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Changing trends in the use of cartilage restoration techniques for the patellofemoral joint: a systematic review

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Abstract

Purpose The patellofemoral (PF) joint contains the thickest articular cartilage in the human body. Chondral lesions to this area are often misdiagnosed and can predispose to secondary osteoarthritis if left untreated. Treatment options range from arthroscopic debridement to cartilage restoration techniques such as microfracture (MFx), autologous chondrocyte implantation (ACI), and osteochondral autograft transplantation. The purpose of this study was to systematically assess the trends in surgical techniques, outcomes, and complications of cartilage restoration of the PF joint.

Methods This review has been conducted according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The electronic databases PubMed, MEDLINE, and EMBASE were searched from January 1, 2007 to April 30, 2018. The Methodological Index for Non-randomized Studies (MINORS) was used to assess study quality. A two-proportion *z* test was used to determine whether the differences between the proportions of cartilage restoration techniques used from 2007 to 2012 and 2013–2018 were statistically significant.

Results Overall, 28 studies were identified, including 708 patients (824 knees) with a mean age of 39.5 ± 10.5 years and a mean follow-up of 39.1 ± 16.0 months. Majority of patients were treated with ACI (45.5%) and MFx (29.6%). A significant increase in the use of the third generation ACI occurred with a simultaneous decreased usage of the conventional MFx over the last 5 years ($p < 0.001$). All techniques had significant ($p < 0.05$) improvements in clinical outcomes. The overall complication rate was 9.2%, of which graft hypertrophy (2.7%) was the most prevalent.

Conclusions ACI was the most common restoration technique. The use of third generation ACI has increased with a concurrent decline in the use of conventional MFx over the latter half of the past decade ($p < 0.001$). Overall, the various cartilage restoration techniques reported improvements in patient reported outcomes with low complication rates. Definitive conclusions on the optimal treatment remain elusive due to a lack of high-quality comparative studies.

Level of evidence Level IV, Systematic Review of Level-II–IV studies.

Keywords Patellofemoral joint · Osteochondral defect · Cartilage restoration · Osteoarthritis

Introduction

The patellofemoral (PF) joint contains the thickest articular cartilage in the human body [1]. Under physiologic conditions, the articular cartilage is able to transmit forces and disperse loads placed onto the joint. Though the PF cartilage can be considered a biphasic material similar to any other human articular cartilage, it is both more permeable and pliable than cartilage in other areas of the human body such as the tibio-femoral joint, thus causing increased susceptibility to injury [2]. Furthermore, this area is commonly prone to injury due to the high axial and shearing forces experienced by the joint [2–5]. In a retrospective analysis of 15,074 patients with chondral lesions of the knee, the patella and trochlea accounted for 36% and 8% of these lesions, respectively [6]. A major limitation to the healing of articular cartilage is its avascular quality which precludes its ability to regenerate damaged tissue [1]. With limited healing capacity, combined with the complex biomechanical environment

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and significant joint reactive forces, chondral defects of the PF joint are often difficult to manage [2–5].

Lesions of the PF joint are often misdiagnosed and usually recognized during treatments of other pathologies [7]. Leaving the joint untreated may predispose to secondary osteoarthritis [8, 9]. Though no gold standard exists [10], treatment options for chondral defects of the PF joint range from non-operative to various operative procedures. Surgical options range from arthroscopic debridement to cartilage restoration procedures such as conventional microfracture (MFx), autologous matrix-induced chondrogenesis (AMIC), autologous chondrocyte implantation (ACI), osteochondral autograft transfer (OAT), osteochondral allograft transplantation (OCA), and arthroplasty [11–15]. Three generations of ACI techniques exist and include: (1) ACI with a periosteal cover (ACI-P) [16, 17]; (2) ACI with a collagen cover (ACI-C) [17]; and (3) ACI with a collagen matrix (ACI-M) [17].

Historically, cartilage restoration procedures have been reserved for the tibio-femoral joint, but recent advances in technology have expanded the applications to the PF joint. The purpose of this study was to systematically assess the trends in surgical techniques, outcomes, and complications of cartilage restoration of the patellofemoral (PF) joint. It was hypothesized that ACI would be the most commonly reported cartilage restoration technique with short-term outcomes similar to other procedures used to treat chondral defects of the PF joint.

Materials and methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed in the development of this study [18]. Three online databases EMBASE, MEDLINE, and PubMed were searched for literature addressing the surgical techniques to treat cartilage defects of the PF joint from January 1, 2007 to April 30, 2018. Articles were searched from 2007 and onwards to determine the overall trends in cartilage restoration techniques used in the past decade for focal cartilage defects of the PF joint. The search terms included "patellofemoral joint", "cartilage", "trochlear groove", and similar phrases (Supplementary Table 1). The research question, and inclusion and exclusion criteria were established a priori. Inclusion criteria were: (1) all levels of evidence; (2) surgical studies treating isolated patellofemoral chondral defects (all grades) using one or more of the following: any generation of ACI, conventional MFx, AMIC, OCA, OAT, cell-free osteochondral scaffold (COS), and De Novo NT® graft; (3) studies reporting clinical outcomes; (4) English studies; (5) human studies; and (6) patients aged ≥ 18 years. The exclusion criteria were (1) studies reporting non-surgical treatment; (2) studies with < 5 patients; and (3) arthroplasty.

Study screening

A systematic screening approach in accordance with PRISMA was employed in duplicate by two independent reviewers from title to full-text screening stages. Discrepancies at the title and abstract stages were resolved by automatic inclusion to ensure that relevant articles were not missed. Discrepancies at the full-text stage were resolved by consensus between the reviewers. The input of a third, senior reviewer was used if a consensus could not be reached. Search terms were entered onto Google Scholar and references of included studies were also screened using the same systematic approach to capture any additional relevant articles.

Quality assessment of included studies

The methodological index for non-randomized studies (MINORS) appraisal tool was used to assess the quality of the included, nonrandomized studies (e.g., case reports, case series, cohorts, etc.) by two independent reviewers with discrepancies resolved by consensus discussion [19]. A score of 0, 1, or 2 is given for each of the 12 items on the MINORS checklist with a maximum score of 16 for non-comparative studies and 24 for comparative studies. To the authors' knowledge, there is no evidence to categorize the MINORS score. Thus, methodologic quality was categorized a priori as follows: a score of 0–8 or 0–12 was considered poor quality, 9–12 or 13–18 was considered fair quality, and 13–16 or 19–24 was considered excellent quality, for non-comparative and comparative studies, respectively.

Data abstraction

Two reviewers independently abstracted relevant data from included articles and recorded the data onto a Google Spreadsheet designed a priori. Demographic data included author, year of publication, sample size, study design, level of evidence [20], patient demographics (e.g., sex, age, etc.), and details of surgical techniques used to treat osteochondral defects. Furthermore, any information regarding rehabilitation protocols, post-operative outcomes (surgical and radiographic), concomitant lesions, associated procedures, and complications were documented.

Statistical analysis

In consultation with the study statistician, the high statistical and methodological heterogeneity amongst included studies precluded performing a meta-analysis. Descriptive statistics such as mean, range, and measures of variance (e.g., standard deviations, 95% CI) are presented where applicable. A weighted intraclass correlation coefficient (ICC) was used to evaluate inter-reviewer agreement for the MINORS score. A kappa (κ) statistic was used to evaluate inter-reviewer agreement at all screening stages. Agreement was categorized a priori as follows: ICC/κ of 0.81–0.99 was considered as almost perfect agreement; ICC/κ of 0.61–0.80 was substantial agreement; ICC/κ of 0.41–0.60 was moderate agreement; 0.21–0.40 fair agreement and a ICC/κ value of 0.20 or less was considered slight agreement [21]. A two-proportion z test was used to determine whether the differences between the proportions of cartilage restoration techniques used from 2007 to 2012 and 2013 to 2018 were statistically significant. These time frames were selected to determine if the proportion of cartilage restoration techniques for the PF joint changed over the latter half of the past decade.

Results

Study characteristics

The initial search yielded 4022 studies, of which 27 met the inclusion for this review (Fig. 1). Upon reviewing references of included studies and a search on Google Scholar, an additional study was retrieved from the references and included in the review for a total of 28 studies. Of the 28 included studies published between 2007 and 2018, there were seven prospective cohorts, one retrospective cohort, one case–control, and 19 case series. There were no studies published in 2018 (Table 1).

Patient characteristics

There were 708 patients (824 knees) with a mean age of 39.5 ± 10.5 years; two studies did not report the mean age [22, 23]. Patients had a mean follow-up of 39.1 ± 16.0 months. At the final follow-up, 92.3% ($n=653$) of patients were available. Of the patients available at the final follow-up, 40.1% ($n=284$) were male; sex distribution was not specified in 15.7% ($n=111$) of the patients. The mean patellofemoral cartilaginous defect size was 4.2 ± 2.2 cm^2, and patients were treated with either ACI (45.5%; $n=375$), conventional MFx (29.6%; $n=244$), AMIC (9.1%; $n=75$), OAT (8.1%; $n=67$), COS (4.1%; $n=34$), De Novo NT® graft (1.8%; $n=15$), or OCA (1.7%; $n=14$). The ACI techniques used in this review were either ACI-M (22.2%; $n=183$), unspecified (12.1%; $n=100$), ACI-C (8.1%; $n=67$), or ACI-P (3.0%; $n=25$). From 2007 to 2012 and 2013 to 2018, the proportion of PF cartilage restoration techniques varied (Fig. 2). There was a significant decrease in the use of the first and second generation ACI ($p<0.\ 001$), AMIC ($p=0.02$), and conventional MFx ($p<0.001$) between 2007 and 2012 and 2013 to 2018. Meanwhile, there was a significant increase in the use of ACI-M ($p<0.001$), OAT ($p<0.001$), COS ($p<0.001$), De Novo NT® graft ($p<0.001$), and OCA ($p<0.001$) between 2007 and 2012 and 2013 to 2018. The defect locations included the patella (51.1%; $n=421$), unspecified (33.6%; $n=277$), trochlea (12.6%; $n=104$), and both the patella and trochlea (i.e., bipolar/kissing lesions) (2.5%; $n=20$). Only one study reported concomitant chondral defects in the tibio-femoral joint; however, only defects of the PF joint were treated.

Study quality

Seven of the included studies represented Level-II evidence, two studies represented Level-III evidence, and 19 studies represented Level-IV evidence (Table 1). There was excellent agreement among reviewers at the screening stages involving the title ($k=0.797$; 95% CI 0.767–0.828), abstract ($k=0.913$; 95% CI, 0.877–0.950), and full text ($k=0.914$; 95% CI 0.856–0.972). There was high agreement among the quality assessment scores based on the MINORS criteria (ICC = 0.912; 95% CI 0.891–0.928). The mean MINORS score for non-comparative and comparative studies was 11.3 ± 2.3 and 16.3 ± 2.6, respectively, indicating fair quality of evidence for non-randomized studies (Table 1).

Patient outcomes

ACI outcomes (first, second, and third generations)

The mean defect size for patients treated with ACI was 4.9 ± 1.9 cm^2; two studies did not report the mean defect size [36, 47]. Overall, 12 out of 13 studies ($n=351$) reported significant post-operative improvement on a wide range of patient important outcome measures. Specifically, of the eight studies ($n=208$) reporting the Subjective International Knee Documentation Committee (IKDC) score, a significant ($p<0.05$) improvement post-operatively was found in six studies ($n=114$). The Tegner score was reported in three studies ($n=82$), of which all found significant improvement post-operatively ($p<0.001$). Seven studies ($n=168$) reported the Lysholm Knee Score, of which five studies ($n=74$) found a significant improvement post-operatively ($p<0.05$). Finally, four studies ($n=119$) reported significant improvements in the Cincinnati scores post-operatively ($p<0.05$) (Table 2).

AMIC outcomes

The mean defect size for patients treated with AMIC was 3.6 ± 1.1 cm^2. In the studies that used AMIC for PF joint

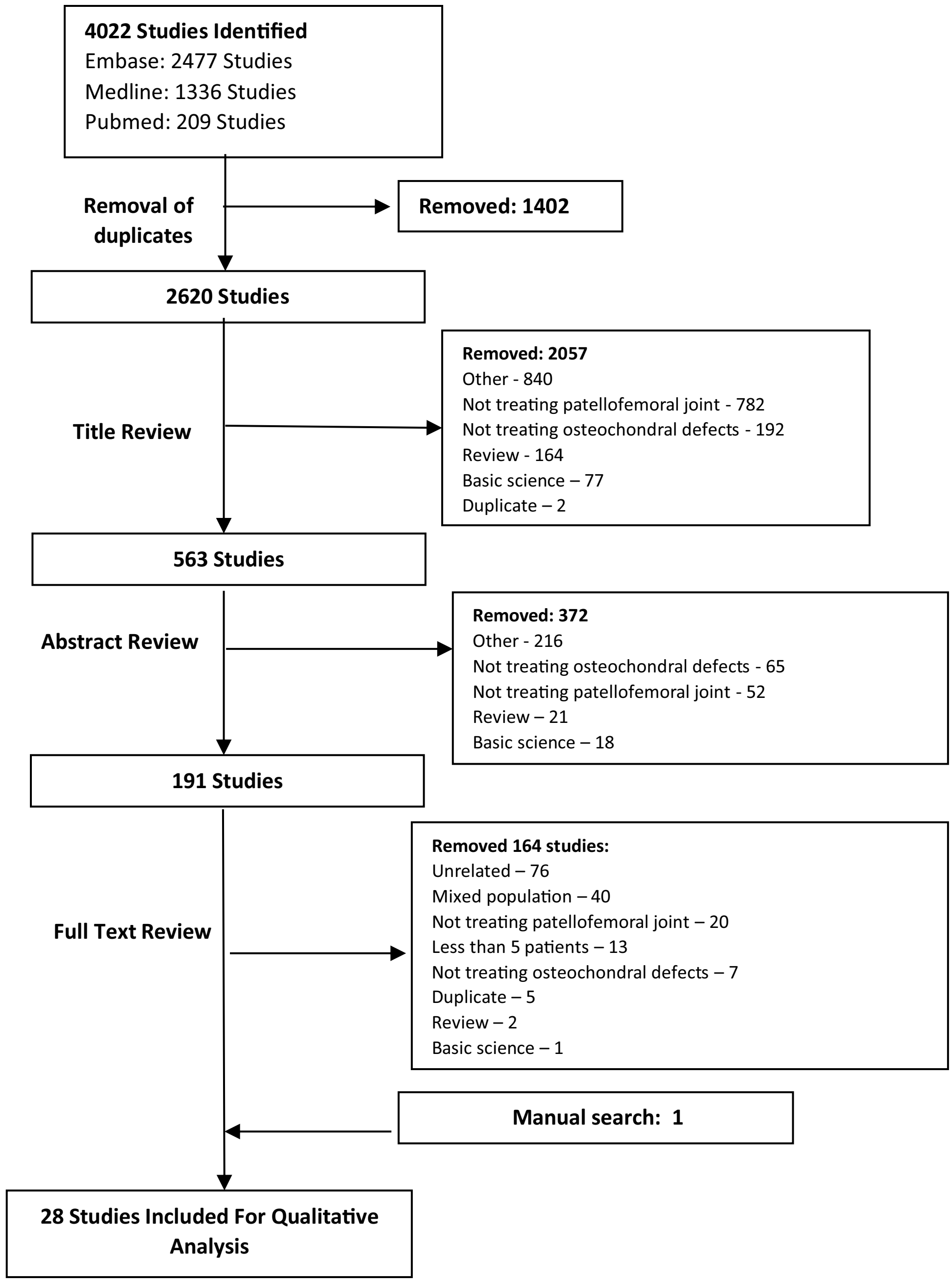

Fig. 1 PRISMA flow diagram

cartilage restoration, four studies reported on the Visual Analog Scale (VAS), of which three studies ($n=35$) found improvement post-operatively ($p<0.0001$–0.01), whereas one other study ($n=5$) found improvement, but did not report p value. Two studies ($n=30$) reported subjective IKDC score—both these studies found improvement post-operatively ($p<0.0001$–0.01). Two out of the three studies that reported the on the Knee Injury and Osteoarthritis Outcome Score (KOOS) ($n=20$) found improvement post-operatively ($p<0.01$–0.047), whereas the one other study ($n=5$) found improvement, but did not report a p value. Two out of the three studies that reported the Tegner score ($n=30$) found improvement post-operatively ($p=0.006$–0.047), while the one other study ($n=5$) found improvement, but did not report p value (Table 2).

Other techniques/associated procedures

The outcomes of COS, De Novo NT®, OCA, OAT, and conventional MFx are summarized in Supplementary Tables 2–6. The types of concomitant PF realignment procedures included proximal (30.6%; $n=252$), distal (12.4%; $n=102$), combined proximal and distal (2.3%; $n=19$), and unspecified (1.0%; $n=8$). Meanwhile, of the 12 studies that

Table 1 Characteristics of included studies

Primary Author	Year	Study design	Level of evidence	Restoration technique	Patients	Knees	% Males	Mean age	Age range	Mean follow-up (months)	Consensus MINORS Score[a]
Yabumoto et al. [24]	2017	Case series	IV	OAT	7	7	86	61.1	47–74	46.9	13/16
Sadlik [25]	2017	Case series	IV	AMIC	12	12	58	36	22–52	38	10/16
Perdisa [26]	2017	Case series	IV	COS	34	34	53	30	20–40	24	14/16
Cotter [27]	2017	Case series	IV	OCA	14	14	28.6	32.8	20–40	43.2	10/16
Emre [28]	2016	Case series	IV	OAT	33	33	76	31.3	22–47	19.3	11/16
Astur [22]	2016	Case series	IV	OAT	20	20	45	NR	26–45	24	13/16
Gobbi [29]	2015	Prospective cohort	II	ACI-M	19	19	47	43.1	NR	59.7	20/24
Ebert [30]	2015	Case series	IV	ACI-M	47	47	64	37.6	20–61	24	15/16
Muller [31]	2014	Prospective cohort	II	ACI-M	16	16	50	35.3	22–51	48	9/16
Dhollander [32]	2014	Case series	IV	AMIC	10	10	80	37.2	NR	24	14/16
Gillogly [33]	2014	Case series	IV	ACI-P	23	25	48	31	NR	90.7	10/16
Filardo [34]	2013	Prospective cohort	II	ACI-M	49	49	67	31.5	NR	60	11/16
Kreuz [35]	2013	Prospective cohort	II	ACI-M	20	20	40	35	18–51	48	17/24
Pachowsky [36]	2013	Case–control	III	ACI-M	5	5	80	34.3	NR	NR	16/24
Pascual-Garrido [37]	2013	Case series	IV	De Novo NT®	15	15	NR	30	NR	12	10/16
Petri (ACI-M) [38]	2012	Prospective cohort	II	ACI-M	10	10	40	35.8	NR	36	18/24
Petri (MFx) [38]	2012	Prospective cohort	II	MFx	10	10	60	41.7	NR	36	18/24
Von Keudell [39]	2012	Case series	IV	ACI-NS	30	30	40	32	NR	24–174	10/16
Kusano [40]	2011	Case series	IV	AMIC	20	20	50	39.2	NR	29.3	14/16
Wu [41]	2011	Case series	IV	MFx	126	234	20	72	65–78	50.4	12/1
Dhollander [42]	2010	Case series	IV	AMIC	5	5	60	27	24–45	24	12/16
Kusano [23]	2010	Case series	IV	AMIC	21	23	NR	NR	NR	NR	6/16
Satake [43]	2010	Case series	IV	OAT	5	7	NR	63	55–74	39.1	11/16
Sadlik [44]	2010	Case series	IV	AMIC	5	5	40	41	NR	NR	7/16
Niemeyer [45]	2008	Retrospective cohort	III	ACI-Mixed	70	70	NR	34.3	NR	38.4	14/16
Welsch [46]	2008	Prospective cohort	II	ACI-M	17	17	53	36.3	23–49	29.3	14/24
Gigante [47]	2008	Case series	IV	ACI-C	12	14	50	31	25–35	36	13/16
Niemeyer (double eye technique) [48]	2007	Prospective cohort	II	ACI-C	11	11	45	40.4	21–54	41.6	13/24
Niemeyer (ACI) [48]	2007	Prospective cohort	II	ACI-C	13	13	54	35.2	23–48	47.1	13/24
Steinwachs [49]	2007	Case series	IV	ACI-C	29	29	51	33	18–50	36	10

OAT osteochondral autologous transfer, *OCA* osteochondral allograft transplantation, *AMIC* autologous matrix-induced chondrogenesis, *COS* cell-free osteochondral scaffold, *NR* not reported, *ACI-M* autologous chondrocyte implantation with a collagen matrix, *ACI-P* autologous chondrocyte implantation with a periosteal cover, *ACI-NS* autologous chondrocyte implantation generation not specified, *MFx* microfracture, *ACI-Mixed* mixed population (i.e., all three generations) of autologous chondrocyte implantation, *ACI-C* autologous chondrocyte implantation with a collagen cover

[a]0–16 for non-comparative studies, 0–24 for comparative studies

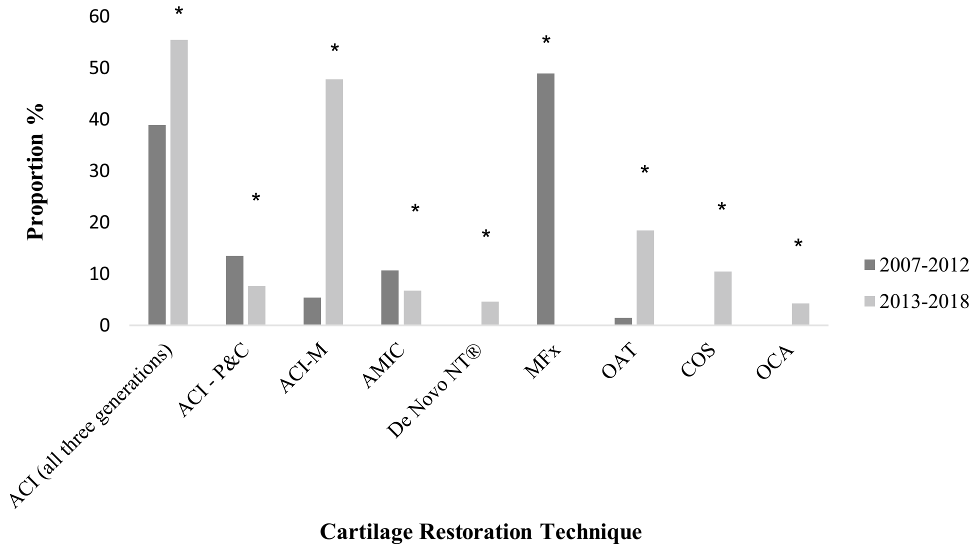

Fig. 2 Proportion of patellofemoral cartilage restoration techniques used in 2007–2012 and 2013–2018. Asterisk indictates statistically significant differences between 2007 to 2012 and 2013 to 2018. *ACI* autologous chondrocyte implantation, *ACI P&C* ACI with a periosteal cover and collagen cover, *ACI-M* ACI with a collagen matrix, *AMIC* autologous matrix-induced chondrogenesis, *MFx* microfracture, OAT osteochondral autograft transfer, *COS* cell-free osteochondral scaffold, *OCA* osteochondral allograft transplantation

reported the concomitant use of PF realignment procedures in select patients, six studies did not stratify their results. Patients undergoing PF realignment (32.4%; 11/34) in addition to COS, had a slower recovery and lower functional scores (e.g., IKDC subjective and Tegner activity scores) at 12 months post-operatively, but no differences at 24 months when compared to those without realignment (Table 3).

Complications

There were a total of 76 (9.2%) complications of which graft hypertrophy (29.7%; $n=22$) was the most prevalent. Of the patients with graft hypertrophy, 36.3% (8/22) underwent ACI-P as their index procedure. Meanwhile, there were a total of eight failures in this systematic review: three patients received an unspecified generation of ACI, two patients received ACI-M, two patients received OCA, and one patient received ACI-P. The most common causes of a failure were: (1) > 25% delamination, revision cartilage repair surgery, or prosthesis implantation (37.5%; 3/8) and (2) graft delamination and/or exposed subchondral bone on MRI (25%; 2/8). Conversion to joint arthroplasty occurred in 3 patients: total knee arthroplasty (25%; 2/8) and PF arthroplasty (16%; 1/8). The distribution of complications for restoration techniques was as follows: AMIC (31.6%; 24/76), ACI-P (19.7%; 15/76), ACI-M (13.2%; 10/76), OAT (9.2%; 7/76), ACI-C (6.6%; 5/76), and OCA (2.6%; 2/76). There were no complications reported in the conventional MFx group. The complications in this systematic review are summarized in Table 4.

Discussion

Key findings

The most striking finding was the change in practice trends over the last 5 years: a rise in newer generation ACI techniques and a decrease in conventional MFx. Although conventional MFx has been considered the historical gold standard for treating cartilage defects of the tibio-femoral joint, there was limited use of this procedure for the PF joint. Only two of the included studies, both published in the 2007–2012 period (comprising 30.1% of the total sample size), used conventional MFx to treat PF cartilage defects [38, 41]. There was also a statistically significant decrease in the use of the AMIC technique, an enhanced MFx technique that uses a protecting membrane [38]. This may be in part due to the growing understanding that MFx is not suitable for larger, uncontained lesions; the mean defect size of included patients in this review was > 4 cm^2. In addition, surgeons at large academic centers are more likely to adopt, investigate, and publish the results of newer techniques and technologies. Finally, the a priori hypothesis that ACI would be the most commonly reported cartilage restoration technique with short-term outcomes similar to other procedures used to treat chondral defects of the PF joint has been confirmed.

When comparing the use of the conventional MFx for different compartments in the knee, those treated for

Table 2 First, second, and third generation ACI outcomes

	Pre-operative mean ± SD	Post-operative mean ± SD	Statistical significance p
VAS			
Gobbi et al. [29]	5.53 ± 0.90	0.84 ± 0.68	< 0.01
VAS severity			
Ebert et al. [30]	5.4 ± 1.4	1.8 ± 1.1	< 0.01
VAS frequency			
Ebert et al. [30]	6.4 ± 1.6	2.1 ± 1.4	< 0.01
Mean EQ-VAS			
Filardo et al. [34]	57.3 ± 19.8	84.4 ± 11.8	< 0.01
IKDC—Subjective Score			
Muller et al. [31]	44.4 ± 10.5	71.4 ± 16.6	< 0.05
Gillogly et al. [33]	42.5	75.7	< 0.01
Kreuz et al. (male) [35]	47.37 ± 12.77	72.55 ± 15.80	< 0.05
Kreuz et al. (female) [35]	45.51 ± 11.16	64.26 ± 18.67	< 0.05
Niemeyer et al. (double eye technique) [48]	NR	60 ± 14	n.s
Niemeyer et al. (ACI) [48]	NR	58 ± 19	n.s
Niemeyer et al. [45]	NR	62 ± 21.5	0.01
Gobbi et al. [29]	46.37 ± 14.44	75.70 ± 9.85	< 0.01
Filardo et al. [34]	38.1 ± 14.0	76.7 ± 18.5	< 0.01
Petri et al. [38]	31.7 ± 12.7	61.3 ± 18.2	< 0.05
IKDC Objective Score			
Gobbi et al. [29]	9C, 10D	10A, 8B, 1C	< 0.01
12-item SF Health Survey (Physical)			
Gillogly et al. [33]	41.2	47.6	< 0.01
12-item SF Health Survey (Mental)			
Gillogly et al. [33]	48.1	60.7	< 0.01
SF-36a (Physical Component)			
Ebert et al. [30]	34.9 ± 9.7	47.1 ± 10.20	< 0.01
SF-36a (Mental Component)			
Ebert et al. [30]	51.3 ± 8.8	55.7 ± 6.1	< 0.01
Tegner Score			
Gigante et al. [47]	1	4	< 0.01
Gobbi et al. [29]	2.1 ± 0.73	5.26 ± 1.14	<0.01
Filardo et al. [34]	1.9 ± 1.2	4.7 ± 2.0	< 0.01
Kujala Score			
Gigante et al. [47]	52	88.5	< 0.01
Filardo et al. [34]	48.7 ± 14.8	85.7 ± 14.2	< 0.01
Lysholm Knee Score			
Gillogly et al. [33]	40.2	79.3	< 0.01
Kreuz et al. (male) [35]	54.71 ± 12.53	82.25 ± 14.17	< 0.05
Kreuz et al. (female) [35]	45.50 ± 10.11	71.50 ± 25.73	< 0.05
Gigante et al. [47]	55	92.5	< 0.01
Niemeyer et al. (double eye technique) [48]	NR	75.5 ± 14	n.s
Niemeyer et al. (ACI) [48]	NR	60 ± 14	n.s
Niemeyer et al. [45]	NR	73.0 ± 22.4	0.02
Pachowsky et al. [36]	51.0 ± 6.8	78.8 ± 10.4	< 0.01
Petri et al. [38]	43.6 ± 11.4	64.7 ± 17.1	< 0.05
ICRS			
Muller et al. [31]	3.9 ± 0.3	1.9 ± 0.8	< 0.05

Table 2 (continued)

	Pre-operative mean ± SD	Post-operative mean ± SD	Statistical significance *p*
Modified Cincinnati Score			
Gigante et al. [47]	2	8	< 0.01
Gillogly et al. [33]	3.0	7.0	< 0.01
Cincinnati Score			
Niemeyer et al. (double eye technique) [48]	30.5 ± 32.1	56.4 ± 31.4	n.s
Niemeyer et al. (ACI) [48]	27 ± 31.8	63.2 ± 27.5	n.s
Niemeyer et al. [45]	34.44 ± 33.98	61.5 ± 21.5	< 0.01
Petri et al. [38]	31.5 ± 13.1	56.2 ± 13.9	< 0.05
KOOS pain			
Ebert et al. [30]	61.4 6 ± 15.6	83.3 ± 11.4	< 0.01
Gobbi et al. [29]	44.26 ± 14.46	80.73 ± 11.79	< 0.01
KOOS symptoms/stiffness			
Ebert et al. [30]	64.7 ± 17.2	86.4 ± 9.8	< 0.01
Gobbi et al. [29]	50.53 ± 13.22	81.05 ± 11.04	< 0.01
KOOS ADL			
Ebert et al. [30]	69.0 ± 16.1	87.5 ± 11.0	< 0.01
Gobbi et al. [29]	50.42 ± 12.5	82.15 ± 11.29	< 0.01
KOOS sport			
Ebert et al. [30]	24.6 ± 21.0	50.1 ± 29.4	< 0.01
Gobbi et al. [29]	32.21 ± 16.92	68.84 ± 15.25	< 0.01
KOOS QOL			
Ebert et al. [30]	22.9 ± 16.0	53.3 ± 23.0	< 0.01
Gobbi et al. [29]	33.63 ± 10.74	76.10 ± 16.90	< 0.01

VAS Visual Analog Score, *EQ-VAS* EuroQol Visual Analog Scales, *NR* not reported, *n.s* not significant, *SI* significant Improvement, *IKDC* International Knee Documentation Committee, *SF* short form, *ICRS* International Cartilage Repair Society, *KOOS* Knee Injury and Osteoarthritis Score, *ADL* activities of daily living, *QOL* quality of life

chondral defects of the femoral condyles had significantly better ($p < 0.02$) defect filling when confirmed by MRI at 36 months post-operatively compared to the trochlear, tibial, and retropatellar lesions [50]. Moreover, the quality of bone marrow that can be stimulated from the patella (a sesamoid bone), particularly in a patient population with a mean age of nearly 40 years, such as found in this review, may not be ideal to produce the desired effect of MFx. In an age-dependent study of patients with full-thickness, multi-compartmental chondral lesions in the knee (i.e., both tibio-femoral and PF) treated with conventional MFx, it was found that deterioration was significantly pronounced in those aged 40 years or older [51]. The authors concluded that the reduced regenerative capacity in older patients may be a result of aging chondrocytes having decreased functionality [51]. Though there are conflicting reports of the long-term durability of MFx,[52], its prevalent use comes into question given its production of fibrocartilage repair tissue as opposed to hyaline or hyaline-like repair tissue [53]. As the PF joint experiences a greater compressive force at a greater knee flexion angle compared to the tibio-femoral joint [54], intuitively, it is without surprise that MFx is not as durable in these patients. Finally, there is mounting evidence that the previous MFx can compromise outcomes of revision surgery using cell-based cartilage repair therapy due to its disruption of the subchondral plate [38, 55, 56].

Noyes and Barber-Westin conducted a systematic review of cartilage defects of the PF joint treated with arthroplasty and a limited number of restoration techniques [15]. The focus of the review was on patients under 50 years of age with patellar defects larger than 4 cm^2, and studies were included from 1992 to 2012. Their findings revealed high failure rates across ACI, OAT/OCA, and arthroplasty techniques (22–60%) with no ideal technique identified. Similarly, our review did not find any one technique to be superior to others, even in the two comparative studies that were included. In contrast to the earlier article, however, our review found much lower complication and failure rates, though these were still not uncommon occurrences. This may be a reflection of improving technology, increased familiarity with novel techniques, and more awareness of the

Table 3 AMIC outcomes

	Pre-operative mean ± SD	Post-operative mean ± SD	Statistical significance *p*
VAS			
Dhollander et al. [32]	73.9 ± 20.8	39.4 ± 28.8	0.01
Kusano et al. [40]	6 ± 2	2 ± 2	< 0.01
Dhollander et al. [42]	52 mm (median) (range 14–86 mm)	14 mm (5–19 mm)	NR
Sadlik et al. [25]	7.8 (range 3–10)	2.3 (range 0–6)	< 0.01
IKDC—Subjective Score			
Kusano et al. [40]	51 ± 25	74 ± 17	< 0.01
Sadlik et al. [25]	37.4 (range 4.6–90.8)	90.1 points (range 42.5–100)	< 0.01
KOOS total			
Dhollander et al. [32]	176.5 ± 83.2	243.9 ± 85.9	0.05
Sadlik et al. [25]	50.3 points (range 17.3–83.9)	90.1 points (range 77.4–100)	< 0.01
KOOS Pain			
Dhollander et al. [32]	44.5 ± 17.5	65.0 ± 23.3	0.03
Dhollander et al. [42]	64 (median) (range 39–92)	92 (range 61–97)	NR
KOOS Symptoms/Stiffness			
Dhollander et al. [32]	50.4 ± 18.3	63.2 ± 18.8	n.s
Dhollander et al. [42]	39 (median) (range 36–86)	82 (range 75–100)	NR
KOOS ADL			
Dhollander et al. [32]	42.9 ± 25.6	63.4 ± 20.8	0.03
Dhollander et al. [42]	65 (median) (range 38–76)	93 (range 62–97)	NR
KOOS Sport			
Dhollander et al. [32]	20.0 ± 20.3	24.0 ± 19.7	n.s
Dhollander et al. [42]	15 (median) (range 0–20)	40 (range 10–45)	NR
KOOS QOL			
Dhollander et al. [32]	18.7 ± 16.9	28.3 ± 14.8	n.s
Dhollander et al. [42]	25 (median) (range 19–31)	50 (range 38–56)	NR
Tegner Score			
Dhollander et al. [32]	1.5 ± 1.4	2.5 ± 1.5	0.05
Kusano et al. [40]	3 ± 2	4 ± 1	0.01
Dhollander et al. [42]	2 (median) (range 1–3)	3 (range 2–3)	NR
Kujala Score			
Dhollander et al. [32]	41.9 ± 15.1	59.8 ± 21.2	0.05
Dhollander et al. [42]	38 (median) (range 30–55)	71 (range 53–82)	NR
Lysholm Knee Score			
Kusano et al. [40]	58 ± 17	85 ± 13	< 0.01

VAS Visual Analog Score, *NR* not reported, *IKDC* International Knee Documentation, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *n.s* not significant, *ADL* activities of daily living, *QOL* quality of life

appropriate indications for the use of each technique since the publication of Noyes et al. [15]. Jungmann et al. identified risk factors associated with need for revision surgery in 413 patients after ACI (first, second, and third generations) [57]. At average follow-up of 4.4 ± 0.9 years, ACI-P was a significant predictor of revision and failure ($p < 0.28$) [57]. Similarly, this systematic review found higher complication rates with older generation ACI techniques, with graft hypertrophy being most common, which has been a particular concern with the periosteum patch-covered ACI technique [58].

Tibio-femoral or tricompartmental osteoarthritis is more common than isolated PF osteoarthritis, and this has been borne out in both radiographic and population-based studies [59–61]. Perhaps, for this reason, among others, the literature on tibio-femoral cartilage preservation and restoration is much more abundant than the literature on the use of these techniques in the PF joint. Mundi et al. conducted a systematic review and meta-analysis of level 1 studies for cartilage restoration of the knee (i.e., tibio-femoral joint) [62]. When comparing ACI to marrow stimulation (MFx), there

Table 4 Complications

Primary author	Year	Restorative technique	Complications
Ebert [30]	2015	ACI-M	3 graft hypertrophy 2 clinical failures; graft delamination and/or exposed subchondral bone on MRI 1 DVT
Welsch [46]	2008	ACI-M	5 graft hypertrophy
Gillogly [33]	2014	ACI-P	10 knees underwent a total of 15 subsequent surgical procedures 5 arthroscopic debridement for graft hypertrophy and hardware removal 3 arthroscopic debridement for graft hypertrophy Each knee underwent loose body removal and chondroplasty for a new lesion in another compartment 2 meniscal repairs 1 patient underwent 3 additional procedures including debridement, lateral release and excision of a cutaneous neuroma of the infrapatellar branch of the saphenous nerve 1 clinical failure; PF arthroplasty 5.9 years post-operatively 1 DVT treated with anticoagulation for 3 months without sequelae
Gigante [33]	2008	ACI-C	2 knees required screw removal during FU
Steinwachs [49]	2007	ACI-C	2 graft hypertrophy—no clinical symptoms 1 incomplete defect filling—treated with revision ACI surgery
Niemeyer [48]	2008	ACI-Mixed	5 limited range of motion 3 painful retropatellar crepitations—MRI revealed an incomplete or total absence of defect filling 2 graft hypertrophy—treated with arthroscopic debridement 1 persistent effusion 1 minor wound healing in one patient
Von Keudell [39]	2012	ACI-NS	3 clinical failures; failures were defined as > 25% delamination, revision cartilage repair surgery or prosthesis implantation
Dhollander [32]	2014	AMIC	2 hypertrophy of regenerated tissue, treated with arthroscopic shaving 2 hypertrophic filling—revealed in an MRI 4 bone marrow changes—revealed in an MRI 3 intralesional osteophytes—revealed in an MRI
Kusano [40]	2011	AMIC	9 NM
Kusano [23]	2010	AMIC	1 reoperation 1 partial menisectomy 1 TKA 1 patellar osteolysis—revealed in radiograph
Yabumoto [24]	2017	OAT	2 PNO
Emre [28]	2016	OAT	5 mildly painful hemarthroses
Cotter [27]	2017	OCA	Two patients had a knee arthroplasty 2.7 years post-operatively

ACI-M autologous chondrocyte implantation with a collagen matrix, *MRI* magnetic resonance imaging, *DVT* deep vein thrombosis, *ACI-P* autologous chondrocyte implantation with a periosteal cover, *PF* patellofemoral, *ACI-C* autologous chondrocyte implantation with a collagen cover, *FU* follow-up, *ACI-Mixed* mixed population (i.e., all three generations) of autologous chondrocyte implantation, *ACI-NS* autologous chondrocyte implantation generation not specified, *AMIC* autologous matrix-induced chondrogenesis, *NM* needed mobilization under anesthesia due to knee stiffness, *TKA* total knee arthroplasty, *OAT* osteochondral autograft transfer, *PNO* donor plug could not be obtained, and OAT could not be performed, OCA osteochondral allograft transplantation

was a trend toward favoring ACI in functional outcomes (i.e., IKDC, Lysholm and KOOS; $p = \text{n.s}$) and no difference between the two techniques for pain score outcomes. Since that meta-analysis, a number of new randomized controlled trials (RCTs) have been conducted on this topic all with mixed results [52, 63–65]. Overall, our findings regarding the PF joint are consistent with the tibio-femoral literature in that no technique is clearly superior to others and that most techniques do provide significant post-operative improvement, but those with longer term follow-up, appear to show higher rates of failure and/or revision surgery.

Finally, in a climate of rapidly growing healthcare costs [66], cost-effectiveness is an important consideration in assessing the overall value of a new technique or technology. A recent systematic review comparing the three most common surgical procedures for treatment of focal cartilage defects of the knee found that older generation ACI when compared to conventional MFx and OAT was least cost-effective. Moreover, authors of this study concluded that although it may result in smaller functional gains, the conventional MFx remains a reasonable, cost-effective option for cartilage restoration given its technical simplicity, widespread availability, and minimal invasiveness [67]. Treatment of chondral defects of the PF joint, with the various cell-based therapies, has tremendous potential for impact given the young age of patients and associated functional limitations. As the prevalence of newer generation ACI rises, the value in generating economic benefits to society relative to the direct costs of surgery and rehabilitation needs to be explored.

The strengths of this systematic review stem from its thorough methodology on a novel topic of expanding research. The systematic screening approach was employed in duplicate, thus minimizing reviewer bias. Moreover, the comprehensive search used ensured that all relevant articles were captured. There was excellent agreement between the two reviewers at all screening stages and quality assessment. This systematic review also consisted of numerous studies with moderate-to-large sample sizes, resulting in an overall large sample size with moderate length follow-up.

This review had some limitations. First, there was large variability in the outcomes used and inconsistent reporting of post-operative outcomes in patients across studies. Consequently, estimating the efficacy of cartilage restoration techniques for the PF joint and analyzing the differences between subgroups (e.g., PF realignment versus no realignment) were limited. With moderate follow-up periods across studies, long-term complications such as time to PF arthroplasty and graft failure could potentially be underreported. Moreover, the high statistical and methodological heterogeneity amongst included studies precluded the performance of a meta-analysis. Studies also did not have consistent documentation of their complications and thus may have been poorly reflected during the follow-up period. Finally, though there was a high quantity of studies available on the topic, the available quality of evidence limited the ability to make definitive conclusions on a superior restoration technique.

This manuscript provides clinicians/knee specialists insight into the changing trends of cartilage restoration of the PF joint. The advent of innovative cell-based therapies has brought new applications to the field, particularly for the PF joint, which historically has been met with unfavorable results. Future studies should better document and report their surgical and/or radiographic outcomes. By standardizing the instruments used to evaluate patient outcomes, accurate analyses can be made for each cartilage restoration technique. Future studies should also consider the use of either RCT study designs, large prospective cohorts, or patient registries with longer term follow-up to better evaluate and compare cartilage restoration techniques and assess revision rates and conversion time to PF arthroplasty. Finally, a cost–benefit analysis of each cartilage restoration technique is required to further guide clinicians on the optimal treatment for focal cartilage defects of the PF joint.

Conclusion

ACI was the most common restoration technique. The use of the third generation ACI has increased with a concurrent decline in the use of conventional MFx over the latter half of the past decade ($p < 0.001$). Overall, the various cartilage restoration techniques reported improvements in patient reported outcomes with low complication rates. Definitive conclusions on the optimal treatment remain elusive due to a lack of high-quality comparative studies.

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Compliance with ethical standards

Conflict of interest ORA is a paid consultant for ConMed. VM is an education consultant for Smith & Nephew. The authors have no other potential conflicts of interests to declare.

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