATS, the predominant repair tissue observed was hyaline cartilage. However, these results must be taken in the light of the wide range of follow-up reported by the included studies (12–75 months). These findings are consistent with the specific features of the respective techniques. In OATS and MO, plugs of cartilage and bone are taken from non-weight-bearing portions of the knee and then inserted into predrilled holes at the cartilage defect site. Thus, the existing healthy cartilage of the plugs persists and repair tissue forms around it. In contrast, ACI-P, MACI, and ACI-C implant differentiated chondrocytes and MF allows stem cells to form new chondrocytes and a new cartilage surface. This process allows for the formation of fibrocartilaginous repair tissue.

The nature of the repair tissue formed postoperatively may potentially affect clinical outcome [24,39,43]. While clinical outcomes did not correlate with ICRS scores, we found that a higher percent of hyaline cartilage does correlate with better clinical outcomes. However, this result needs to be taken with caution as studies often provide overall clinical outcomes on patients, and then subsequently provide histological analysis on a subset of patients receiving biopsy, making a direct comparison impossible. However, only studies that offered biopsy/s-look arthroscopy to all patients as part of a study protocol were included in analysis, this theoretically eliminating the bias of including studies where only symptomatic patients were biopsied/offered a second-look arthroscopy. Level I evidence on the subject remains divided and numerous factors including characteristics of the lesion, patient factors and desires, and surgeon preference and skill set continue to drive this discussion.

An important limitation of the current meta-analysis is the unequal number of studies for each repair technique evaluated. More studies evaluating ACI-P and MACI were reviewed than those evaluating ACI-C, MF, OATS, and MO. More studies related to the last four categories are required to make definitive recommendations for treatment. Low numbers persist due to the challenges of assessing histologic outcomes of cartilage repair. MRI is a useful noninvasive technique for clinical follow-up and evaluation of tissue repair in the knee joint post-operatively, but to date has been unable to provide consistent information regarding the repair histology. [41] Unfortunately, repeat arthroscopy is the only technique capable of gathering such information. Most studies included in this analysis only had a portion of the subjects with histological assessment.

Another important limitation lies in the reasons given for second-look arthroscopies. While most studies indicated that biopsies were taken according to study protocol, six studies (Behrens, Gobbi 2006 and 2009, Gudas 2005, Henderson 2004, and Enea) indicated that biopsies were taken at second-look arthroscopy due to another reason. Reasons for second-look arthroscopies included mechanical symptoms (clicking, catching, locking), other procedures unrelated to the original cartilage repair procedure, or simply that patients were “symptomatic.” This indicates that possibly at least some biopsies in this review came from symptomatic patients.

In addition, given the nature of the present study (analysis of histological outcomes related to cartilage repair techniques and clinical outcomes) and the paucity of literature evaluating techniques compared to each other while also taking biopsies for histologic analysis, the present study may suffer from inter-observer biases among studies. However, the funnel plot (Figure 2) and a non-significant Begg's ($p = 0.48$) and Egger's ($p = 0.81$) tests showed no graphical or statistical evidence of reporting bias. While not eliminating the possibility of inter-observer biases among studies, we have attempted to appropriately address this limitation using the above statistical methods.

Further, a number of studies in the review are not comparative and no single study compared all possible techniques. Having a single surgeon or single group of surgeons compare histological outcomes for all procedures would be preferable but is logistically difficult. Although all studies were assessed based on several categories, other potential differences between studies remain that could alter findings. Variations within treatment techniques (e.g., performing OATS by open arthrotomy versus arthroscopy) clearly have the potential to influence outcomes. It is difficult to characterize precisely where biopsies are taken and no standardized technique for reporting such data exists. In addition, we are unable to control for concomitant procedures performed for various reasons in specific patients in each study. Finally, the present review includes level 4 evidence due to the paucity of randomized controlled trials related to the subject.

5. Conclusions

Percent change of clinical outcome scores did correlate with biopsies revealing high amounts of hyaline cartilage, however this percent change in reported histological outcome did not correlate with ICRS scores. No correlation between lesion size and histology outcome was found and no correlation between lesion site. Microfracture has lower percentage of hyaline cartilage and poorer histologic outcomes than other cartilage repair techniques. Osteochondral autografting produces repairs are more likely to be comprised of mostly hyaline cartilage, followed closely by cell based techniques.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.knee.2016.01.017.

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