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*Autologe Chondrozytenimplantation der dritten Generation –  
Langzeitdaten und detaillierte Sportanalyse*

*Third-generation autologous chondrocyte implantation –  
Long-term results and comprehensive sports analysis*

Dissertation

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## Eidesstattliche Versicherung

Ich versichere hiermit an Eides statt, dass die vorgelegte Dissertation von mir selbständig und ohne unerlaubte Hilfe angefertigt ist.

München, den 19.02.2022

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## Erklärung

Hiermit erkläre ich,

dass die Dissertation nicht ganz oder in wesentlichen Teilen einer anderen Prüfungskommission vorgelegt worden ist.

dass ich mich anderweitig einer Doktorprüfung ohne Erfolg **nicht** unterzogen habe.

München, den 19.02.2022

Daniel Altmann  
(Unterschrift)

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# 1. Abkürzungsverzeichnis

|              |                                                                                                                  |
|--------------|------------------------------------------------------------------------------------------------------------------|
| ACI          | autologe Chondrozytenimplantation bzw.<br>autologous chondrocyte implantation                                    |
| ACI-C        | kollagengedeckte autologe Chondrozytenimplantation bzw.<br>collagene-covered autologous chondrocyte implantation |
| ACI-M        | matrixgestützte autologe Chondrozytenimplantation bzw.<br>matrix-supported autologous chondrocyte implantation   |
| ACI-P        | periostgedeckte autologe Chondrozytenimplantation bzw.<br>Periosteal autologous chondrocyte implantation         |
| BMI          | Body-Mass-Index bzw. body mass index                                                                             |
| DGOU         | Deutschen Gesellschaft für Orthopädie und Unfallchirurgie bzw.<br>German Society for Orthopaedics and Trauma     |
| ICRS         | International Cartilage Repair Society                                                                           |
| IKDC         | International Knee Documentation Committee Subjective Knee<br>Form                                               |
| KOOS         | Knee Injury Osteoarthritis Outcome Score                                                                         |
| MFX          | Mikrofrakturierung bzw. microfracture                                                                            |
| MOCART       | Magnetic Resonance Observation of Cartilage Repair Tissue                                                        |
| MRT bzw. MRI | Magnetresonanztomographie bzw.<br>magnetic resonance imaging                                                     |

|      |                                                                                  |
|------|----------------------------------------------------------------------------------|
| OAT  | osteocondrale Autotransplantation bzw.<br>osteocondral autograft transfer        |
| OCA  | osteocondrale Allotransplantation bzw.<br>osteocondral allograft transplantation |
| SPSS | Statistical Package for the Social Sciences                                      |
| UCLA | University of California at Los Angeles                                          |
| VAS  | visuellen Analogskala bzw. visual analog scale                                   |

## 2. Publikationsliste

1. Niethammer TR\*, **Altmann D\***, Holzgruber M, Gülecyüz MF, Notohamiprodjo S, Baur-Melnyk A, Müller PE. *Patient-Reported and Magnetic Resonance Imaging Outcomes of Third-Generation Autologous Chondrocyte Implantation After 10 Years*. Arthroscopy. 2020 Jul;36(7):1928-1938. doi: 10.1016/j.arthro.2020.03.009. Epub 2020 Mar 19. PMID: 32200064.
2. Niethammer TR, **Altmann D**, Holzgruber M, Goller S, Fischer A, Müller PE. *Third generation autologous chondrocyte implantation is a good treatment option for athletic persons*. Knee Surg Sports Traumatol Arthrosc. 2021 Apr;29(4):1215-1223. doi: 10.1007/s00167-020-06148-5. Epub 2020 Jul 15. PMID: 32671436; PMCID: PMC7973642.

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\*geteilte Erstautorenschaft

### 3. Einleitung

Der Gelenkknorpel nimmt eine entscheidende Rolle bei der Funktionsfähigkeit von Gelenken ein. Neben der Bildung einer glatten Oberfläche für eine reibungslose Beweglichkeit sorgt er für eine gleichmäßige Verteilung von Druck- und Stoßbelastungen auf den darunterliegenden Knochen [1]. Durch akute Verletzungen oder chronische Fehlbelastungen kann es zu einer Beschädigung kommen. Oftmals sind davon jüngere, sportlich aktive Menschen betroffen. Der Knorpelschaden kann sich dann durch Schmerzen und Schwellungen des betroffenen Gelenkes nach längerer Belastung bemerkbar machen. Dies sorgt bei den Patienten zu einer Einschränkung der Mobilität und Lebensqualität. Erschwerend kommt hinzu, dass hyaliner Gelenkknorpel aufgrund seiner biologischen Eigenschaften nur eine begrenzte intrinsische Regenerationsfähigkeit besitzt [2]. Bezüglich dem Spontanverlauf primärer Knorpelschäden herrscht daher in der Fachwelt weitestgehend Einigkeit, dass die Entwicklung einer vorzeitigen Gonarthrose, insbesondere nach dem Schluss der Wachstumsfugen, begünstigt wird [2, 3]. Eine zeitnahe Defektsanierung ist somit in jedem Fall angezeigt und sollte eine baldige Rückkehr in einen schmerzfreien Alltag begünstigen.

In den letzten Jahrzehnten hat sich die Behandlung von Gelenkknorpelschäden stark weiterentwickelt und viele neue Techniken wurden eingeführt. Historisch gesehen umfasste die Erstbehandlung von Knorpelverletzungen das arthroskopische Debridement, um die Oberfläche zu glätten und Ablagerungen zu entfernen, welche eine entzündliche Reaktion hervorrufen könnten. Reporative Techniken wie die Knochenmarkstimulation stellten eine weitere Möglichkeit dar. Durch arthroskopische Mikrofrakturierung (MFX), Anbohrung oder Abrasion des subchondralen Knochens wird dabei die Blutung und Rekrutierung von pluripotenten mesenchymalen Stammzellen des Knochenmarks stimuliert, welche sich ausdifferenzieren und hauptsächlich Faserknorpel bilden [3]. Zu den Versorgungsmöglichkeiten, die zum Ersatz des beschädigten Knorpels eingesetzt werden, gehören die osteochondrale Auto- (OAT) sowie Allotransplantation (OCA), welche die Entnahme von Knorpel-Knochenzylindern aus einem wenig belasteten Bereich und deren

Verpflanzung in den Defektbereich beinhaltet [4]. Bei der autologen Chondrozytenimplantation (ACI) geht es schließlich um den biologischen Ersatz von Gelenkknorpel. Sie beinhaltet eine Knorpelentnahme, Erstellung eines Transplantats durch Zellanzüchtung sowie die anschließende Implantation der gezüchteten Zellen unter einen Knochenhautlappen oder mittels einer speziellen Matrix.

Die ACI wurde erstmals 1994 von Brittberg et al. [5] und später von mehreren anderen Autoren berichtet [6, 7]. Seit der ersten Studie wurde die ACI bis in die dritte Generation kontinuierlich verbessert. Während zum Zeitpunkt der ersten und zweiten Generation der ACI die Implantation der kultivierten Chondrozyten noch unter einem Periostlappen (erste Generation: periostgedeckte autologe Chondrozytenimplantation (ACI-P)) bzw. einer Kollagenabdeckung (zweite Generation: kollagengedeckte autologe Chondrozytenimplantation (ACI-C)) stattfand, so wurden mittlerweile Trägermedien entwickelt, welche es ermöglichen, das Transplantat direkt in den Defekt zu implantieren [8]. Ein Gerüst aus Kollagen I/III wird hierbei zur Behandlung von größeren Knorpelschäden verwendet (dritte Generation: matrixgestützte autologe Chondrozytenimplantation; ACI-M) [9, 10]. Durch die kontinuierliche Vereinfachung und Verbesserung des Operationsverfahrens konnte die dritte Generation der ACI weiterverbreitet werden. In kurz- bis mittelfristigen Follow-ups konnten klinische Ergebnisse, Gelenkfunktion und Defektfüllung in der Magnetresonanztomographie (MRT) überzeugende Ergebnisse bei der Behandlung schwerer Knorpeldefekte zeigen und die ACI so als effektives und zuverlässiges Verfahren darstellen [11-17].

Die Wirksamkeit und Zuverlässigkeit des Transplantats für die ACI ist im kurz- bis mittelfristigen Verlauf gut beschrieben und das Verfahren hat sich zu einer Erstlinientherapie für symptomatische Knorpeldefekte bei entsprechend indizierten Patienten entwickelt. Nach den klinischen Richtlinien umfasst die Indikation für ACI symptomatische Vollknorpeldefekte mit Defekten größer als 3-4 cm<sup>2</sup>; bei jungen und körperlich aktiven Patienten können auch kleinere Defekte ab einer Defektgröße von 2,5 cm<sup>2</sup> behandelt werden [2]. Kleinere Defekte werden auch weiterhin mit markstimulierenden Techniken, wie der MFX, behandelt.

Die kurz- bis mittelfristigen Ergebnisse nach ACI sind gut dokumentiert und erste Langzeitdaten [18-20] in kleineren Patientenkohorten wurden kürzlich veröffentlicht und bestätigen die vielversprechenden Ergebnisse des mittelfristigen Follow-ups. Dennoch fehlt es weiterhin an belastbaren Daten über die Langzeitergebnisse der ACI der dritten Generation.

Aldrian et al. [18] präsentierte 10-Jahres-Daten von 16 Patienten, welche entweder mittels einer Kollagen-Doppelschichtmembran Typ I/ Typ III (ACI-M, Genzyme) oder eines Gerüsts auf Hyaluronsäurebasis (Hyalograft-C, Fidia Advanced Biopolymers) operiert wurden. Es konnte eine Verbesserung der klinischen Ergebnisse sowie ein hochwertiges Reparaturgewebe bei der MRT-Kontrolle gezeigt werden. Gille et al. [19] berichteten von 14 Patienten mit einer Follow-up-Periode von mindestens 15 Jahren. Nach ACI auf Basis einer Kollagen-I/III-Matrix (Chondro-Gide, Geistlich Pharma, Wollhusen, Schweiz) konnten für Schmerzlinderung und Rehabilitation der Kniefunktion zufriedenstellende klinische Ergebnisse gezeigt werden. Kreuz et al. [20] fasste klinische Daten von 21 Patienten zwölf Jahre nach Transplantation mittels BioSeed-C (BioTissue Technologies GmbH, Freiburg, Deutschland) zusammen. Hier konnte für Parameter wie Patientenzufriedenheit, klinisches Ergebnis und Kniefunktion eine signifikante Verbesserung gezeigt werden. Zudem konnten in dieser Studie MRT-Daten von 14 Patienten morphologisch ausgewertet werden und für mehr als 70% der Patienten normale bis fast normale Werte gezeigt werden.

Die vorliegende Arbeit liefert nun weitere belastbare Langzeitdaten nach ACI der dritten Generation. Die klinischen und radiologischen Ergebnisse von 30 Patienten zehn Jahre nach ACI der dritten Generation wurden ausgewertet. Diese Patientenzahl stellt die bisher größte Kohorte dar, welche in einer Langzeitstudie untersucht und ausgewertet wurde.

Ziel der vorliegenden wissenschaftlichen Arbeit war es, die langfristigen klinischen und radiologischen Ergebnisse der ACI der dritten Generation zur Behandlung von fokalen Vollknorpeldefekten des Knies zu bewerten und den langfristigen Erfolg nachzuweisen. Unsere Hypothese war, dass die ACI als Behandlung von fokalen Knorpeldefekten des Knies auch zehn Jahre nach der Operation gute klinische und radiologische Ergebnisse zeigt und

sich daher auch im langfristigen Verlauf als eine geeignete Behandlungsoption für diese Indikation bestätigt. Die entsprechenden Ergebnisse wurden im Paper „*Patient-Reported and Magnetic Resonance Imaging Outcomes of Third-Generation Autologous Chondrocyte Implantation After 10 Years*“ veröffentlicht und werden in der Zusammenfassung näher beschrieben.

Neben den fehlenden Langzeitdaten, fehlen des Weiteren belastbare Daten, inwieweit die ACI der dritten Generation im mittel- bis langfristigen Verlauf ein geeignetes Verfahren für Patienten mit einer hohen postoperativen sportlichen Aktivität ist. Für viele dieser Patienten ist die Wiedererlangung der sportlichen Fitness zum Zeitpunkt vor dem Knorpelschaden von großer Bedeutung und stellt ein zentrales Ziel dar [21, 22].

Ganz allgemein hat die zunehmende Intensität der sportlichen Belastung zu einer erhöhten Prävalenz von Gelenkknorpelschäden bei Sportlern geführt [10, 51, 64], was diese Personen zu einer frühen sekundären Osteoarthritis prädisponiert und häufig zu Lebensstiländerungen zwingt [23-26]. Aufgrund des geringen Potenzials für die intrinsische Heilung besteht bei Knorpelverletzungen ein hohes Progressionsrisiko der posttraumatischen Arthritis - insbesondere bei Athleten mit wiederholter Gelenkbelastung im Sport [23, 26-29].

Die Beurteilung der wiedererlangten körperlichen Aktivität und der sportlichen Leistungsfähigkeit nach ACI ist in diesem Zusammenhang von großer Bedeutung, da die Rückkehr zum Sport und zur körperlichen Aktivität einer der Hauptgründe dafür ist, dass sich Patienten für eine Operation entscheiden [30]. Wie es scheint, ist eine schnelle Belastungssteigerung und die Wiederaufnahme des Sports mit einem reizfreien Kniegelenk nicht nur möglich und empfehlenswert [31], sondern auch einer der wichtigen prognostischen Faktoren nach ACI [32]. Die kurz- bis mittelfristige Wiederaufnahme der sportlichen Aktivitäten nach ACI der ersten und zweiten Generation der ACI ist in der Fachliteratur gut beschrieben [26]. Es fehlen jedoch belastbare Daten über den mittel- bis langfristigen Verlauf nach ACI der dritten Generation. Auch die Bedeutung des präoperativen Sportniveaus der Patienten sowie die Rückkehr zum Sport und dessen Einfluss auf den Erfolg nach ACI der dritten Generation

wurden bisher nicht untersucht. Im kurzfristigen Verlauf konnte die sportliche Aktivität als möglicher Einfluss- und Prognosefaktor herausgestellt werden.

Kreuz et al. [32] führten eine prospektive Studie an Patienten durch, welche mittels ACI der ersten Generation mittels Periostlappen behandelt wurden. Die Arbeitsgruppe konnte die Bedeutung von sportlicher Aktivität für die Knorpelregeneration nach ACI darstellen und kam zu dem Schluss, dass körperliche Aktivität und insbesondere mäßiger Sport ein wichtiges Instrument im Rahmen der postoperativen Rehabilitation darstellen. Diese sollte für mindestens zwei bis drei Jahre nach der Operation durchgeführt werden.

Krych et al. [26] verglichen verschiedene chirurgische Behandlungsoptionen von Gelenkknorpelschäden im Kniegelenk und berichteten über die anschließende Rückkehr zum Sport auf Meta-Analyse-Basis. Verfahrenübergreifend schlussfolgerte diese Meta-Analyse eine Rückkehr zum Sport von 76%. Die höchste Rate konnte nach OAT (93%) erreicht werden, gefolgt von OCA (88%), ACI (82%) und MFX (58%). Für die ACI wurde gezeigt, dass sie die längste notwendige Rehabilitationszeit aufweist.

Erdle et al. [33] veröffentlichten eine Studie zum Thema Sport und Freizeitaktivität nach ACI der ersten Generation. Sie kamen zu dem Schluss, dass das prämorbidale Niveau 11 Jahre nach periostgedeckter autologer Chondrozytenimplantation (ACI-P) nicht erreicht werden konnte.

Ziel der vorliegenden Arbeit war es nun, erstmals zu analysieren, inwieweit die ACI der dritten Generation im mittel- bis langfristigen Verlauf eine effektive und geeignete Therapie für Sportler mit fokalem vollschichtigem Knorpeldefekt im Kniegelenk darstellt. Auch die Bedeutung der prä- und postoperativen sportlichen Aktivität als möglicher Einflussfaktor auf das mittel- bis langfristige Outcome sollten bewertet werden. Darüber hinaus wurde die sportliche Aktivität im postoperativen Verlauf analysiert und die Rückkehr zum Sport ermittelt. In unserer Arbeitshypothese postulierten wir, dass die ACI der dritten Generation über den mittel- bis langfristigen Verlauf eine geeignete Therapieoption für Sportler darstellt, und weiter,



dass sowohl die präoperative als auch die postoperative sportliche Aktivität einen positiven Einfluss auf das Ergebnis nach ACI der dritten Generation haben und mittel- bis langfristig zu besseren Therapieerfolgen führen. Die entsprechenden Ergebnisse wurden im Paper „*Third generation autologous chondrocyte implantation is a good treatment option for athletic persons*“ veröffentlicht und werden in der Zusammenfassung näher beschrieben.

### **Eigenanteil der Arbeiten:**

Das Paper „*Patient-Reported and Magnetic Resonance Imaging Outcomes of Third-Generation Autologous Chondrocyte Implantation After 10 Years*“ wurde als geteilte Erstautorenschaft, das Paper „*Third generation autologous chondrocyte implantation is a good treatment option for athletic persons*“ als Koautorenschaft veröffentlicht. Der Eigenanteil beider Arbeiten umfasste neben der Konzeption der Studien in direkter Zusammenarbeit mit PD Dr. med. T. Niethammer und Prof. Dr. med. P. Müller die umfangreiche Literaturrecherche, die eigenständige Datenerfassung mittels eines standardisierten Fragebogens sowie anhand von bildgebenden Untersuchungen mittels MRT, die Datenauswertung mittels Erhebung anerkannter orthopädischer Scores (Ausnahme: Erhebung des MOCART-Score), die Verarbeitung der Daten in einer Exceltabelle und die Auswertung der Daten mittels SPSS sowie das vollständige und selbstständige Verfassen der Paper im stetigen Austausch mit PD Dr. med. T. Niethammer. Die Auswertung der radiologischen Ergebnisse (Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART)-Score) für das Paper „*Patient-Reported and Magnetic Resonance Imaging Outcomes of Third-Generation Autologous Chondrocyte Implantation After 10 Years*“ erfolgte durch Susan Notohamiprodjo.

Im folgenden Kapitel werden die publizierten Ergebnisse zusammengefasst. Es wird dargestellt, inwieweit unsere Ergebnisse die ACI der dritten Generation als anerkanntes und etabliertes Verfahren zur Behandlung lokalisierter vollschichtiger Knorpelschäden des Kniegelenks bestätigen. Beide Arbeiten tragen damit wichtige Erkenntnisse zur Weiterentwicklung der Indikationsstellung der ACI der dritten Generation bei.

## 4. Zusammenfassung

Mittels zweier separater Publikationen konnten in der vorliegenden Arbeit sowohl die ersten Langzeitergebnisse der ACI der dritten Generation zusammengestellt, als auch die Eignung des Verfahrens für sportliche Patienten sowie die sportliche Aktivität als wichtiger Einfluss- und Prognosefaktor für den langfristigen Erfolg der ACI der dritten Generation gezeigt werden. Im folgenden Abschnitt werden nun der einheitliche Methodenteil sowie die Auswertung beider Paper beschrieben. Ergebnisse und Diskussion finden sich in den anschließenden separaten Abschnitten des jeweiligen Papers.

### Methoden

Die Indikationsstellung zur Knorpeltherapie erfolgte jeweils gemäß den Empfehlungen der Deutschen Gesellschaft für Orthopädie und Unfallchirurgie (DGOU) Clinical Tissue Regeneration Working Group [2]. Die nachfolgenden Parameter wurden basierend auf diesen Empfehlungen von der Therapie mittels ACI der dritten Generation ausgeschlossen: kausale, nicht parallel mitbehandelte Begleitpathologien (z. B. Achsfehlstellung), fortgeschrittene Arthrose, subtotal resezierter Meniskus im betroffenen Kompartiment, rheumatoide Arthritis mit relevanter Synovialitis, sowie Hämophilie-assoziierte Arthropathie. Alle Defekte wurden mittels offener Knorpelzelltransplantation, der sogenannten matrixgestützten ACI mit NOVOCART® 3D (TETEC AG, Reutlingen, Deutschland) und folglich einheitlich mittels ACI der dritten Generation behandelt.

Nach einem standardisierten Schema erfolgte die klinische Beurteilung. Vor dem medizinischen Eingriff erfolgte die Erhebung eines Fragebogens zur Erfassung der präoperativen Ausgangssituation. Dieser beinhaltete unter anderem die Beurteilung der sportlichen Aktivität vor der Knieverletzung mittels University of California at Los Angeles (UCLA)-Score und Tegner-Activity Scale. Sechs und zwölf Wochen postoperativ und anschließend im jährlichen Intervall erfolgten die klinischen Follow-up-Bewertungen. Zur subjektiven Beurteilung des Knies erfolgte die Erfassung mehrerer orthopädscher Scores wie

dem International Knee Documentation Committee Subjective Knee Form (IKDC)-, Knee Injury Osteoarthritis Outcome Score (KOOS) und Tegner-Lysholm-Score. Zudem wurden mittels einer visuellen Analogskala [34] Daten zur Schmerzbeurteilung in Ruhe und bei Belastung erfasst. Ebenso wurden andere relevante patientenbezogene Parameter wie unter anderem Alter, Geschlecht, Körpergewicht, Größe und Body-Mass-Index (BMI) sowie defektspezifische Daten wie Defektgröße, Ätiologie, Lokalisation und Informationen zur Erst- oder Zweitlinientherapie vom behandelnden Zentrum dokumentiert.

Zur radiologischen Auswertung der Ergebnisse erfolgten außerdem jährliche postoperative Magnetresonanztomographie (MRT)-Untersuchungen nach einem standardisierten Verfahren.

Die statistische Auswertung erfolgte mithilfe des Statistikprogramms Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA).

**Paper 1: „*Patient-Reported and Magnetic Resonance Imaging Outcomes of Third-Generation Autologous Chondrocyte Implantation After 10 Years*“**

Die Studie hatte zum Ziel, die klinischen und radiologischen Langzeitergebnisse nach ACI der dritten Generation für die Behandlung von fokalen Knorpeldefekten des Knies zu bewerten und den langfristigen Erfolg nachzuweisen.

Die Daten wurden in den Jahren 2004 bis 2018 erhoben. Eingeschlossen wurden Patienten mit Knorpeldefekten des Kniegelenks Grad III oder IV (nach International Cartilage Repair Society (ICRS)). Des Weiteren mussten diese Patienten mit ACI der dritten Generation behandelt worden sein und eine Nachbeobachtungszeit von mindestens 10 Jahren aufweisen. Der IKDC-Score und die Bewertung des Ruhe- und Bewegungsschmerzes mittels VAS-Score wurden zu verschiedenen Zeitpunkten erhoben: präoperativ, 6 Monaten nach dem operativen Eingriff und anschließend im jährlichen Intervall. Nach 10 Jahren wurde für 13 Patienten zusätzlich eine Kernspintomographie durchgeführt. Der Zustand des ACI-Knorpels wurde für diese Patienten anhand des MOCART-Scores beurteilt.

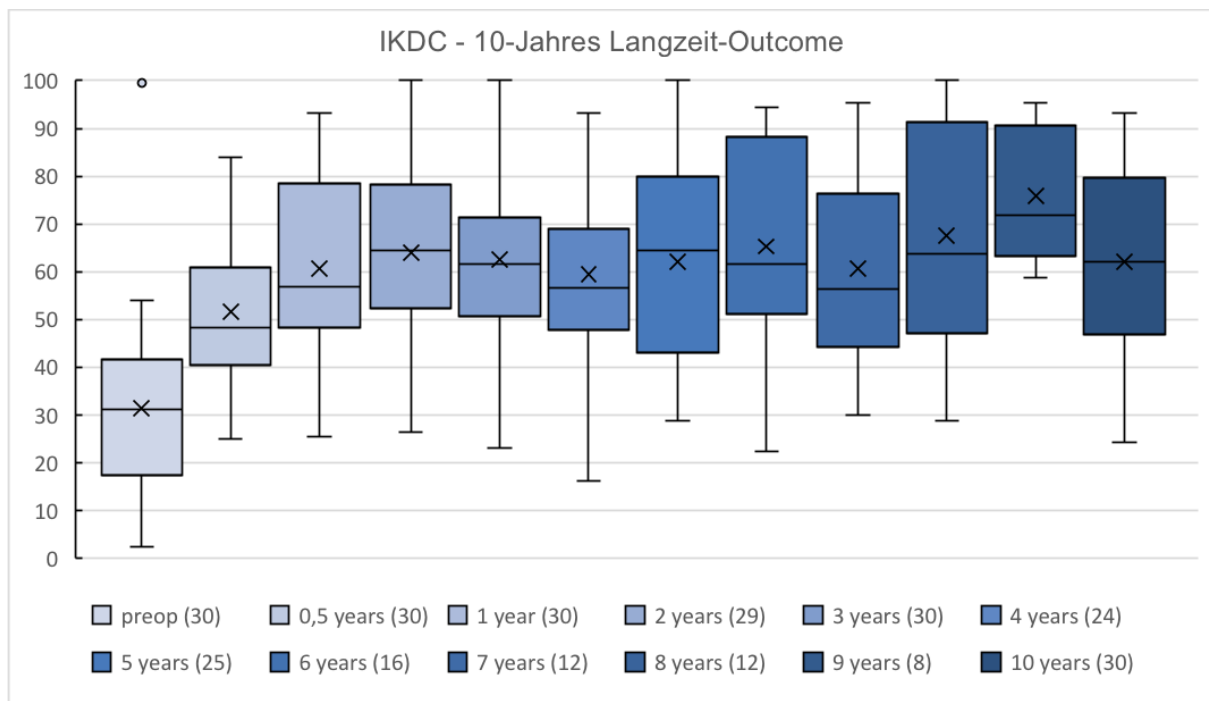
|                            | <b>Präoperativer Score</b> | <b>Postoperativer Score (10J)</b> | <b>P-Wert (test)</b> |
|----------------------------|----------------------------|-----------------------------------|----------------------|
| <b>IKDC</b>                | 31.3 ± 19.5                | 62.1 ± 19.3                       | < 0.001 (t-Test)     |
| <b>VAS in Ruhe</b>         | 3.7 ± 3.1                  | 1.4 ± 1.5                         | < 0.001 (Wilcoxon)   |
| <b>VAS unter Belastung</b> | 7.7 ± 2.2                  | 3.7 ± 2.8                         | < 0.001 (Wilcoxon)   |

Tabelle 1: Klinisches Outcome 10 Jahre nach autologer Chondrozytenimplantation  
(in Anlehnung an: Niethammer TR, 2020, S.1931)

54 Patienten qualifizierten sich anhand der vordefinierten Einschlusskriterien. Davon erreichten 30 den 10-Jahres-Follow-up-Punkt und wurden somit in die Auswertung einbezogen. Verglichen mit der präoperativen Situation konnte für alle klinischen Ergebnisparameter eine statistisch hochsignifikante Verbesserung 10 Jahre nach der Operation nachgewiesen werden (Tabelle 1). Die Responderrate lag bei 70 %. Der IKDC stieg von einem Mittelwert von 31,3 präoperativ auf 62,1 zehn Jahre postoperativ ( $p < 0,001$ ) (Grafik 1). Die Auswertung der Daten der VAS-Skala ergab ebenfalls eine statistisch hochsignifikante Verbesserung: Die Patienten beurteilten ihren Ruheschmerz präoperativ mit einem Mittelwert von 3,7, während 10 Jahre nach der Operation der Ruheschmerz auf 1,4 sank ( $p < 0,001$ ). Ebenso sank die subjektive Schmerzbeurteilung bei Belastung von durchschnittlich 7,7 (präoperativ) auf 3,7 (10 Jahre postoperativ) ( $p < 0,001$ ). Auch die Auswertung der MRTs lieferte überzeugende Ergebnisse: 10 Jahre postoperativ wurde ein durchschnittlicher MOCART-Score von 59,2 Punkten (Bereich, 20-100 Punkte) erreicht. Über 60 Prozent dieser analysierten Patienten bestätigten eine gute Integration des Implantats.

Für die Langzeitergebnisse der ACI der ersten Generation sowie für die kurz- bis mittelfristigen Ergebnisse der ACI der dritten Generation liegen in der Literatur fundierte Daten vor, die auf positive Therapieergebnisse hinweisen [11-17]. Für die ACI der dritten Generation stehen jedoch nur begrenzte Langzeitdaten zur Verfügung [18-20]. In dieser Studie konnte auf Basis der hohen Fallzahlen eine Langzeitauswertung (10 Jahre) der klinischen und radiologischen Ergebnisse erfolgen und die ersten Hinweise aus Langzeitstudien bestätigt werden. Auch zehn Jahre nach der Operation zeigt die ACI der dritten Generation stabile Ergebnisse und führt zu einer hochsignifikanten Verbesserung aller klinischer Ergebnisparameter. Die Analyse dieser Daten bestätigt die ACI der dritten Generation als geeignete und effektive Option in der Therapie von vollschichtigen Knorpeldefekten des Kniegelenks. Ebenso konnte radiologisch

der Nachweis erbracht werden, dass das Implantat über den Beobachtungszeitraum von zehn Jahren stabil integriert wird. Trotz dieser guten Ergebnisse war in dieser Studie eine Revisionsoperation nach ACI der dritten Generation für fast jeden 4. Patienten (23%) notwendig. Es bedarf daher weiterer Untersuchungen, um die Auswirkung von Einflussfaktoren auf das Langzeitergebnis zu erfassen und damit die Indikation zur ACI der dritten Generation weiter zu entwickeln.

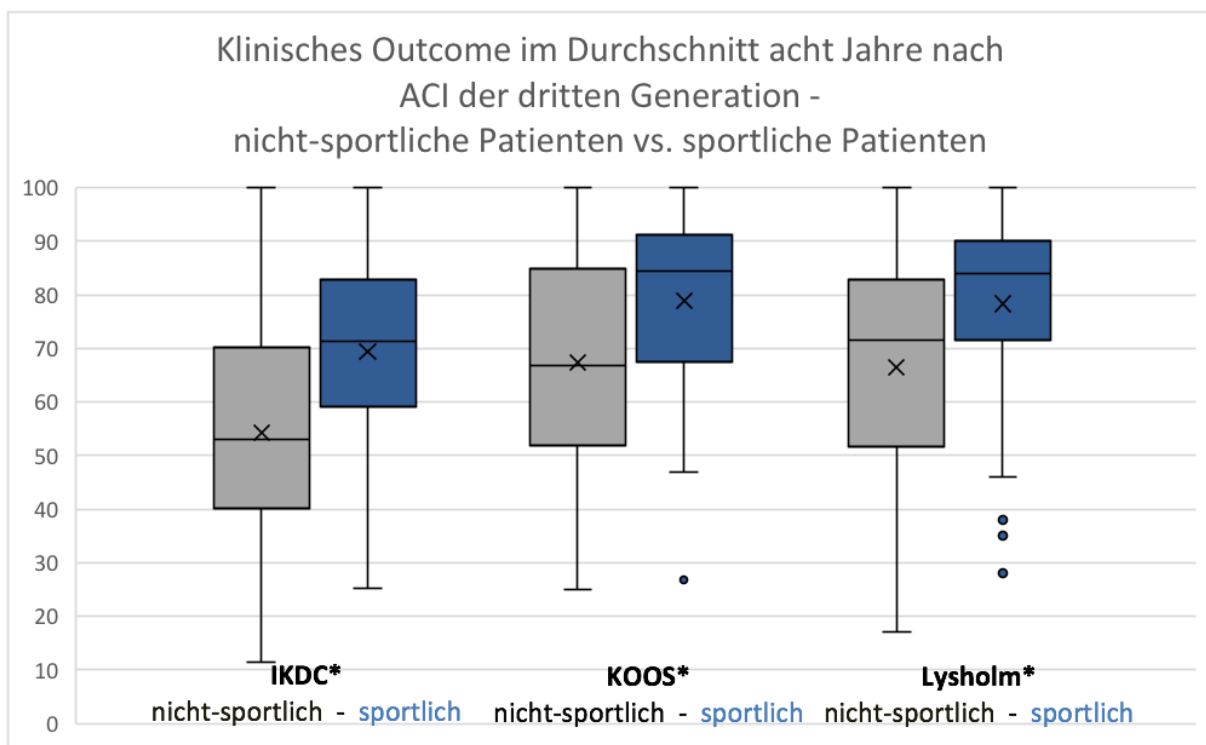


**Grafik 1:** Der IKDC-Score zeigte in der Langzeitauswertung eine homogene Entwicklung. Er stieg von einem Mittelwert von 31,3 präoperativ auf 62,1 zehn Jahre postoperativ (t-Test:  $p < 0.001$ ). (in Anlehnung an: Niethammer TR, 2020, S.1932)

## **Paper 2: „Third generation autologous chondrocyte implantation is a good treatment option for athletic persons“**

In dieser Studie war es das Ziel, zu untersuchen, inwieweit die ACI der dritten Generation als eine effektive Therapie für sportliche Personen mit fokalen vollschichtigen Knorpeldefekt der Kniegelenke angesehen werden kann. Darüber hinaus wurde in dieser Arbeit der Einfluss der sportlichen Aktivität (prä- und postoperativ) im mittel- bis langfristigen Follow-up evaluiert sowie die sportliche Aktivität im postoperativen Verlauf analysiert und die Rückkehr zum Sport beurteilt.

In diese Analyse wurden 84 Patienten eingeschlossen, welche sich der ACI der dritten Generation (NOVOCART® 3D) unterzogen. Der Beobachtungszeitraum betrug durchschnittlich 8 Jahre (5-14). Zur Beurteilung der sportlichen Aktivität wurden sowohl der UCLA Score als auch die Tegner Activity Scale verwendet. Die klinische Analyse erfolgte vor dem Auftreten der Knieschmerzen sowie postoperativ im jährlichen Intervall. Für die Untersuchung wurden zwei Gruppen aus 41 sportliche Personen und 43 nicht-sportliche Personen gebildet (UCLA-Cut-off: 7; Tegner Activity Scale-Cut-off: 4). Zur Erfassung der von den Patienten berichteten klinischen Ergebnisse wurden anerkannte orthopädische Scores wie der IKDC-, KOOS- und Lysholm-Score sowie der VAS-Score unter Belastung verwendet.



Grafik 2: Klinisches Outcome im Durchschnitt acht Jahre nach der dritten Generation der ACI – nicht sportliche Personen vs. sportliche Personen. Die Ergebnisparameter IKDC, KOOS und Lysholm-Score zeigten signifikante\* ( $p < 0,01$ ) Unterschiede zwischen den sportlichen und nicht-sportlichen Personen. (in Anlehnung an: Niethammer TR, 2020, S.1220)

Die Analyse der gesamten Patientenkohorte (sportliche und nicht-sportliche Personen) ergab postoperativ eine signifikante Verbesserung ( $p < 0,001$ ) aller klinischer Parameter. Die separate Analyse der beiden Gruppen (sportliche vs. nicht-sportliche Personen) zeigte, dass sportliche Personen einen signifikant besseren Outcome-Score aufwiesen im Vergleich zu nicht-sportlichen Personen (IKDC:  $p < 0,01$ , KOOS:  $p < 0,01$ , Lysholm-Score:  $p < 0,01$ ) (Grafik 2).

Fast alle Patienten (96,4%) kehrten zu sportlichen Aktivitäten zurück und mehr als die Hälfte erreichten oder übertrafen ihr sportliches Niveau vor der Verletzung. Die restlichen Patienten konnten ihr sportliches Niveau postoperativ nicht mehr erreichen. Für diese Patienten sank der UCLA-Score im Median um 2 Punkte, die Tegner-Aktivitätsskala um 2,5 Punkte. Die sportliche Aktivität verlagerte sich im postoperativen Verlauf verglichen zur präoperativen Situation von hochbelastenden Sportarten zu aktiven Veranstaltungen und moderaten oder leichten Aktivitäten (Tabelle 2). Des Weiteren zeigte sich eine signifikante Korrelation zwischen präoperativem sportlichen Niveau (UCLA-Score und Tegner-Aktivitätsskala) und postoperativem Outcome – je sportlicher die Patienten präoperativ waren, desto besser war das klinische Ergebnis nach ACI der dritten Generation.

| <b>Sportarten</b>                            | <b>Vor Schmerzbeginn</b> | <b>Postoperativ</b> |
|----------------------------------------------|--------------------------|---------------------|
| <b>Inaktiv, n (%)</b>                        | 5 (6.0)                  | 3 (3.6)             |
| <b>Milde Aktivitäten, n (%)</b>              | 0 (0.0)                  | 7 (8.3)             |
| <b>Moderate Aktivitäten, n (%)</b>           | 14 (16.7)                | 18 (21.4)           |
| <b>Aktive Veranstaltungen, n (%)</b>         | 32 (38.1)                | 39 (46.4)           |
| <b>Sportarten mit hoher Belastung, n (%)</b> | 33 (39.3)                | 17 (20.2)           |

Tabelle 2: Änderung der ausgeübten Sportarten. Im Laufe der Zeit kam es zu einer Verlagerung von Sportarten mit hoher Belastung hin zu aktiven Veranstaltungen und moderaten oder leichten Aktivitäten. (in Anlehnung an: Niethammer TR, 2020, S.1220)

Die sportliche Aktivität nach ACI der ersten und zweiten Generation sind in der Fachliteratur gut beschrieben [26, 32]. Weitere Untersuchungen waren allerdings notwendig, um zu klären, inwieweit die ACI der dritten Generation als eine geeignete Therapie für sportliche Personen mit fokalen vollschichtigen Knorpeldefekten eingesetzt werden kann. Diese Studie bestätigt nun die ACI der dritten Generation als effektive Therapieoption für sportliche Personen mit vollschichtigem Knorpeldefekten des Kniegelenks. Nach erfolgreicher Operation ist eine Rückkehr zur sportlichen Aktivität möglich. Es wurde jedoch eine Verlagerung von hochbelastenden Sportarten zu weniger belastenden sportlichen Aktivitäten nachgewiesen. Des Weiteren konnte das vor und nach der Operation ausgeübte sportliche Aktivitätsniveau als wichtiger Einflussfaktor auf das mittel- bis langfristige klinische Outcome nach ACI der dritten Generation ermittelt werden. Dies stellt eine weitere wichtige Entscheidungshilfe für die

Indikation zur ACI der dritten Generation dar. Für Patienten mit höherer sportlicher Aktivität präoperativ dürfen bessere Ergebnisse erwartet werden.



## Summary

Based on two separate publications, the present study provides the first long-term results of third-generation autologous chondrocyte implantation (ACI) and also demonstrates the efficacy of the procedure for athletic patients and athletic activity as an important influencing and prognostic factor for the long-term success of third-generation ACI. The following section describes the standardized methods of both papers. Results and discussion are presented in the subsequent individual sections of the respective paper.

## Methods

The determination of the indication of cartilage therapy followed the guidelines of the Clinical Tissue Regeneration Working Group of the German Society for Orthopedics and Trauma Surgery (DGOU) [2]. Based on these guidelines, the following parameters lead to exclusion from third-generation ACI therapy: not in parallel treated causal concomitant pathologies (e.g. malalignment of the axis), advanced osteoarthritis, subtotally resected meniscus in the affected segment, rheumatoid arthritis with profound synovitis, hemophilia-associated arthropathy. A matrix-assisted ACI with NOVOCART® 3D (TETEC AG, Reutlingen, Germany), also known as third generation ACI, was applied.

Following a standardized scheme, the clinical assessment was performed. Prior to the medical intervention, a questionnaire was used to evaluate the preoperative baseline situation. Among others, this included the assessment of sporting activity prior to the knee injury using the University of California at Los Angeles (UCLA) score and the Tegner Activity Scale. Six and twelve weeks postoperatively and then at annual intervals, clinical follow-up assessments were performed. For subjective assessment of the knee, several orthopedic scores such as the International Knee Documentation Committee Subjective Knee Form (IKDC) score, Knee Injury Osteoarthritis Outcome Score (KOOS), and Tegner-Lysholm score were documented. In addition, visual analog scale [34] was used to collect data on pain assessment at rest and during exercise. Likewise, other relevant patient-related characteristics, including age, sex,

body weight, height, and body mass index (BMI), as well as defect-specific data such as defect size, etiology, location, and information on first- or second-line therapy were captured by the treating center.

For radiological evaluation of the data, annual postoperative magnetic resonance imaging (MRI) examinations were performed according to a standardized procedure.

Data were analyzed using the statistical program Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA).

**Paper 1: „Patient-Reported and Magnetic Resonance Imaging Outcomes of Third-Generation Autologous Chondrocyte Implantation After 10 Years “**

In this study the long-term clinical and radiological outcomes of third-generation ACI for the treatment of focal cartilage defects of the knee were evaluated.

Data were collected over a period of 15 years from 2004 to 2018. Only patients with at least grade III cartilage defects of the knee based on the International Cartilage Repair Society were included. Furthermore, these patients had to have a third-generation ACI treatment and a minimum of 10 years follow-up. International Knee Documentation Committee scores and assessment of pain at rest and on movement using VAS scores were collected at different time points: preoperatively, 6 months after surgery, and at annual intervals thereafter. After 10 years, additional magnetic resonance imaging was performed for 13 patients. The condition of the ACI cartilage was assessed for these patients using the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score.

|                        | <b>preoperative score</b> | <b>postoperative score (10y)</b> | <b>P-value (test)</b> |
|------------------------|---------------------------|----------------------------------|-----------------------|
| <b>IKDC</b>            | 31.3 ± 19.5               | 62.1 ± 19.3                      | < 0.001 (t-Test)      |
| <b>VAS at rest</b>     | 3.7 ± 3.1                 | 1.4 ± 1.5                        | < 0.001 (Wilcoxon)    |
| <b>VAS on movement</b> | 7.7 ± 2.2                 | 3.7 ± 2.8                        | < 0.001 (Wilcoxon)    |

Table 1: Clinical outcome 10 years after autologous chondrocyte implantation (Niethammer TR, 2020, p.1931)

54 patients qualified based on the predefined inclusion criteria. Of these, 30 reached the 10-year follow-up point and were thus included in this evaluation. Compared with the preoperative situation, a statistically highly significant improvement 10 years after surgery was demonstrated for all clinical outcome parameters (Table 1). The responder rate was 70%. The IKDC increased from a mean of 31.3 preoperative to 62.1 ten years postoperative ( $p < 0.001$ ) (Figure 1). Analysis of the data using the VAS scale also revealed a highly statistically significant improvement: patients rated their pain at rest with a mean of 3.7 preoperatively, while 10 years after surgery rest pain decreased to 1.4 ( $p < 0.001$ ). Similarly, subjective pain ratings [34] on movement decreased from a mean of 7.7 (preoperatively) to 3.7 (10 years postoperatively) ( $p < 0.001$ ). At 10 years postoperatively, the average MOCART score was 59.2 points (range, 20-100 points). More than 60% of these analyzed patients confirmed good integration of the implant.

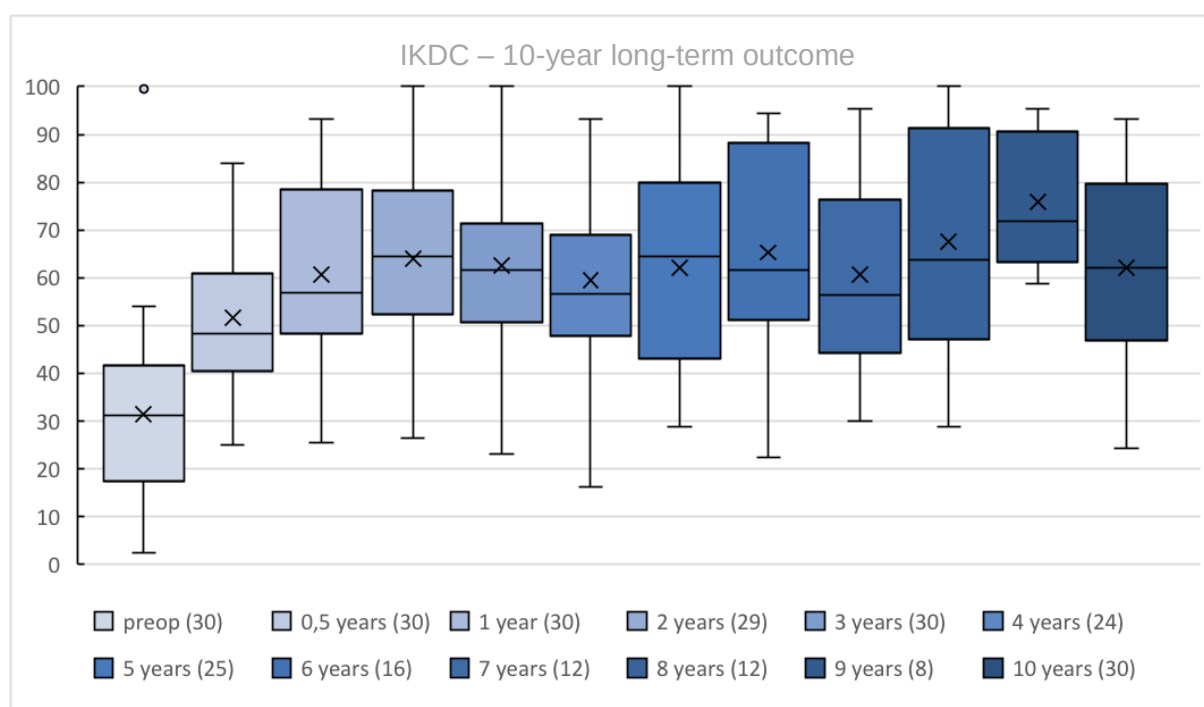


Figure 1: IKDC score showed a homogeneous development in the long-term evaluation. It increased from a mean of 31.3 preoperatively to 62.1 ten years postoperatively (t-test:  $p < 0.001$ ). (adapted from: Niethammer TR, 2020, p.1932)

Long-term results of first-generation ACI as well as short- and medium-term results of third-generation ACI have already demonstrated positive therapeutic outcomes in published literature [11-17]. However, only limited long-term data are available for third-generation ACI

[18-20]. In this study, a long-term evaluation (10 years) could be performed based on a high number of cases. The analysis of the data confirms third-generation ACI as a suitable and effective option in the treatment of full-thickness cartilage defects of the knee joint. Likewise, evidence was obtained that the implant is stably integrated over the ten-year period. Despite these good results, revision surgery was necessary for almost 1 in 4 patients (23%) in this study. Therefore, further studies are needed to better understand the impact of influencing factors on the long-term outcomes and thus to further improve the indication for third-generation ACI.

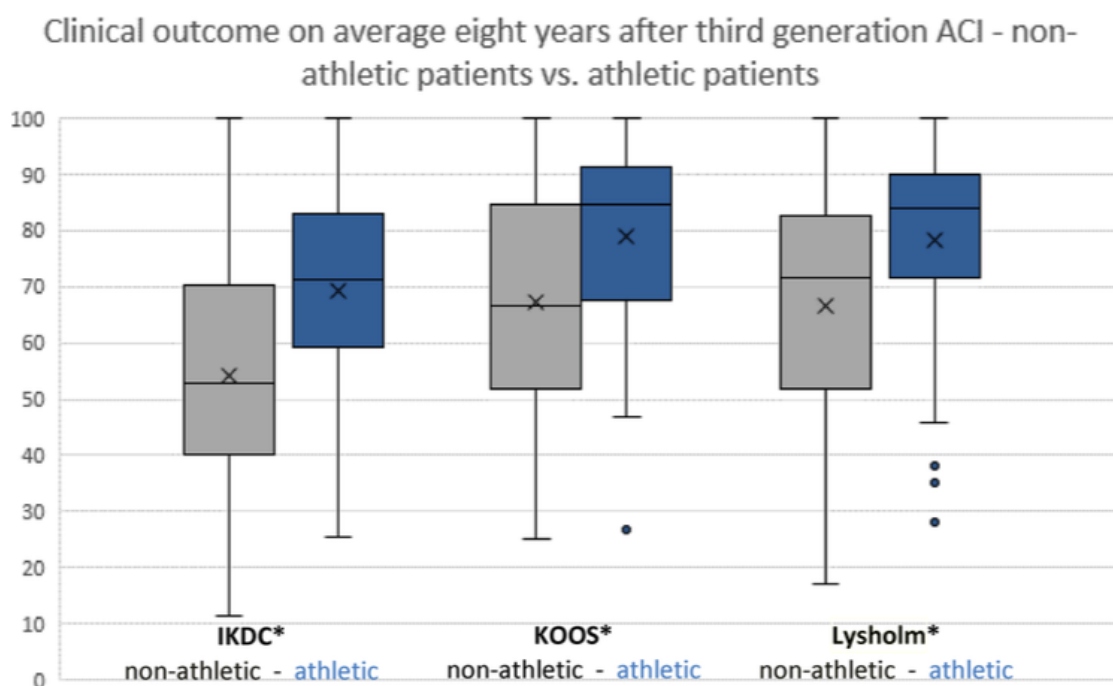
**Paper 2: „Third generation autologous chondrocyte implantation is a good treatment option for athletic persons“**

This study investigated third-generation ACI as an effective therapy for athletic individuals with focal full-thickness cartilage defects of the knee. In addition, this analysis evaluated the influence of sports activity (preoperative and postoperative) in the mid- to long-term follow-up, analyzed sports activity in the postoperative course, and assessed the return to sports.

84 patients who underwent third-generation ACI (NOVOCART® 3D) were included in this analysis. The observation period was 8 years in average (5-14). Both the UCLA Activity Score and the Tegner Activity Scale were used to assess sports activity. This clinical analysis was performed before the onset of knee pain and postoperatively at annual intervals. Two groups were formed for the study (UCLA cut-off: 7; Tegner Activity Scale cut-off: 4): 41 athletic persons and 43 non-athletic persons. Patient reported outcome data were analyzed based on established orthopedic scores: IKDC subjective, KOOS, Lysholm score, and VAS score on movement.

Analysis of the entire patient cohort (athletic and non-athletic persons) showed significant improvement ( $p < 0.001$ ) in all clinical parameters (IKDC, VAS at rest, VAS on movement) postoperatively, while separate analysis of the two groups (athletic vs. non-athletic persons) showed that athletic persons had a significantly better outcome score compared to non-athletic

persons (IKDC:  $p < 0.01$ , KOOS:  $p < 0.01$ , Lysholm score:  $p < 0.01$ ) (Figure 2). Almost all patients (96.4%) returned to sports activities and more than half reached or exceeded their preinjury sports level. The remaining patients were unable to reach their athletic level postoperatively. For them the UCLA score decreased by a median of two points, and the Tegner activity scale by 2.5 points. Sports activity shifted from high-impact sports to active events and moderate or light activities during the postoperative course (Table 2). Furthermore, there was a significant correlation between preoperative sports level (UCLA score and Tegner activity scale) and postoperative outcome scores (IKDC, VAS at rest, VAS on movement) – the more athletic the patients were preoperatively, the better the clinical outcome after third-generation ACI.



**Figure 2:** Clinical outcome on average eight years after third generation ACI – non-athletic patients vs. athletic patients. IKDC, KOOS and Lysholm Score showed significant\* ( $p < 0.01$ ) differences between athletic and non-athletic persons. (Niethammer TR, 2020, p.1220)

| <b>Types of sports</b>           | <b>before onset of pain</b> | <b>postoperatively</b> |
|----------------------------------|-----------------------------|------------------------|
| <b>Inactive, n (%)</b>           | 5 (6.0)                     | 3 (3.6)                |
| <b>Mild activity, n (%)</b>      | 0 (0.0)                     | 7 (8.3)                |
| <b>Moderate activity, n (%)</b>  | 14 (16.7)                   | 18 (21.4)              |
| <b>Active events, n (%)</b>      | 32 (38.1)                   | 39 (46.4)              |
| <b>High impact sports, n (%)</b> | 33 (39.3)                   | 17 (20.2)              |

Table 2: Change in types of sports participated. Over the course of time, a shift from high-impact sports to active events and moderate or mild activities was observed.  
(adapted from: Niethammer TR, 2020, p.1220)

Sports activity after first- and second-generation ACI are well described in scientific literature [26, 32]. However, further studies were needed to clarify the extent to which third-generation ACI can be used as an effective therapy for athletic individuals with focal cartilage defects. This study confirms third-generation ACI as an effective treatment option for athletic individuals with full-thickness cartilage defects of the knee joint. After successful surgery, a return to sports activity is possible. However, a shift from high-impact sports to lower-impact sports and activities has been demonstrated. Furthermore, the level of sports activity practiced before and after surgery was identified as an important influencing factor on the mid- to long-term clinical outcome after third-generation ACI. This represents an important decision support for the indication of third-generation ACI. Better results may be expected for patients with higher preoperative sports activity.

## 5. Literaturverzeichnis

1. Sophia Fox, A.J., A. Bedi, and S.A. Rodeo, *The basic science of articular cartilage: structure, composition, and function*. Sports Health, 2009. **1**(6): p. 461-8.
2. Niemeyer, P., et al., *Autologous chondrocyte implantation (ACI) for cartilage defects of the knee: A guideline by the working group "Clinical Tissue Regeneration" of the German Society of Orthopaedics and Trauma (DGOU)*. Knee, 2016. **23**(3): p. 426-35.
3. Fritz, J., et al., *[Cartilage repair in the knee joint]*. Unfallchirurg, 2006. **109**(7): p. 563-74; quiz 575-6.
4. Simon, T.M. and D.W. Jackson, *Articular Cartilage: Injury Pathways and Treatment Options*. Sports Med Arthrosc Rev, 2018. **26**(1): p. 31-39.
5. Brittberg, M., et al., *Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation*. N Engl J Med, 1994. **331**(14): p. 889-95.
6. Mandelbaum, B.R., et al., *Articular cartilage lesions of the knee*. Am J Sports Med, 1998. **26**(6): p. 853-61.
7. Minas, T., *Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life*. Am J Orthop (Belle Mead NJ), 1998. **27**(11): p. 739-44.
8. Krill, M., et al., *Autologous Chondrocyte Implantation (ACI) for Knee Cartilage Defects: A Review of Indications, Technique, and Outcomes*. JBJS Rev, 2018. **6**(2): p. e5.
9. Anders, S., et al., *[Matrix-associated autologous chondrocyte transplantation (MACT). Minimally invasive technique in the knee]*. Oper Orthop Traumatol, 2008. **20**(3): p. 208-19.
10. Behrens, P., et al., *Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI)--5-year follow-up*. Knee, 2006. **13**(3): p. 194-202.
11. Kreuz, P.C., et al., *Treatment of focal degenerative cartilage defects with polymer-based autologous chondrocyte grafts: four-year clinical results*. Arthritis Res Ther, 2009. **11**(2): p. R33.
12. Ossendorf, C., et al., *Treatment of posttraumatic and focal osteoarthritic cartilage defects of the knee with autologous polymer-based three-dimensional chondrocyte grafts: 2-year clinical results*. Arthritis Res Ther, 2007. **9**(2): p. R41.
13. Kreuz, P.C., et al., *Repair of focal cartilage defects with scaffold-assisted autologous chondrocyte grafts: clinical and biomechanical results 48 months after transplantation*. Am J Sports Med, 2011. **39**(8): p. 1697-705.
14. Zak, L., et al., *Results 2 Years After Matrix-Associated Autologous Chondrocyte Transplantation Using the Novocart 3D Scaffold: An Analysis of Clinical and Radiological Data*. Am J Sports Med, 2014. **42**(7): p. 1618-27.

15. Niethammer, T.R., et al., *Matrix based autologous chondrocyte implantation in children and adolescents: a match paired analysis in a follow-up over three years post-operation*. Int Orthop, 2017. **41**(2): p. 343-350.
16. Niethammer, T.R., et al., *Analysis of the autologous chondrocyte quality of matrix-based autologous chondrocyte implantation in the knee joint*. Int Orthop, 2016. **40**(1): p. 205-12.
17. Niethammer, T.R., et al., *Early resumption of physical activities leads to inferior clinical outcomes after matrix-based autologous chondrocyte implantation in the knee*. Knee Surg Sports Traumatol Arthrosc, 2014. **22**(6): p. 1345-52.
18. Aldrian, S., et al., *Clinical and radiological long-term outcomes after matrix-induced autologous chondrocyte transplantation: a prospective follow-up at a minimum of 10 years*. Am J Sports Med, 2014. **42**(11): p. 2680-8.
19. Gille, J., et al., *Matrix-Associated Autologous Chondrocyte Implantation: A Clinical Follow-Up at 15 Years*. Cartilage, 2016. **7**(4): p. 309-15.
20. Kreuz, P.C., et al., *Long-Term Clinical and MRI Results of Matrix-Assisted Autologous Chondrocyte Implantation for Articular Cartilage Defects of the Knee*. Cartilage, 2018: p. 1947603518756463.
21. Harris, J.D., et al., *Treatment of chondral defects in the athlete's knee*. Arthroscopy, 2010. **26**(6): p. 841-52.
22. Mithoefer, K., et al., *Current concepts for rehabilitation and return to sport after knee articular cartilage repair in the athlete*. J Orthop Sports Phys Ther, 2012. **42**(3): p. 254-73.
23. Chalmers, P.N., et al., *Activity-Related Outcomes of Articular Cartilage Surgery: A Systematic Review*. Cartilage, 2013. **4**(3): p. 193-203.
24. Mithoefer, K., et al., *Return to sports participation after articular cartilage repair in the knee: scientific evidence*. Am J Sports Med, 2009. **37 Suppl 1**: p. 167s-76s.
25. Mithoefer, K., et al., *High-impact athletics after knee articular cartilage repair: a prospective evaluation of the microfracture technique*. Am J Sports Med, 2006. **34**(9): p. 1413-8.
26. Krych, A.J., et al., *Return to sport after the surgical management of articular cartilage lesions in the knee: a meta-analysis*. Knee Surg Sports Traumatol Arthrosc, 2017. **25**(10): p. 3186-3196.
27. Ferruzzi, A., et al., *Cartilage repair procedures associated with high tibial osteotomy in varus knees: clinical results at 11 years' follow-up*. Knee, 2014. **21**(2): p. 445-50.
28. Kon, E., et al., *Second-generation autologous chondrocyte implantation: results in patients older than 40 years*. Am J Sports Med, 2011. **39**(8): p. 1668-75.
29. Murray, I.R., M.T. Benke, and B.R. Mandelbaum, *Management of knee articular cartilage injuries in athletes: chondroprotection, chondrofacilitation, and resurfacing*. Knee Surg Sports Traumatol Arthrosc, 2016. **24**(5): p. 1617-26.



30. Harris, J.D., et al., *Autologous chondrocyte implantation: a systematic review*. J Bone Joint Surg Am, 2010. **92**(12): p. 2220-33.
31. Wondrasch, B., et al., *Effect of accelerated weightbearing after matrix-associated autologous chondrocyte implantation on the femoral condyle on radiographic and clinical outcome after 2 years: a prospective, randomized controlled pilot study*. Am J Sports Med, 2009. **37 Suppl 1**: p. 88s-96s.
32. Kreuz, P.C., et al., *Importance of sports in cartilage regeneration after autologous chondrocyte implantation: a prospective study with a 3-year follow-up*. Am J Sports Med, 2007. **35**(8): p. 1261-8.
33. Erdle, B., et al., *Sporting Activity Is Reduced 11 Years After First-Generation Autologous Chondrocyte Implantation in the Knee Joint*. Am J Sports Med, 2017. **45**(12): p. 2762-2773.
34. Peterson, L., et al., *Autologous chondrocyte implantation: a long-term follow-up*. Am J Sports Med, 2010. **38**(6): p. 1117-24.

## 6. Abbildungs- und Tabellenverzeichnis

- Tabelle 1      Niethammer TR\*, Altmann D\*, Holzgruber M, Gülecyüz MF, Notohamiprodjo S, Baur-Melnyk A, Müller PE. *Patient-Reported and Magnetic Resonance Imaging Outcomes of Third-Generation Autologous Chondrocyte Implantation After 10 Years.*      Arthroscopy.      2020      Jul;36(7):1928-1938.      doi: 10.1016/j.arthro.2020.03.009. Epub 2020 Mar 19. PMID: 32200064.
- Tabelle 2      Niethammer TR, Altmann D, Holzgruber M, Goller S, Fischer A, Müller PE. *Third generation autologous chondrocyte implantation is a good treatment option for athletic persons.* Knee Surg Sports Traumatol Arthrosc. 2021 Apr;29(4):1215-1223. doi: 10.1007/s00167-020-06148-5. Epub 2020 Jul 15. PMID: 32671436; PMCID: PMC7973642.
- Grafik 1      Niethammer TR\*, Altmann D\*, Holzgruber M, Gülecyüz MF, Notohamiprodjo S, Baur-Melnyk A, Müller PE. *Patient-Reported and Magnetic Resonance Imaging Outcomes of Third-Generation Autologous Chondrocyte Implantation After 10 Years.*      Arthroscopy.      2020      Jul;36(7):1928-1938.      doi: 10.1016/j.arthro.2020.03.009. Epub 2020 Mar 19. PMID: 32200064.
- Grafik 2      Niethammer TR, Altmann D, Holzgruber M, Goller S, Fischer A, Müller PE. *Third generation autologous chondrocyte implantation is a good treatment option for athletic persons.* Knee Surg Sports Traumatol Arthrosc. 2021 Apr;29(4):1215-1223. doi: 10.1007/s00167-020-06148-5. Epub 2020 Jul 15. PMID: 32671436; PMCID: PMC7973642.

## Patient-Reported and Magnetic Resonance Imaging Outcomes of Third-Generation Autologous Chondrocyte Implantation After 10 Years



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**Purpose:** To evaluate the long-term clinical and radiologic outcomes of third-generation autologous chondrocyte implantation (ACI) for the treatment of focal cartilage defects of the knee. **Methods:** Data capture was carried out between 2004 and 2018. Included were patients with cartilage defects of the knee joint with an International Cartilage Repair Society grade of III or higher treated with third-generation ACI who had a minimum follow-up period of 10 years. International Knee Documentation Committee scores and assessment of pain at rest and on movement using visual analog scale scores were captured preoperatively and at 6 months postoperatively, as well as annually thereafter. In addition, we performed magnetic resonance imaging examinations in 13 cases after 10 years. The MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) score was used to evaluate the ACI cartilage. **Results:** A total of 54 patients met the inclusion criteria. Of these, 30 reached the 10-year follow-up point and were included in this assessment. At 10 years postoperatively, all clinical outcome parameters showed a statistically significant improvement compared with the preoperative situation, with a responder rate of 70%. The average MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) score after 10 years was 59.2 points (range, 20-100 points), and over 60% of the evaluated patients showed good integration of the implant at 10 years postoperatively. **Conclusions:** The clinical and radiologic findings of this study show that third-generation ACI is a suitable and effective option in the treatment of full-thickness cartilage defects of the knee. At 10 years after surgery, third-generation ACI shows stable results and leads to significant improvement in all clinical outcome parameters. Despite these results, revision surgery after third-generation ACI is common and was needed in 23% of patients in this study. **Level of Evidence:** Level IV, therapeutic case series.

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Autologous chondrocyte implantation (ACI) was first reported by Brittberg et al.<sup>1</sup> in 1994. Cartilage defects were covered with a periosteal flap (first-

generation ACI) or a collagen membrane (second-generation ACI). A scaffold of type I–type III collagen (third-generation ACI) is used for the treatment of major cartilage damage.<sup>2,3</sup>

In short- to medium-term follow-up studies, ACI was found to be effective and reliable.<sup>4–10</sup> Clinical results, joint function, and defect filling on magnetic resonance imaging (MRI) showed convincing results in the treatment of severe cartilage defects.<sup>11–13</sup>

Although the short- to medium-term outcomes are well documented, data regarding the long-term results of third-generation ACI are still lacking. The first long-term studies have recently been published and confirmed the promising results of medium-term follow-up.<sup>11–13</sup>

The purpose of this study was to evaluate the long-term clinical and radiologic outcomes of third-generation ACI for the treatment of focal cartilage defects of the knee. Our hypothesis was that ACI would show superior

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clinical and radiologic outcomes even 10 years after surgery and that ACI would therefore be a suitable treatment option for this injury with an acceptable revision rate, low pain level, and high activity level.

### Methods

Data capture was carried out between 2004 and 2018 with local institutional review board approval. Included were all patients with cartilage defects of the knee joint with an International Cartilage Repair Society grade of III or higher treated with third-generation ACI (Novocart 3D; TETEC, Reutlingen, Germany) who had a follow-up period of 10 years. The exclusion criteria for third-generation ACI were causally associated pathologies not treated in parallel (e.g., malalignment with  $>5^\circ$  of mechanical axis deviation or severe malrotation), advanced osteoarthritis (Kellgren-Lawrence grade higher than 2), subtotal resection of the meniscus in the affected compartment, rheumatoid arthritis with relevant synovitis, hemophilia-associated arthropathy, and corresponding bipolar cartilage defects. The indication for cartilage therapy was given in accordance with the recommendations of the DGOU (German Society for Orthopaedics and Trauma) Clinical Tissue Regeneration Working Group (Table 1).<sup>14</sup>

### Surgical Technique

All defects were treated with an open cartilage cell transplantation, so-called matrix-supported ACI, with Novocart 3D, as described in previous studies.<sup>7,15</sup> In a first arthroscopic operation, 2 osteochondral cylinders with a diameter of 3 mm and a thickness of approximately 5 to 10 mm were obtained from an unloaded

area of the lateral intercondylar notch. These were then sent, cooled in sterile nutrient solution, to the manufacturer (TETEC). The chondrocytes were isolated from the biopsy specimens in its special laboratory, multiplied in vitro, and applied to a type I–type III collagen scaffold. With a cultivation time of 3 to 4 weeks, the graft was created. The type I–type III collagen scaffold we used is derived from bovine and has a biphasic structure with a dense membrane and a spongy part with pores arranged in columns. Both the membrane and spongy part are cleared of noncollagenous components and are firmly connected.

Novocart 3D was then implanted in a second, open surgical procedure. This was performed via a minimally invasive parapatellar knee arthrotomy. First, the cartilage defect was precisely measured and prepared with a suitable cutter (Aesculap, Tuttlingen, Germany) to create a stable rim of healthy surrounding cartilage. Defect tissue was carefully removed down to the subchondral bone with curettes. The scaffold with the seeded chondrocytes was precisely prepared with the cutter. The cartilage graft was then inserted into the prepared cartilage defect. The scaffold was fixed to the healthy surrounding articular cartilage using Vicryl USP No. 5-0 suture (Ethicon [Johnson & Johnson], Norderstedt, Germany). In cases without a stable margin, additional fixation with resorbable polylactide pins (Novocart-Pin; TETEC) was conducted. Fibrin glue was not used.

### Rehabilitation

After ACI implantation, patients underwent 24 hours of bed rest. In cases with femoral defects, knee loading was limited to 20 kg for the first 6 weeks, followed by a weekly increase of 20 kg up to full loading. Patients were guided by a physiotherapist and a weighing scale. In patients with retropatellar cartilage defects, flexion was restricted by using a brace for 6 weeks. During this time, flexion was continually increased by about  $20^\circ$  every 2 weeks. After removal of the drain, the affected joint was treated with continuous passive motion therapy from the second postoperative day depending on the localization of the treated cartilage defects. Rehabilitation started during the 2-day inpatient treatment period. After discharge, all patients received ambulatory physiotherapeutic treatment. Moderate sports activities (e.g., cycling, swimming, or Nordic walking) were allowed after 3 months postoperatively. Impact sports were not recommended before 12 months after the operation.

### Patient-Reported Outcomes

Clinical evaluation was carried out according to a standardized scheme. The first interviews took place at 6 months postoperatively. Subsequently, annual clinical evaluations were carried out with a mailed questionnaire. If we received no response, we tried to contact the patient by phone. In addition to the

**Table 1.** Indications and Contraindications for Cartilage Therapy Based on Recommendations of DGOU Clinical Tissue Regeneration Working Group

|                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Indications                                                                                                                                           |
| Cartilage defect: symptomatic cartilage defects of ICRS grade III-IV (subchondral bone loss $> 2$ mm, bone grafting is needed)                        |
| Osteochondritis dissecans: stage III-IV according to ICRS osteochondritis dissecans criteria                                                          |
| Defect size: minimum size of $2.5\text{--}3\text{ cm}^2$ ; maximum size without limit                                                                 |
| Defect localization: no restriction (femoral, tibial, patellar, trochlear)                                                                            |
| Age: no restriction (in cases without contraindications)                                                                                              |
| Contraindications                                                                                                                                     |
| Causally associated pathologies not treated in parallel (e.g., malalignment with $>3^\circ$ to $5^\circ$ of mechanical axis deviation or malrotation) |
| Osteoarthritis (Kellgren-Lawrence grade higher than 2)                                                                                                |
| Subtotal resection of meniscus in affected compartment                                                                                                |
| Rheumatoid arthritis with relevant synovitis                                                                                                          |
| Hemophilia-associated arthropathy                                                                                                                     |
| Corresponding bipolar cartilage defects                                                                                                               |

DGOU, German Society for Orthopaedics and Trauma; ICRS, International Cartilage Repair Society.

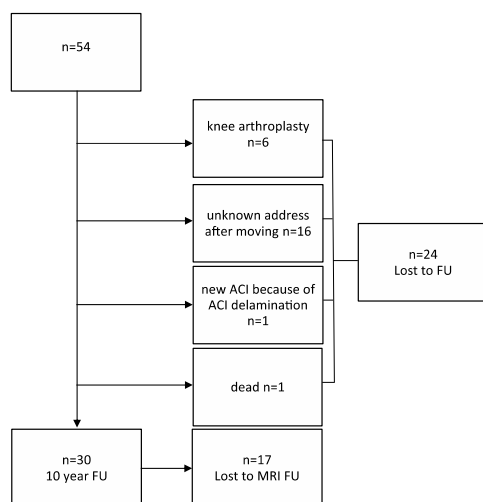
**Table 2.** Characteristics of Patient Population

| Characteristic                                                             | 10-yr Long-Term Study Population                               | Initial Study Population                                     |
|----------------------------------------------------------------------------|----------------------------------------------------------------|--------------------------------------------------------------|
| Total number of patients, n (%)                                            | 30 (55.6)                                                      | 54                                                           |
| Age, yr                                                                    |                                                                |                                                              |
| Mean (range)                                                               | 33.9 (15-57)                                                   | 34.7 (15-57)                                                 |
| Median                                                                     | 36                                                             | 37                                                           |
| Sex, n (%)                                                                 |                                                                |                                                              |
| Male                                                                       | 19 (63.3)                                                      | 32 (59.3)                                                    |
| Female                                                                     | 11 (36.7)                                                      | 22 (40.7)                                                    |
| BMI                                                                        |                                                                |                                                              |
| Mean (range)                                                               | 25.3 (19.0-35.4)                                               | 25.9 (19.0-35.8)                                             |
| Median                                                                     | 24.3                                                           | 25.3                                                         |
| Smoking status, n (%)                                                      |                                                                |                                                              |
| Smoker                                                                     | 8 (26.7)                                                       | 12 (22.2)                                                    |
| Nonsmoker                                                                  | 21 (70)                                                        | 29 (53.7)                                                    |
| Unknown                                                                    | 1 (3.3)                                                        | 13 (24.1)                                                    |
| Defects                                                                    |                                                                |                                                              |
| No. of lesions, n (%)                                                      |                                                                |                                                              |
| 1 defect                                                                   | 29 (96.7)                                                      | 49 (90.7)                                                    |
| 2 defects                                                                  | 1 (3.3)                                                        | 5 (9.3)                                                      |
| Defect size, cm <sup>2</sup>                                               |                                                                |                                                              |
| Mean (range)                                                               | 5.5 (2.25-10.0) (second defects: 4.0)                          | 6.5 (2.25-15) (second defects: 4.5)                          |
| Median                                                                     | 5.0                                                            | 6.0                                                          |
| Defect localization, n (%)                                                 |                                                                |                                                              |
| Femoral condyle                                                            | 16 (53.3) (second defects: 1)<br>(medial, 14 [+1]; lateral, 2) | 27 (50) (second defects: 5)<br>(medial, 24 [+5]; lateral, 3) |
| Patella                                                                    | 14 (46.7)                                                      | 25 (46.3)                                                    |
| Trochlea                                                                   | 0 (0)                                                          | 2 (3.7)                                                      |
| Cause, n (%)                                                               |                                                                |                                                              |
| OCD                                                                        | 7 (23.3)                                                       | 10 (18.5)                                                    |
| New trauma                                                                 | 3 (10)                                                         | 6 (11.1)                                                     |
| Old trauma                                                                 | 9 (30)                                                         | 16 (29.6)                                                    |
| Unknown                                                                    | 11 (36.7)                                                      | 22 (40.7)                                                    |
| ICRS classification                                                        | III-IV                                                         | III-IV                                                       |
| Previous surgical procedure, n (%)                                         |                                                                |                                                              |
| No                                                                         | 21 (70)                                                        | 36 (66.7)                                                    |
| Microfracture                                                              | 5 (16.7)                                                       | 10 (18.5)                                                    |
| Classic ACI                                                                | —                                                              | 3 (5.6)                                                      |
| HTO                                                                        | 1 (3.3)                                                        | 1 (1.9)                                                      |
| Pridie drilling                                                            | 3 (10)                                                         | 3 (5.6)                                                      |
| Partial meniscal resection, cartilage shaving, and transposition osteotomy | —                                                              | 1 (1.9)                                                      |
| Concomitant surgery, n (%)                                                 |                                                                |                                                              |
| No                                                                         | 22 (73.3)                                                      | 38 (70.4)                                                    |
| Medial gathering                                                           | —                                                              | 4 (7.4)                                                      |
| HTO                                                                        | 2 (6.7)                                                        | 3 (5.6)                                                      |
| Autologous bone grafting                                                   | 5 (16.7)                                                       | 8 (14.8)                                                     |
| Anterior cruciate ligament—plasty                                          | 1 (3.3)                                                        | 1 (1.9)                                                      |
| Dropout reason, n (%)                                                      |                                                                |                                                              |
| No feedback                                                                | —                                                              | 16 (66.7)                                                    |
| Repeated ACI procedure                                                     | —                                                              | 1 (4.2)                                                      |
| Joint replacement                                                          | —                                                              | 6 (25.0)                                                     |
| Death                                                                      | —                                                              | 1 (4.2)                                                      |

ACI, autologous chondrocyte implantation; BMI, body mass index; HTO, high tibial osteotomy; ICRS, International Cartilage Repair Society; OCD, osteochondritis dissecans.

subjective assessment of the knee by the International Knee Documentation Committee (IKDC) questionnaire, data for pain detection at rest and on movement were collected using a visual analog scale (VAS). Regarding the clinical significance, we analyzed the minimal clinically important difference (MCID) in the IKDC score. The MCID in the IKDC score was reported

to be 16.7 points at 12 months.<sup>16</sup> We conducted a responder analysis using the IKDC score. Responders were defined as patients whose IKDC score increased by at least 20.5 points at 10 years after ACI.<sup>17,18</sup> In addition, several other patient-specific parameters, such as age, sex, body weight, height, and body mass index, as well as defect-specific data, such as defect size, cause,



**Fig 1.** A total of 30 patients with a follow-up period of 10 years were included in this assessment. The initial study population included 54 patients. The reasons for loss to follow-up (FU) were lack of participation and compliance (no feedback because of an unknown address after moving,  $n = 16$ ), change in therapy (joint replacement,  $n = 6$ ), repeated autologous chondrocyte implantation (ACI) ( $n = 1$ ), and death ( $n = 1$ ). (MRI, magnetic resonance imaging.)

localization, and information on first- or second-line therapy, were collected by the treating center.

### Magnetic Resonance Imaging

At 10 years after ACI, MRI examinations were performed following a standardized procedure. A 1.5-T MRI tomograph (Magnetom-Sonata; Siemens, Erlangen, Germany) with a conventional circular polarizing 1-channel knee coil was used. Fast spin echo (dual T2-FSE) and fat-saturated gradient echo (3D FS GE) images were made. In addition, the patients underwent a modified investigation that included a proton-weighted fat-saturated T1-weighted sequence and a fast low-angle shot sequence (FLASH) with selective water excitation. Analysis of the MRI images was performed using the MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) score,<sup>19</sup> which contains 9 variables, by a radiologist (S.N.) who specialized in

musculoskeletal radiology. The morphology and signal intensity of cartilage replacement tissue are described and compared with the adjacent healthy cartilage. In successful cartilage replacement therapy, the replacement tissue should have the same thickness as and a comparable surface area to the surrounding healthy cartilage. In addition, the tissue should be completely integrated into the chondral connective tissue and show no adhesions and an intact subchondral bone lamella and underlying bone marrow. The criteria examined result in a score between 0 and 100. Altogether, the study collected and evaluated MRI scans for 13 patients.

### Statistical Analysis

The SPSS Statistics program (SPSS, Chicago, IL) was used for statistical evaluation of the data. The Kolmogorov-Smirnov test was performed to test the respective patient groups for normal distribution. Depending on the test result, either the  $t$  test or Wilcoxon test was used to identify differences between the groups. Because the IKDC score showed a normal distribution in the preoperative situation and postoperative situation, the  $t$  test was used. For the VAS scores at rest as well as on movement, no normal distribution was found. Therefore, the Wilcoxon test was applied for their analysis. The Spearman correlation coefficient was used to analyze the correlation between clinical values and MRI parameters.

### Results

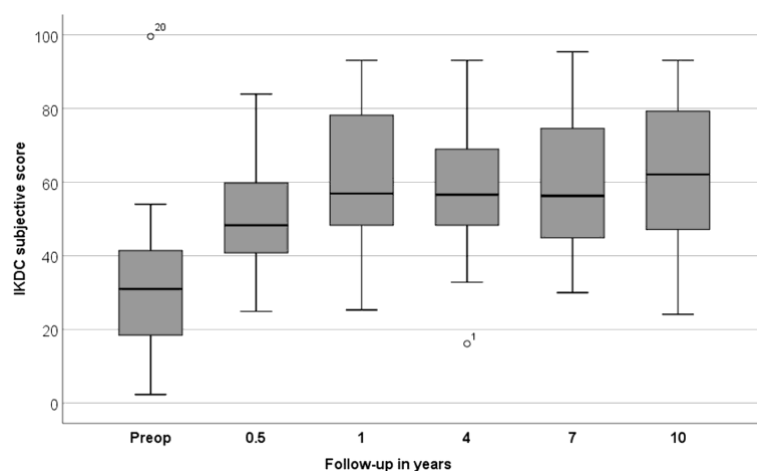
A total of 54 patients met the inclusion criteria. Of these, 30 reached the 10-year follow-up point and could be included in this assessment. Some patients were part of a previous analysis with a maximum follow-up period of 5 years.<sup>20</sup> All included patients had full-thickness cartilage defects, which were classified according to the International Cartilage Repair Society grade (grade IVa,  $n = 25$ ; grade IVb,  $n = 5$ ). On average, patients were aged 33.9 years (age range, 15-57 years). Of the patients, 63.3% were male and 36.7% were female patients. The average body mass index was 25.3 (range, 19.0-35.4). Of the defects, 53.3% were femoral ( $n = 16$ ) and 46.7% were patellar ( $n = 14$ ). The femoral defects were mainly in the medial femoral condyle (87.5%,  $n = 14$ ). The average defect size was 5.5 cm<sup>2</sup> (range, 2.25-10.0 cm<sup>2</sup>), and ACI was used as first-line therapy in 70% of patients. In the remaining

**Table 3.** Clinical Outcome 10 Years After Third-Generation ACI

|                       | Preoperatively             | Postoperatively (10 yr)     | P Value               |
|-----------------------|----------------------------|-----------------------------|-----------------------|
| IKDC score            | 31.3 $\pm$ 19.5 (2.3-99.6) | 62.1 $\pm$ 19.3 (24.1-93.1) | <.001 ( $t$ test)     |
| VAS score at rest     | 3.7 $\pm$ 3.1 (0-10)       | 1.4 $\pm$ 1.5 (0-5)         | <.001 (Wilcoxon test) |
| VAS score on movement | 7.7 $\pm$ 2.2 (0-10)       | 3.7 $\pm$ 2.8 (0-8)         | <.001 (Wilcoxon test) |

NOTE. Data are presented as mean  $\pm$  standard deviation (range).

ACI, autologous chondrocyte implantation; IKDC, International Knee Documentation Committee; VAS, visual analog scale.



**Fig 2.** The International Knee Documentation Committee (IKDC) score showed homogeneous development in the long-term evaluation. The mean score increased from 31.3 preoperatively to 62.1 at 10 years postoperatively ( $P < .001$ ,  $t$  test).

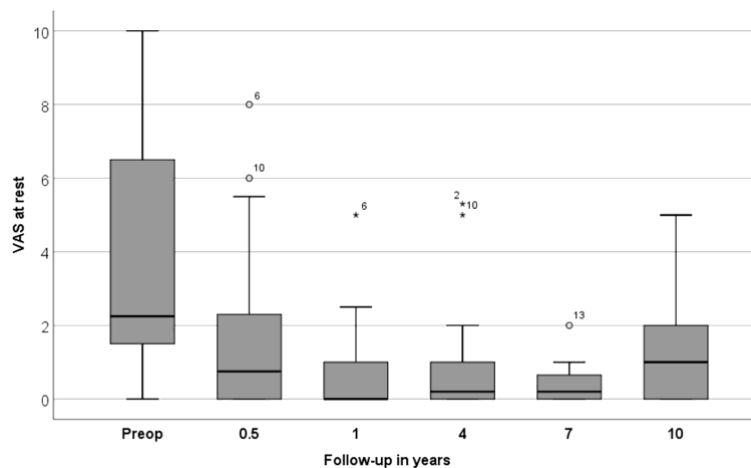
patients (30%), a failed cartilage repair procedure (e.g., microfracture, drilling, first-generation ACI, or third-generation ACI) was previously performed and documented. In 1 case, an additional cartilage defect was treated with ACI ( $n = 1$ , 3.3%; initial study population:  $n = 5$ , 9.3%). Patients characteristics of the initial study population are shown in Table 2; the initial study population included 54 patients. The reasons for loss to follow-up were lack of participation and compliance (no feedback because of an unknown address after moving,  $n = 16$ ), change in therapy (joint replacement,  $n = 6$ ), repeated ACI procedure ( $n = 1$ ), and death ( $n = 1$ ) (Fig 1). Joint replacement

was performed on average 7.2 years (range, 4-10 years) after ACI. At the time of this surgical procedure, patients were aged 52.2 years (range, 46-58 years) (Table 2).

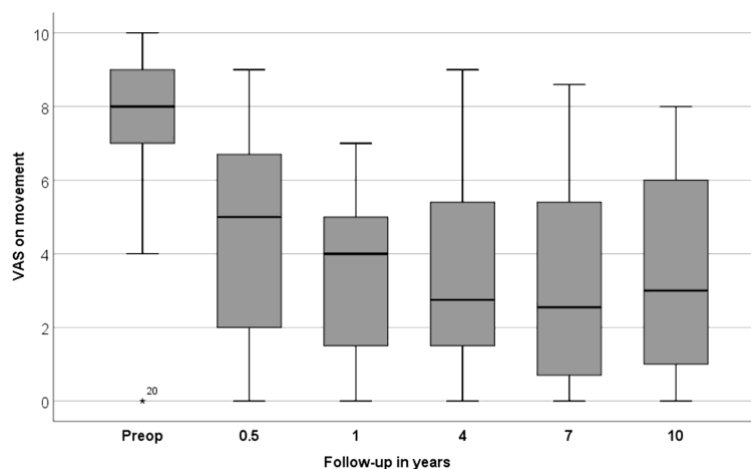
#### Patient-Reported Outcomes

All clinical scores showed a statistically significant improvement (Table 3). The IKDC score increased from a mean of 31.3 (range, 2.3-99.6) preoperatively to 62.1 (range, 24.1-93.1) at 10 years postoperatively ( $P < .001$ ). This improvement was observed at 1 year postoperatively as well and showed no significant change thereafter (Fig 2).

**Fig 3.** The visual analog scale (VAS) score at rest decreased from 3.7 preoperatively to 1.4 at 10 years after third-generation autologous chondrocyte implantation ( $P < .001$ , Wilcoxon test).



**Fig 4.** The subjective assessment of pain on movement (on a visual analog scale [VAS]) showed an improvement from an average of 7.7 preoperatively to 3.7 at 10 years after surgery ( $P < .001$ , Wilcoxon test).



**Table 4.** Responder Analyses for 10-Year Long-Term Population and Initial Study Population

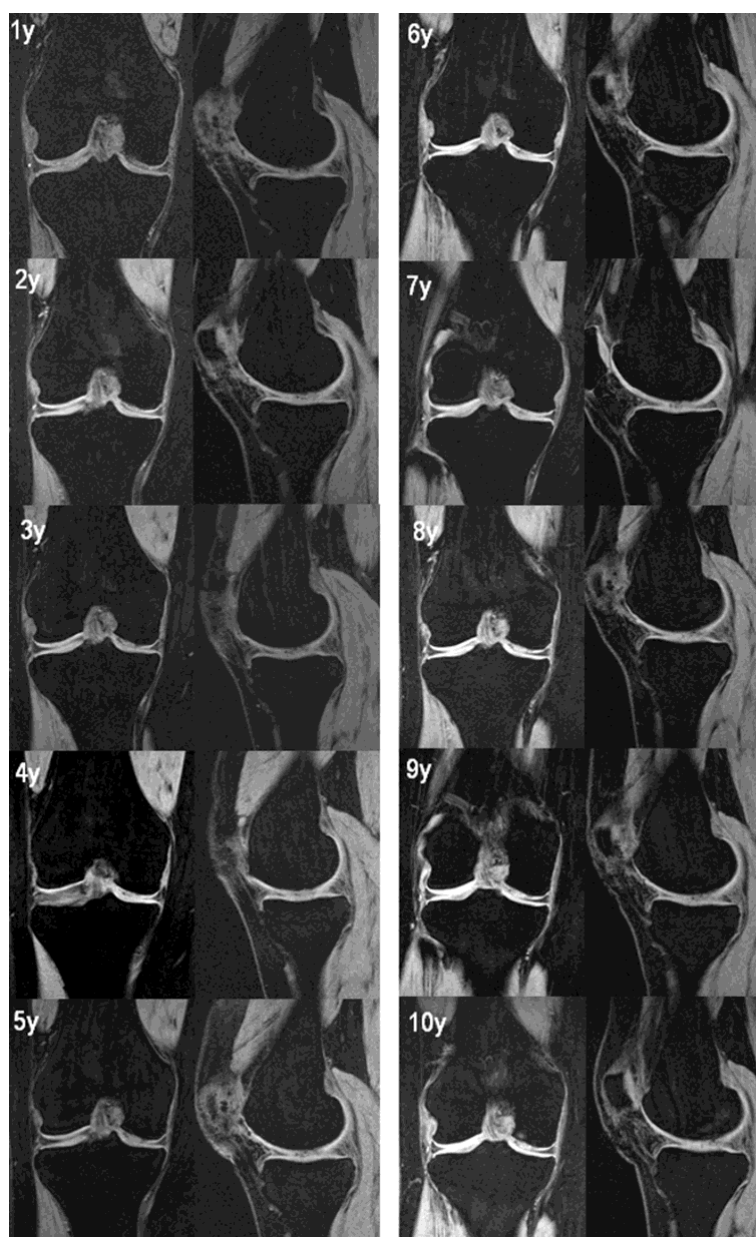
|                                            | 10-yr Long-Term Study Population (n = 30) |                      |         | Initial Study Population (n = 54) |                       |         |
|--------------------------------------------|-------------------------------------------|----------------------|---------|-----------------------------------|-----------------------|---------|
|                                            | Responder (n = 21)                        | Nonresponder (n = 9) | P Value | Responder (n = 34)                | Nonresponder (n = 20) | P Value |
| Age, mean (range), yr                      | 32.8 (15-57)                              | 36.4 (21-49)         | .414    | 33.2 (15-57)                      | 37.3 (21-49)          | .251    |
| Sex, n                                     |                                           |                      |         |                                   |                       |         |
| Male                                       | 11                                        | 8                    | .057    | 17                                | 15                    | .071    |
| Female                                     | 10                                        | 1                    |         | 17                                | 5                     |         |
| BMI, mean (range)                          | 24.3 (19.0-35.4)                          | 27.7 (19.6-33.2)     | .067    | 24.8 (19.0-35.3)                  | 27.6 (19.6-35.8)      | .009*   |
| Smoking status, n                          |                                           |                      |         |                                   |                       |         |
| Smoker                                     | 6                                         | 2                    | .665    | 8                                 | 4                     | .955    |
| Nonsmoker                                  | 14                                        | 7                    |         | 18                                | 11                    |         |
| Unknown                                    | —                                         | —                    |         | 8                                 | 5                     |         |
| No. of lesions, n                          |                                           |                      |         |                                   |                       |         |
| 1 defect                                   | 20                                        | 9                    | .506    | 31                                | 18                    | .885    |
| 2 defects                                  | 1                                         | 0                    |         | 3                                 | 2                     |         |
| Defect size, mean (range), cm <sup>2</sup> | 5.4 (3.0-10.0)                            | 5.6 (2.3-8.8)        | .730    | 6.2 (3.0-12.0)                    | 6.9 (2.3-15.0)        | .315    |
| Defect localization, n                     |                                           |                      |         |                                   |                       |         |
| Medial femoral condyle                     | 9                                         | 5                    | .508    | 13                                | 11                    | .290    |
| Lateral femoral condyle                    | 2                                         | 0                    |         | 3                                 | 0                     |         |
| Patella                                    | 10                                        | 4                    |         | 16                                | 9                     |         |
| Trochlea                                   | —                                         | —                    |         | 2                                 | 0                     |         |
| Cause, n                                   |                                           |                      |         |                                   |                       |         |
| OCD                                        | 4                                         | 3                    | .834    | 6                                 | 4                     | .887    |
| Acute trauma                               | 2                                         | 1                    |         | 4                                 | 2                     |         |
| Old trauma                                 | 7                                         | 2                    |         | 9                                 | 7                     |         |
| Unknown                                    | 8                                         | 3                    |         | 15                                | 7                     |         |
| Previous surgical procedure, n             |                                           |                      |         |                                   |                       |         |
| Yes                                        | 8                                         | 1                    | .139    | 12                                | 6                     | .690    |
| No                                         | 13                                        | 8                    |         | 22                                | 14                    |         |
| Concomitant surgery, n                     |                                           |                      |         |                                   |                       |         |
| Yes                                        | 3                                         | 4                    | .019*   | 9                                 | 7                     | .507    |
| No                                         | 18                                        | 5                    |         | 25                                | 13                    |         |

NOTE. Only for concomitant surgery for the 10-year long-term study population and BMI for the initial study population were statistically significant differences between responders and nonresponders observed. All other analyzed patient- and defect-specific parameters did not reach statistical significance.

BMI, body mass index; OCD, osteochondritis dissecans.

\*Statistically significant difference.





**Fig 5.** Magnetic resonance imaging follow-up over a period of 10 years (y) in a 24-year-old female patient who underwent autologous chondrocyte implantation of the medial femoral condyle.

The results of the VAS scale also showed a statistically significant improvement. At rest, the patients assessed their pain preoperatively at an average score of

3.7 (range, 0-10). At 10 years postoperatively, the pain experience was rated at a mean score of 1.4 (range, 0-5) ( $P < .001$ ) (Fig 3).

The subjective assessment of pain on movement (VAS) showed improvement from an average score of 7.7 (range, 0-10) preoperatively to 3.7 (range, 0-8) at 10 years after third-generation ACI ( $P < .001$ ) (Fig 4). A slight minimal downward tendency, which was not statistically significant, was identified over the course of 10 years in absolute VAS scores.

In line with other studies, our study used an IKDC score greater than 20.5 for additional responder analysis.<sup>17,18</sup> Twenty-one patients showed an IKDC score increase of more than 20.5 points (thus exceeding the aforementioned MCID of 16.7 points), resulting in a responder rate of 70% at 10 years postoperatively. Differences in patient-specific and defect-associated criteria regarding the responder rate are summarized in Table 4.

### MRI Results

The average MOCART score of the 13 evaluated patients was 59.2 points (range, 20-100 points) after 10 years. The remaining patients could not be examined because of limited patient participation and compliance (with reasons including travel distance or time expense). When the individual diagnostic criteria were analyzed, 6 of the 13 patients (46.2%) showed complete defect filling. Hypertrophy was noted in 4 patients (30.7%). In 2 patients (15.4%), incomplete filling of greater than 50% of the defect was present, and only 1 patient (7.7%) showed incomplete defect filling of less than 50% compared with the healthy surrounding cartilage. No uncovered subchondral bone was observed in any patient (0%). The implant was fully integrated into the surrounding cartilage in most cases (8 of 13 patients, 61.5%). In 2 of the investigated cartilage defects (15.4%), a demarcating border between the implant and joint cartilage was visible (Fig 5).

### Complications

During the postoperative course, a total of 7 patients had complications requiring revision; these included pain, arthrofibrosis (3 cases), partial graft deficiency with small cartilage defects (2 cases), and bone marrow edema with cyst. The overall revision rate was 23.3%. These patients were treated by diagnostic arthroscopy (no need for intervention), arthroscopic arthrolysis (in cases with limitation of flexion postoperatively), microfracturing, retrograde drilling, and iloprost therapy.

### Discussion

The major findings of this study are that 10 years after surgery, all clinical scores showed a significant improvement compared with the preoperative situation. The MRI results confirmed sufficient graft integration in most of the patients evaluated.

Third-generation ACI is an established, effective, reliable surgical method for the treatment of large cartilage defects of the knee joint.<sup>14</sup> Short- and

medium-term results are well described,<sup>4-7</sup> but data for the long-term development of the surgical results are still limited. With 30 patients in our study, this is one of the first as well as the largest long-term studies to describe clinical and radiologic results after third-generation ACI.

Three studies on long-term results after third-generation ACI have been published.<sup>11-13</sup> Aldrian et al.<sup>11</sup> showed an improvement in clinical scores, as well as high-quality repair tissue, on MRI controls in 16 patients at 10 years postoperatively. For implantation, either a type I–type III collagen bilayer membrane (MACI; Genzyme) or a hyaluronic acid–based scaffold (Hyalograft-C; Fidia Advanced Biopolymers) was used. Gille et al.<sup>12</sup> reported satisfactory clinical results for both pain relief and rehabilitation of knee function in 14 patients with a follow-up period of at least 15 years. A type I–type III collagen matrix (Chondro-Gide; Geistlich Pharma) was used for ACI. Kreuz et al.<sup>13</sup> found significant improvements in patient satisfaction, clinical outcome, and knee function 12 years after transplantation in a study population of 21 patients treated with BioSeed-C (BioTissue Technologies). In addition, this study reported normal or almost normal values in more than 70% of patients in the morphologic evaluation of 14 patients by MRI.

In our study, the patient-related outcomes of 30 patients after third-generation ACI have been evaluated over a period of 10 years. The data collected during the 10-year period after third-generation ACI confirm long-term stability and sustainable clinical outcomes in the largest number of patient cases evaluated so far.

In this study, the morphologic assessment of the knee joint and especially the knee cartilage was performed using MRI. As described in the literature, the sequences used here are particularly suitable for imaging articular cartilage and represent an established variant for measurement in the knee joint.<sup>21-23</sup> For the evaluation, the MOCART score was used. The MOCART value has proved to be a reliable and reproducible evaluation method for long-term follow-up<sup>24</sup> and is frequently used for the evaluation of articular cartilage.<sup>25-27</sup> It represents a score with low interobserver variability.<sup>19</sup>

Regarding medium-term data, clinically good outcomes after third-generation ACI have already been shown in many studies.<sup>4-6</sup> Results of previous long-term studies showed significant improvements in clinical and radiologic outcomes compared with the preoperative condition. However, different trends were observed in the long-term evaluation of such data.

Whereas Aldrian et al.<sup>11</sup> reported a slight downward tendency for all clinical scores after 5 years, Gille et al.<sup>12</sup> found a further increase in clinical scores over the long-term course. None of these findings were statistically significant. This study—similarly to that of Kreuz

et al.<sup>13</sup>—showed homogeneous development in the long-term evaluation.

In a 2-year follow-up study of 137 patients, Saris et al.<sup>28</sup> presented a significantly better response rate for ACI than for microfracture (87.5% vs 68.1%). Crawford et al.<sup>29</sup> showed response rates of 76.2% (16 of 21) at 12 months and 78.9% (15 of 19) at 24 months after ACI. Over a 10-year period, our study showed a response rate of 70.0% for 30 evaluated patients. Some patients who were lost to follow-up were included in a separate analysis. In this analysis of the initial study population (54 patients), a response rate of 63.0% (34 of 54 patients) was obtained from the preoperative condition to the endpoint of the measurement. Statistically significant differences between responders and nonresponders were observed only regarding cooperation for the 10-year long-term study population and body mass index for the initial study population. All other patient- and defect-specific parameters analyzed did not reach statistical significance (Table 4).

Several clinical trials have confirmed the long-term success of first-generation ACI.<sup>30-33</sup> Over a period of more than 10 years, good or acceptable clinical results were reported regarding patient satisfaction, pain reduction, and improvement in knee function. Similarly to the first long-term studies of third-generation ACI,<sup>11</sup> the studies of first-generation ACI showed a slight worsening between mid- and long-term evaluations.<sup>34</sup> IKDC assessment in our study showed a significant improvement in knee function, which is in line with the results of earlier studies. In addition, we were able to show a significant improvement in the subjective evaluation of pain at rest and on movement according to the VAS scores. A downward trend between medium- and long-term evaluations was not observed. As already well documented for first-generation ACI,<sup>30,35,36</sup> we were able to show a sustained and reliable clinical result for third-generation ACI 10 years after the procedure.

In this study, the clinical results of 30 patients and the radiographic results of 13 patients were evaluated 10 years after third-generation ACI. This study shows significant improvements in all clinical outcome parameters 10 years postoperatively and shows a responder rate of 70% of treated patients over the long term. The data collected 10 years after third-generation ACI therefore confirm long-term stability and sustained clinical outcomes and provide further evidence that third-generation ACI is a suitable surgical method for the treatment of focal cartilage defects of the knee.

### Limitations

One limitation of the study is the relatively low number of cases without a comparison group. Another limitation is the inability to follow up patients over the full study period with a relatively high rate of loss to

follow-up. In addition, heterogeneity existed in the follow-up dates and the treated cartilage defects, with various defect sizes and previous surgical procedures. In short- to mid-term follow-up studies, partly histologic analyses could be performed to show the filling and integration of the graft, as well as the formation of hyaline-like repair tissue.<sup>4,37</sup> Because of their invasiveness, such examinations were not performed in long-term assessments and represent a limitation of our study. Finally, the number of cases with MRI after 10 years is low. Because the results of this study are also based on a relatively small follow-up study population of 13 patients, a larger number of cases may have to be assessed to prove a correlation between MRI and clinical outcomes.

### Conclusions

The clinical and radiologic findings of this study show that third-generation ACI is a suitable and effective option in the treatment of full-thickness cartilage defects of the knee. At 10 years after surgery, third-generation ACI shows stable results and leads to significant improvement in all clinical outcome parameters. Despite these results, revision surgery after third-generation ACI is common and was needed in 23% of patients in this study.

### References

1. Brittberg M, Lindahl A, 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.
2. Anders S, Schaumburger J, Schubert T, Grifka J, Behrens P. Matrix-associated autologous chondrocyte transplantation (MACT). Minimally invasive technique in the knee. *Oper Orthop Traumatol* 2008;20:208-219 [in German].
3. Behrens P, Bitter T, Kurz B, Russlies M. Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI)—5-Year follow-up. *Knee* 2006;13:194-202.
4. Ossendorf C, Kaps C, Kreuz PC, Burmester GR, Sittlinger M, Erggelet C. Treatment of posttraumatic and focal osteoarthritic cartilage defects of the knee with autologous polymer-based three-dimensional chondrocyte grafts: 2-Year clinical results. *Arthritis Res Ther* 2007;9:R41.
5. Kreuz PC, Muller S, Freymann U, et al. Repair of focal cartilage defects with scaffold-assisted autologous chondrocyte grafts: Clinical and biomechanical results 48 months after transplantation. *Am J Sports Med* 2011;39:1697-1705.
6. Kreuz PC, Muller S, Ossendorf C, Kaps C, Erggelet C. Treatment of focal degenerative cartilage defects with polymer-based autologous chondrocyte grafts: Four-year clinical results. *Arthritis Res Ther* 2009;11:R33.
7. Zak L, Albrecht C, Wondrasch B, et al. Results 2 years after matrix-associated autologous chondrocyte

- transplantation using the Novocart 3D scaffold: An analysis of clinical and radiological data. *Am J Sports Med* 2014;42:1618-1627.
8. Vasiliadis HS, Wasiak J, Salanti G. Autologous chondrocyte implantation for the treatment of cartilage lesions of the knee: A systematic review of randomized studies. *Knee Surg Sports Traumatol Arthrosc* 2010;18:1645-1655.
  9. Basad E, Ishaque B, 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 Arthrosc* 2010;18:519-527.
  10. Vasiliadis HS, Lindahl A, Georgoulis AD, Peterson L. Malalignment and cartilage lesions in the patellofemoral joint treated with autologous chondrocyte implantation. *Knee Surg Sports Traumatol Arthrosc* 2011;19:452-457.
  11. Aldrian S, Zak L, Wondrasch B, et al. Clinical and radiological long-term outcomes after matrix-induced autologous chondrocyte transplantation: A prospective follow-up at a minimum of 10 years. *Am J Sports Med* 2014;42:2680-2688.
  12. Gille J, Behrens P, Schulz AP, Oheim R, Kienast B. Matrix-associated autologous chondrocyte implantation: A clinical follow-up at 15 years. *Cartilage* 2016;7:309-315.
  13. Kreuz PC, Kalkreuth RH, Niemeyer P, Uhl M, Erggelet C. Long-term clinical and MRI results of matrix-assisted autologous chondrocyte implantation for articular cartilage defects of the knee. *Cartilage* 2019;10:305-313.
  14. Niemeyer P, Albrecht D, Andereya S, et al. Autologous chondrocyte implantation (ACI) for cartilage defects of the knee: A guideline by the working group "Clinical Tissue Regeneration" of the German Society of Orthopaedics and Trauma (DGOU). *Knee* 2016;23:426-435.
  15. Niethammer TR, Valentin S, Ficklscherer A, Gulecyuz M, Pietschmann M, Muller P. Revision surgery after third generation autologous chondrocyte implantation in the knee. *Int Orthop* 2015;39:1615-1622.
  16. Harris JD, Brand JC, Cote MP, Faucett SC, Dhawan A. Research pearls: The significance of statistics and perils of pooling. Part 1: Clinical versus statistical significance. *Arthroscopy* 2017;33:1102-1112.
  17. Roos EM, Engelhart L, Ranstam J, et al. ICRS recommendation document: Patient-reported outcome instruments for use in patients with articular cartilage defects. *Cartilage* 2011;2:122-136.
  18. Irrgang JJ, Anderson AF, Boland AL, et al. Responsiveness of the International Knee Documentation Committee subjective knee form. *Am J Sports Med* 2006;34:1567-1573.
  19. Marlovits S, Singer P, Zeller P, Mandl I, Haller J, Trattnig S. Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: Determination of interobserver variability and correlation to clinical outcome after 2 years. *Eur J Radiol* 2006;57:16-23.
  20. Niethammer TR, Valentin S, Ficklscherer A, Gulecyuz MF, Pietschmann MF, Muller PE. Revision surgery after third generation autologous chondrocyte implantation in the knee. *Int Orthop* 2015;39:1615-1622.
  21. Eckstein F, Sittek H, Milz S, Putz R, Reiser M. The morphology of articular cartilage assessed by magnetic resonance imaging (MRI). Reproducibility and anatomical correlation. *Surg Radiol Anat* 1994;16:429-438.
  22. Graichen H, Springer V, Flaman T, et al. Validation of high-resolution water-excitation magnetic resonance imaging for quantitative assessment of thin cartilage layers. *Osteoarthritis Cartilage* 2000;8:106-114.
  23. Tins BJ, McCall IW, Takahashi T, et al. Autologous chondrocyte implantation in knee joint: MR imaging and histologic features at 1-year follow-up. *Radiology* 2005;234:501-508.
  24. Trattnig S, Millington SA, Szomolanyi P, Marlovits S. MR imaging of osteochondral grafts and autologous chondrocyte implantation. *Eur Radiol* 2007;17:103-118.
  25. Shimozone Y, Donders JCE, Yasui Y, et al. Effect of the containment type on clinical outcomes in osteochondral lesions of the talus treated with autologous osteochondral transplantation. *Am J Sports Med* 2018;46:2096-2102.
  26. Perdisa F, Kon E, Sessa A, et al. Treatment of knee osteochondritis dissecans with a cell-free biomimetic osteochondral scaffold: Clinical and imaging findings at midterm follow-up. *Am J Sports Med* 2018;46:314-321.
  27. Ebert JR, Schneider A, Fallon M, Wood DJ, Janes GC. A comparison of 2-year outcomes in patients undergoing tibiofemoral or patellofemoral matrix-induced autologous chondrocyte implantation. *Am J Sports Med* 2017;45:3243-3253.
  28. 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.
  29. 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 Am* 2012;94:979-989.
  30. Peterson L, Vasiliadis HS, Brittberg M, Lindahl A. Autologous chondrocyte implantation: A long-term follow-up. *Am J Sports Med* 2010;38:1117-1124.
  31. Niemeyer P, Porichis S, Steinwachs M, et al. Long-term outcomes after first-generation autologous chondrocyte implantation for cartilage defects of the knee. *Am J Sports Med* 2014;42:150-157.
  32. Pelissier A, Boyer P, Boussetta Y, et al. Satisfactory long-term MRI after autologous chondrocyte implantation at the knee. *Knee Surg Sports Traumatol Arthrosc* 2014;22:2007-2012.
  33. Rosa D, Balato G, Ciaramella G, Soscia E, Improta G, Triassi M. Long-term clinical results and MRI changes after autologous chondrocyte implantation in the knee of young and active middle aged patients. *J Orthop Traumatol* 2016;17:55-62.

34. Moradi B, Schonit E, Nierhoff C, et al. First-generation autologous chondrocyte implantation in patients with cartilage defects of the knee: 7 to 14 years' clinical and magnetic resonance imaging follow-up evaluation. *Arthroscopy* 2012;28:1851-1861.
35. Peterson L, Brittberg M, Kiviranta I, Akerlund EL, Lindahl A. Autologous chondrocyte transplantation. Biomechanics and long-term durability. *Am J Sports Med* 2002;30:2-12.
36. Peterson L, Minas T, Brittberg M, Nilsson A, Sjogren-Jansson E, Lindahl A. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clin Orthop Relat Res* 2000;212-234.
37. Niethammer TR, Limbrunner K, Betz OB, et al. Analysis of the autologous chondrocyte quality of matrix-based autologous chondrocyte implantation in the knee joint. *Int Orthop* 2016;40:205-212.

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## Third generation autologous chondrocyte implantation is a good treatment option for athletic persons

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### Abstract

**Purpose** Autologous chondrocyte implantation is an established method for the treatment of joint cartilage damage. However, to date it has not been established that autologous chondrocyte implantation is an appropriate procedure for cartilage defects therapy in athletic persons. The aim of this study is to analyze if third-generation autologous chondrocyte implantation is an appropriate treatment for athletic persons with full cartilage defect of the knee joints.

**Methods** A total of 84 patients were treated with third-generation autologous chondrocyte implantation (NOVOCART<sup>®</sup> 3D). The mean follow-up time was 8 years (5–14). Sports activity was measured via UCLA Activity Score and Tegner Activity Scale before the onset of knee pain and postoperatively in an annual clinical evaluation. 41 athletic persons and 43 non-athletic persons (UCLA-Cut-off: 7; Tegner Activity Scale-Cut-off: 4) were analyzed. Patient reported outcomes were captured using IKDC subjective, KOOS, Lysholm score and VAS score on movement.

**Results** Patient reported outcomes (IKDC, VAS at rest, VAS on movement) showed significant improvement ( $p < 0.001$ ) postoperatively. Athletic persons demonstrated significantly better results than non-athletic persons in the analyzed outcome scores (IKDC:  $p < 0.01$ , KOOS:  $p < 0.01$ , Lysholm score:  $p < 0.01$ ). 96.4% of the patients were able to return to sport and over 50% returned or surpassed their preinjury sports level. The remaining patients were downgraded by a median of two points on the UCLA- and 2.5 on the Tegner Activity Scale. A shift from high-impact sports to active events and moderate or mild activities was found. Furthermore, it was shown that preoperative UCLA score and Tegner Activity Scale correlated significantly with the patient reported outcome postoperatively.

**Conclusion** Autologous chondrocyte implantation is a suitable treatment option for athletic persons with full-thickness cartilage defects in the knee. The return to sports activity is possible, but includes a shift from high-impact sports to less strenuous activities.

**Keywords** Cartilage defect · ACI · Knee · Sports · Return to sport

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## Introduction

Autologous chondrocyte implantation (ACI) is well established as a reliable method for the treatment of joint cartilage damage. It was first described in 1994 by Brittberg et al. [6] and subsequently reported on by several other authors [25, 26] using a periosteal flap (ACI-P). Third generation ACI uses a collagen I/III scaffold instead of a periosteal flap (ACI-M) [4]. Short- to medium-term follow-ups demonstrated that the surgical procedure is effective and reliable [22, 32, 41]. Clinical results and joint function as well as defect filling in magnetic resonance imaging provide convincing results in the treatment of severe cartilage defects.

The first data from long-term studies on the third generation ACI have confirmed the promising results from the first generation ACI [1, 15, 21]. However, up to now it has not been established whether ACI is an adequate procedure for athletic persons with a high level of sports activity. Returning to the pre-injured sports level is an important goal for many of these patients [17, 28].

Return to sport and postoperative physical activity are two of the main reasons why patients decide to undergo surgery [18]. Although the resumption of sports activities in the short to medium term is well described for the first- and second-generation of ACI, to date there is a lack of data on the medium- to long-term course after third-generation ACI. The return to the preoperative sports level of the patients as a measure of success after third-generation ACI had also not been investigated. In the short term, sports activity emerged as a possible influencing and prognostic factor.

The aim of this study was to analyze, if third-generation ACI is an appropriate therapy for athletic persons with full cartilage defect of the knee joints. The importance of pre- and postoperative sports activity as a possible influencing factor in the medium to long term follow-up also needed to be evaluated. It was hypothesized that third-generation ACI is a suitable therapy option for athletic persons undergoing surgery. It was also hypothesized that both preoperative and postoperative sports activity have a positive effect on the patient reported outcome after third-generation ACI.

## Materials and methods

With an institutional review board approval from Ludwig-Maximilians-Universität München (ID 344-12), a total of 84 patients were included in the study. The follow-up time was from 5 to 14 years, with an average of 8.0 years.

**Table 1** Characteristics of the patient population (sec (second defects), MPFL (medial patella femoral ligament), HTO (high tibial osteotomy))

| Characteristics                           | Patient cohort                         |
|-------------------------------------------|----------------------------------------|
| Total number of patients, <i>n</i>        | 84                                     |
| Age, years                                |                                        |
| Mean (range)                              | 35.2 (13–66)                           |
| Median                                    | 38.5                                   |
| Sex, <i>n</i> (%)                         |                                        |
| Male                                      | 47 (56.0)                              |
| Female                                    | 37 (44.0)                              |
| BMI, kg/m <sup>2</sup>                    |                                        |
| Mean (range)                              | 26.2 (19.0–35.3)                       |
| Median                                    | 26.0                                   |
| Smokers, <i>n</i> (%)                     |                                        |
| Smokers                                   | 22 (26.2)                              |
| Non-smokers                               | 59 (70.2)                              |
| Unknown                                   | 3 (3.6)                                |
| Defects                                   |                                        |
| Number of lesions, <i>n</i> (%)           |                                        |
| One defect                                | 68 (81)                                |
| Two defects                               | 16 (19)                                |
| Defect size, cm <sup>2</sup>              |                                        |
| Mean (range)                              | 5.1 (2.0–12.0) (sec. <sup>1</sup> 4.5) |
| Median                                    | 5.0                                    |
| Defect localisation, <i>n</i> (%)         |                                        |
| Femoral condyle (med, lat)                | 42 (50.0)                              |
| Patellar                                  | 37 (44.0)                              |
| Trochlea                                  | 5 (6.0)                                |
| Etiology, <i>n</i> (%)                    |                                        |
| OCD                                       | 12 (14.3)                              |
| Trauma (< 1 year ago)                     | 8 (9.5)                                |
| Trauma (> 1 year ago)                     | 25 (29.8)                              |
| Unknown                                   | 39 (46.4)                              |
| ICRS Classification                       | III–IV                                 |
| Previous surgical procedure, <i>n</i> (%) |                                        |
| No                                        | 57 (67.9)                              |
| Microfracturing                           | 13 (15.5)                              |
| Cartilage shaving                         | 2 (2.4)                                |
| Periosteal ACI                            | 3 (3.6)                                |
| HTO                                       | 3 (3.6)                                |
| Pridie drilling                           | 3 (3.6)                                |
| Refixation of flake                       | 1 (1.2)                                |
| MPFL reconstruction                       | 1 (1.2)                                |
| Osteochondral transfer                    | 1 (1.2)                                |
| Concomitant surgery, <i>n</i> (%)         |                                        |
| No                                        | 52 (71.9)                              |
| MPFL reconstruction                       | 13 (15.5)                              |
| HTO                                       | 4 (4.8)                                |
| Bone grafting                             | 8 (9.5)                                |
| Meniscus transplant (allogene)            | 2 (2.4)                                |
| Anterior cruciate ligament reconstruction | 5 (6.0)                                |

Patients with a full thickness cartilage defect ICRS grade III–IV of the knee joint (femoral, tibial, patella) were included. All demographic data are summarized in Table 1. Recommendations of the DGOU Clinical Tissue Regeneration Working Group [30] were used for the indication of cartilage therapy. Criteria for exclusion include axial malalignment  $> 5^\circ$ , severe malrotation, advanced osteoarthritis  $>$  grade II, knee instability, sub-totally resected meniscus in the affected compartment meniscus and corresponding bipolar cartilage defects. The study was performed as a single-center trial and all defects were treated in the University Hospital, LMU Munich.

### Surgical technique and rehabilitation

In an arthroscopic operation, two osteochondral cylinders (diameter 3 mm, thickness: 5–10 mm) were obtained from an unloaded zone of the knee joint. They were then sent to the manufacturer (TETEC GmbH, Reutlingen, Germany). A collagen I/III biphasic scaffold was used and the graft was completed after a cultivation time of 3–4 weeks. The cell-seeded scaffold (NOVOCART® 3D) was implanted using a minimally invasive parapatellar knee arthrotomy. The cartilage defects were debrided with curettes to create a stable rim of healthy surrounding joint cartilage. Subsequently, the cartilage graft was precisely inserted into the prepared cartilage defect and finally attached to the healthy joint cartilage with resorbable suture material without fibrin glue.

Initially, patients were ordered to rest in bed for 24 h. From the second postoperative day, the affected joint was treated with CPM (Continuous Passive Movement) therapy. For femoral cartilage defects, a partial load of 20 kg was recommended for 6 weeks. In patellar cartilage defects flexion was limited for 6 weeks. During these 6 weeks, flexion was continuously increased every 2 weeks (week 1–2 Extension/Flexion 0/0/20°, week 3–4: 0/0/45°, week 5–6: 0/0/60°).

### Patient reported outcome

A questionnaire was completed preoperatively. Sports activity before knee pain was assessed. The patients were classified according to the UCLA [3] activity score and the Tegner Activity Scale [39]. Accordingly, patients were divided into two groups on the basis of the UCLA sports activity and Tegner Activity Scale before knee damage. Patients with a UCLA score of 7 and a Tegner Activity Scale of 4 or smaller were classified as “non-athletic persons”. Patients with a UCLA score larger than 7 and a Tegner Activity Scale larger than 4 were classified as “athletic persons”. 43 patients were assigned to the non-athletic persons group and 41 to the athletic persons group.

Patient related outcomes were evaluated after 12 and 24 months followed by annual evaluations. The following

scores were obtained: IKDC, KOOS, Lysholm and visual analogue scale (VAS) on movement.

### Statistical analysis

The statistical program SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) was used for the statistical evaluation of the data. Prior to this study a power analysis was performed to determine the required number of patients. Powerandsamplesize.com 2013–2019 (HyLown Consulting LLC—Atlanta, GA) was used. Data from a pilot study showed an IKDC score of 64.6 (SD 21.4) for athletic persons, whereas non-athletic persons scored significantly lower with 48.5 (SD 19.2). In order to achieve a power of 80% and a level of significance  $p < 0.05$ , a number of patients of 25 for the group of non-athletic and 25 for the group of athletic persons was estimated. The Kolmogorov–Smirnov test was used to test for normal distribution. Depending on the test result, either the combined  $t$  test or the Wilcoxon test was used to identify differences between the pre- and post-operative scores of the entire patient cohort. Additional analyses tested non-athletic and athletic persons for differences in the surgical outcome. Depending on the Kolmogorov–Smirnov test either an unrelated  $t$  test or the Mann–Whitney- $U$  test was performed. Finally, correlation analyses between UCLA-Scores respectively Tegner Activity Scale and clinical outcome parameters were performed using the Spearman-correlation.

### Results

All scores showed significant improvement (Table 2). In total, IKDC showed a significant ( $p < 0.001$ ) increase from an average of 38.4 preoperatively to 61.6 8 years postoperatively. The results of the VAS scale also showed a significant improvement. At rest, the patients rated their pain preoperatively with an average of 3.0. At the last postoperative examination, the pain sensation was rated with 1.4 ( $p < 0.001$ ). The pain assessment on movement also decreased from an average of 6.2 preoperatively to 3.5 8 years after third-generation ACI ( $p < 0.001$ ).

**Table 2** Regarding the whole patient cohort, third-generation ACI showed highly significant improvement on average 8 years after surgery in all outcome parameters assessed

|                 | Preoperative    | Postoperative   | <i>P</i> value |
|-----------------|-----------------|-----------------|----------------|
| IKDC            | 38.7 $\pm$ 20.8 | 61.6 $\pm$ 20.7 | 0.000          |
| VAS at rest     | 3.0 $\pm$ 3.1   | 1.4 $\pm$ 2.0   | 0.000          |
| VAS on movement | 6.1 $\pm$ 3.1   | 3.5 $\pm$ 2.7   | 0.000          |



Microfracturing was necessary in seven cases with partial insufficiency in the border zone and a high tibial osteotomy was performed because of a complete insufficiency of the ACI graft. Because of arthrofibrosis, we performed an arthrolysis in four cases. In two cases, a diagnostic knee arthroscopy was performed because of persistent pain without intervention. In three cases, a retrograde drilling was performed because of a symptomatic bone marrow edema.

The patient groups categorized according to the UCLA and the Tegner Activity Scale were examined for interfering factors (Table 3). Subsequently, the clinical outcomes of the two groups were compared.

In all analyzed outcome scores, the athletic persons scored significantly better than the non-athletic persons (Table 3). In the IKDC score, non-athletic persons showed an average outcome of 54.2 points. Athletic persons showed significantly better results with 69.4 points ( $p < 0.01$ ) (Fig. 1).

The outcome in the KOOS and in the Lysholm score also showed significant improved results. The KOOS score of the non-athletic persons differed with 67.4 from the score of the athletic persons, which reached a value of 78.9 ( $p < 0.01$ ). Similarly, non-athletic persons showed lower Lysholm scores with 66.4 than athletic persons with 78.3 ( $p < 0.01$ ).

In addition, the pain assessment on movement was analyzed postoperatively. Non-athletic persons assessed their pain on movement 8 years postoperatively with an average of 4.2, whereas athletic persons on movement reported only a VAS score of 2.7 ( $p < 0.05$ ) (Fig. 2).

For the entire patient cohort, sports activities were documented before knee pain and postoperatively. The median sports level before knee pain was 7 for the UCLA score and 4 for the Tegner Activity Scale. Eight years postoperatively the patients still reported a median UCLA score of 7 and a median Tegner Activity Scale of 4. In total, 81 of 84 patients were able to participate in some kind of sports activity ranging from mild activities to high impact sports. This results in a return to sport rate of 96.4%. 50 patients (59.5%) were able to participate in the same type of sports postoperatively. 44 patients (52.4%) achieved at least the same UCLA-score and 48 patients (57.1%) at least the same Tegner Activity Scale postoperatively as before knee pain. Patients who did not manage to return to their level before knee pain deteriorated by a median of two points on the UCLA scale and 2.5 on the Tegner Activity Scale. The types of sports performed changed over the time. While postoperatively fewer patients performed high-impact sports than before knee pain, there was an increase in patients who performed active events and moderate or mild activities (Table 4). Only 42.4% of the patients performing high impact sports preoperatively were able to return to this level (Fig. 3).

Correlation analyses were carried out to analyze the influence of pre- and postoperative sports activity. The

preoperative UCLA score as well as the preoperative Tegner Activity Scale correlated significantly with the patient reported outcome postoperatively. The postoperative UCLA score and Tegner Activity Scale showed significant to highly significant correlation with all patient reported outcome scores postoperatively.

## Discussion

The major finding of the study is that third-generation ACI is a suitable treatment option for athletic persons with full-thickness cartilage defects of the knee joint, with a probable return to sports activity, though often a shift from high-impact sports to active events and moderate or mild activities postoperatively. While sports activity after first- and second-generation ACI is well described, it was still not clear if ACI is a suitable procedure for athletic persons with cartilage defects.

Kreuz et al. [23] conducted a prospective study concerning the importance of sports in cartilage regeneration after autologous chondrocyte implantation. The patients were treated with ACI using a periosteal patch. The authors concluded that physical activity and in particular moderate sports are an important part of postoperative rehabilitation and should be carried out for at least 2–3 years after surgery.

Krych et al. [24] reported on return to sport after the surgical management of articular cartilage lesions in the knee on a meta-analysis basis. This meta-analysis concluded an overall return to sport rate of 76%, with highest rates after osteochondral autograft transfer (93%) followed by osteochondral allograft transplantation (88%), ACI (82%) and microfracture (58%). ACI had the highest rehabilitation time.

Kon et al. [20] conducted a prospective comparative study of arthroscopic second-generation ACI versus microfracture concerning articular cartilage treatment in 41 high-level male soccer players. They concluded that ACI may delay the return to competition, while offering more durable clinical results.

Pestka et al. [35] analyzed the return to sports activity and work after second-generation ACI. The conclusion of this study is that satisfactory results for everyday activities can be achieved and that the return to low- and moderate-intensity activities is realistic in most cases. However, the return rate to highly stressful activities was low.

Erdle et al. [14] published a study regarding sporting activity following first-generation ACI. They concluded that the premorbid level of sports and recreational activity could not be achieved 11 years after first generation ACI.

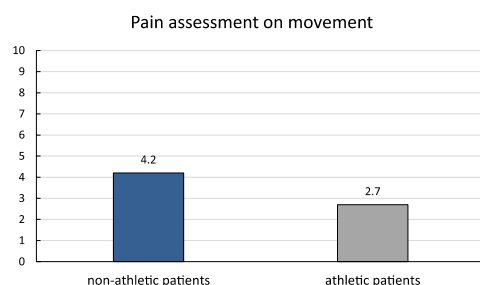
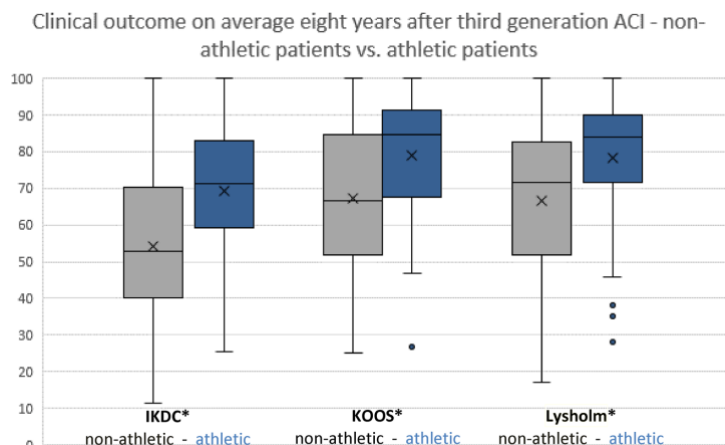
In the present study, the patient reported outcomes of “athletic persons” and “non-athletic persons” after third generation ACI were analyzed to determine if third generation

**Table 3** Group-analysis and clinical outcome—athletic persons vs. non-athletic persons

|                                                    | Non-athletic persons    | Athletic persons        | <i>p</i> value |
|----------------------------------------------------|-------------------------|-------------------------|----------------|
| Age, years (range)                                 | 38.2 (17–66)            | 32.1 (13–57)            | 0.021*         |
| Side, <i>n</i>                                     |                         |                         |                |
| Right                                              | 22                      | 19                      | n.s            |
| Left                                               | 21                      | 22                      |                |
| Sex, <i>n</i>                                      |                         |                         |                |
| Male                                               | 20                      | 27                      | n.s            |
| Female                                             | 23                      | 14                      |                |
| Smoker, <i>n</i>                                   |                         |                         |                |
| Smoker                                             | 12                      | 10                      | n.s            |
| Non-smoker                                         | 31                      | 29                      |                |
| BMI, kg/cm <sup>2</sup> (range)                    | 27.5 (19.6–35.0)        | 24.8 (19.0–35.3)        | 0.002*         |
| Number of lesions, <i>n</i>                        |                         |                         |                |
| One defect                                         | 36                      | 32                      | n.s            |
| Two defects                                        | 7                       | 9                       |                |
| Defect localization, 1st; 2nd defect <i>n</i> (%)  |                         |                         |                |
| Medial femoral                                     | 21 (48.8); 1 (2.3)      | 16 (39.0); 3 (33.3)     | n.s            |
| Lateral femoral                                    | 2 (4.7); 0 (0)          | 5 (12.2); 1 (11.1)      |                |
| Patellar                                           | 19 (44.2); 2(4.7)       | 17 (41.5); 0 (0)        |                |
| Trochlear                                          | 1 (2.3); 4 (9.3)        | 3 (7.3); 4 (44.4)       |                |
| Tibial                                             | 0 (0); 0 (0)            | 0 (0); 1 (11.1)         |                |
| Defect-size, 1st; 2nd cm <sup>2</sup> mean (range) | 5.2 (2–10); 3.4 (1.5–7) | 5.6 (3–12); 3.3 (0.5–5) | n.s            |
| Etiology, <i>n</i>                                 |                         |                         |                |
| OCD                                                | 5                       | 7                       | n.s            |
| Acute trauma                                       | 3                       | 5                       |                |
| Old trauma                                         | 11                      | 14                      |                |
| Unknown                                            | 24                      | 15                      |                |
| Concomitant surgery, <i>n</i>                      |                         |                         |                |
| Yes                                                | 15                      | 17                      | n.s            |
| No                                                 | 28                      | 24                      |                |
| Complications, <i>n</i>                            |                         |                         |                |
| Yes                                                | 10                      | 8                       | n.s            |
| No                                                 | 33                      | 33                      |                |
| Follow-up, years (range)                           | 7.7 (5–13)              | 8.4 (5–14)              | n.s            |
| Clinical outcome                                   |                         |                         |                |
| IKDC                                               | 54.2 ± 21.0             | 69.4 ± 17.4             | 0.001          |
| KOOS                                               | 67.4 ± 20.2             | 78.9 ± 15.9             | 0.007          |
| KOOS symptoms                                      | 52.1 ± 17.5             | 58.5 ± 12.6             | n.s            |
| KOOS pain                                          | 69.7 ± 21.2             | 80.0 ± 16.8             | 0.038          |
| KOOS ADL                                           | 73.3 ± 22.0             | 86.2 ± 18.2             | 0.001          |
| KOOS Sport/Rec                                     | 45.4 ± 32.5             | 63.5 ± 27.5             | 0.016          |
| KOOS QOL                                           | 4.2 ± 2.9               | 58.6 ± 22.3             | 0.040          |
| Lysholm Score                                      | 66.4 ± 23.0             | 78.3 ± 18.6             | 0.006          |
| VAS on movement                                    | 4.2 ± 2.9               | 2.7 ± 2.3               | 0.019          |

The analysis of UCLA- and Tegner Activity Scale-Cut-off showed no significant differences in most of the patient- or defect-specific factors analyzed. This confirms very balanced patient cohorts in this regard. For all clinical outcome parameters assessed, the more athletic group showed significantly better results post-operatively. Athletic persons however were significantly younger and had a smaller BMI (\*)

**Fig. 1** Clinical outcomes on average 8 years after third generation ACI—non-athletic persons vs. athletic persons. The outcome parameters IKDC, KOOS and Lysholm score showed significant\* ( $p < 0.01$ ) differences between the athletic persons and the non-athletic persons group



**Fig. 2** Pain assessment on average 8 years after third-generation ACI—non-athletic vs. athletic persons. Significant differences for the pain assessment on movement between non-athletic and athletic persons were present ( $p < 0.05$ )

**Table 4** Change in types of sports participated

| Types of sports                   | Before onset of pain | postoperatively |
|-----------------------------------|----------------------|-----------------|
| Inactive, <i>n</i> (%)            | 5 (6.0)              | 3 (3.6)         |
| Mild activities, <i>n</i> (%)     | 0 (0.0)              | 7 (8.3)         |
| Moderate activities, <i>n</i> (%) | 14 (16.7)            | 18 (21.4)       |
| Active events, <i>n</i> (%)       | 32 (38.1)            | 39 (46.4)       |
| High impact sports, <i>n</i> (%)  | 33 (39.3)            | 17 (20.2)       |

A shift from high-impact sports to active events and moderate or mild activities was present over the course of time

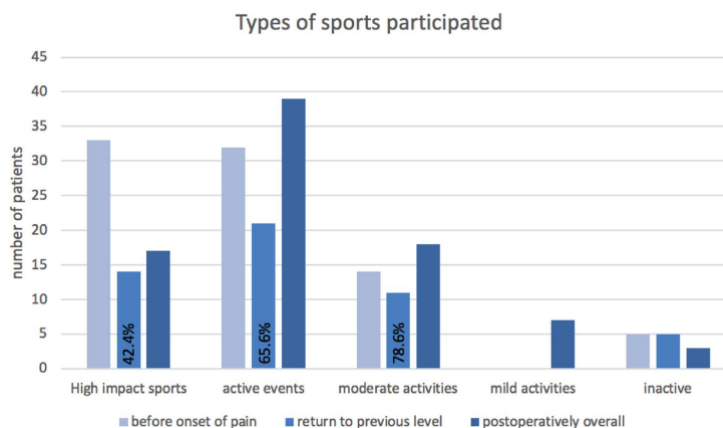
ACI is a suitable treatment option for athletic persons and result in a comparable level of activity before and after knee pain. The UCLA activity score and the Tegner Activity Scale were used to classify patients according to their sporting activity. The UCLA score is a well-established

and widely used score for the assessment of sports activity on a scale of 1 (“completely inactive, dependent on others and unable to leave home”) to 10 (“regularly participate in impact sports”) [11, 29]. The Tegner Activity Scale was first described in 1985 and is a highly recognized and frequently used patient-administered activity rating system for patients with various knee disorders [5, 9]. The clinical outcome of this study was measured using several well-established and widely used parameters such as IKDC [19], KOOS [10, 38] and Lysholm score [5, 9, 37] as well as visual analog scales for pain assessment [8].

The UCLA score and Tegner Activity Scale in this study showed no difference between the median before the onset of pain to eight years postoperatively. 96.4% of the patients returned to sport and more than 50% were able to even regain their preinjury sporting level. The systematic review article by Campbell et al. [7] regarding short- to medium-term return to sport showed an average rate of 84% for ACI, whereas the return to sport at preinjury level was 76%. This review included studies which varied from 31.5% [34] to 100% [23] of patients returning to their preinjury sports level. Peterson et al. [36] showed 3–5 years after ACI-P a continuation of sporting activity of 96% and Mithofer et al. [27] reported results of 52% 7 years postoperatively. These studies confirm our findings of a downward trend in sports activity in an 84 patient cohort over the medium- to long-term (8 years).

Patients who did not return to their previous sporting level postoperatively were downgraded on the UCLA scale by a median of 2 and on the Tegner Activity Scale of 2.5 points. 42.4% of the patients performing high impact sports preoperatively were able to return to this level. The reasons that this percentage is not higher are numerous: strict rehabilitation programs allow the beginning of contact sports

**Fig. 3** Change in types of sports participated. A shift from high-impact sports to active events and moderate or mild activities was present over the course of time



only after more than 1 year after the surgery; recommendations from treating physicians may discourage high impact sports and suggest other active or moderate intensity activities, the fear of re-injury can inhibit patients [16], age also plays an increasingly important role [2, 13]. It is therefore possible that based on the surgery result alone, an even higher postoperative sporting level could be achieved. Similar observations have already been made in earlier studies with first-generation ACI [14].

All clinical scores showed highly significant improvements for the considered patient cohort with an average of 8 years (5–14) after third-generation ACI ( $p < 0.001$ ). Moreover, the study demonstrated that athletic persons showed significantly better results in all clinical outcome parameters than non-athletic persons.

Correlation analyses were performed to evaluate the influence of pre- and post-operative sports activity on the medium- to long-term outcome after third-generation ACI. The UCLA score as well as the Tegner Activity Scale before knee damage showed significant results in all analyzed scores. Postoperative sports activity also showed impressive results and demonstrated significant ( $p < 0.05$ ) correlation with all clinical outcome parameters. These results are in line with previous findings, which also reported significant correlations between pre- and postoperative sports activity and clinical outcome after ACI and microfracture [12, 14, 23]. All these results suggest that the preoperative performance level is an important indicator of the clinical outcome.

In earlier studies, the exact timing of re-entry into sporting activities was examined in detail. This was not possible in this study due to inconsistent information provided by

patients. This study is limited because patients were not explicitly asked at what point in time they changed their sporting behavior and for what reasons. Earlier studies showed that the relatively rapid load build-up as well as the resumption of sport with an irritation-free knee joint is possible and recommended [23, 40]. For this reason, the patients in this study were assigned to a rehabilitation program that recommended rapid load building. The exact time of the resumption of sports could not be determined from the available documentation. Moreover, the group analysis showed that athletic persons were significantly younger and had a lower BMI than non-athletic persons. Even though the differences are small this represents a bias and further limitation of this study. However, it seems logical that younger patients often have a higher sports activity than older ones and that patients with higher sports activity have a lower BMI. Several clinical studies on ACI therapy with NOVOCART have been published in the past. They showed promising results in the medium and long term [31, 33, 41]. However, there is still a lack of randomized controlled trials that allow a final evaluation.

This study demonstrated that third-generation ACI is a suitable therapy option for athletic persons with full-thickness cartilage defects of the knee joint. Athletic persons achieved significantly better results in all outcome parameters than non-athletes. Also, pre- and post-operative sports activity levels were shown to be a very important influencing and prognostic factor for the medium- to long-term outcome after third-generation ACI. This is an important preoperative factor for the decision to use third-generation ACI, as better results can be expected in patients with higher level of sports activities.

## Conclusion

This study was able to show that third-generation ACI is a suitable therapy option for athletic persons with full-thickness cartilage defects of the knee joint. The return to sports activity is possible, and a shift from high-impact sports to less strenuous activities was observed. In addition, the study demonstrated the importance of pre- and postoperative sports activities for the medium- to long-term clinical outcome after third-generation ACI.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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## References

- Aldrian S, Zak L, Wondrasch B, Albrecht C, Stelzeneder B, Binder H et al (2014) Clinical and radiological long-term outcomes after matrix-induced autologous chondrocyte transplantation: a prospective follow-up at a minimum of 10 years. *Am J Sports Med* 42:2680–2688
- Allender S, Hutchinson L, Foster C (2008) Life-change events and participation in physical activity: a systematic review. *Health Promot Int* 23:160–172
- Amstutz HC, Thomas BJ, Jinnah R, Kim W, Grogan T, Yale C (1984) Treatment of primary osteoarthritis of the hip. A comparison of total joint and surface replacement arthroplasty. *J Bone Jt Surg Am* 66:228–241
- Anders S, Schaumburger J, Schubert T, Grifka J, Behrens P (2008) Matrix-associated autologous chondrocyte transplantation (MACT). Minimally invasive technique in the knee. *Oper Orthop Traumatol* 20:208–219
- Briggs KK, Kocher MS, Rodkey WG, Steadman JR (2006) Reliability, validity, and responsiveness of the Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee. *J Bone Jt Surg Am* 88:698–705
- Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L (1994) Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med* 331:889–895
- Campbell AB, Pineda M, Harris JD, Flanigan DC (2016) Return to sport after articular cartilage repair in athletes' knees: a systematic review. *Arthroscopy* 32:651–668.e651
- Chapman CR (1984) New directions in the understanding and management of pain. *Soc Sci Med* 19:1261–1277
- Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM (2011) Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken)* 63(Suppl 11):S208–228
- Collins NJ, Roos EM (2012) Patient-reported outcomes for total hip and knee arthroplasty: commonly used instruments and attributes of a "good" measure. *Clin Geriatr Med* 28:367–394
- Dahm DL, Barnes SA, Harrington JR, Sayeed SA, Berry DJ (2008) Patient-reported activity level after total knee arthroplasty. *J Arthroplasty* 23:401–407
- Della Villa S, Kon E, Filardo G, Ricci M, Vincentelli F, Delcogliano M et al (2010) Does intensive rehabilitation permit early return to sport without compromising the clinical outcome after arthroscopic autologous chondrocyte implantation in highly competitive athletes? *Am J Sports Med* 38:68–77
- Engberg E, Alen M, Kukkonen-Harjula K, Peltonen JE, Tikkanen HO, Pekkariinen H (2012) Life events and change in leisure time physical activity: a systematic review. *Sports Med* 42:433–447
- Erdle B, Herrmann S, Porichis S, Uhl M, Ghanem N, Schmal H et al (2017) Sporting activity is reduced 11 years after first-generation autologous chondrocyte implantation in the knee joint. *Am J Sports Med* 45:2762–2773
- Gille J, Behrens P, Schulz AP, Oheim R, Kienast B (2016) Matrix-associated autologous chondrocyte implantation: a clinical follow-up at 15 years. *Cartilage* 7:309–315
- Gobbi A, Francisco R (2006) Factors affecting return to sports after anterior cruciate ligament reconstruction with patellar tendon and hamstring graft: a prospective clinical investigation. *Knee Surg Sports Traumatol Arthrosc* 14:1021–1028
- Harris JD, Brophy RH, Siston RA, Flanigan DC (2010) Treatment of chondral defects in the athlete's knee. *Arthroscopy* 26:841–852
- Harris JD, Siston RA, Pan X, Flanigan DC (2010) Autologous chondrocyte implantation: a systematic review. *J Bone Jt Surg Am* 92:2220–2233
- Irrgang JJ, Anderson AF, Boland AL, Harner CD, Kurosaka M, Neyret P et al (2001) Development and validation of the international knee documentation committee subjective knee form. *Am J Sports Med* 29:600–613
- Kon E, Filardo G, Berruto M, Benazzo F, Zanon G, Della Villa S et al (2011) Articular cartilage treatment in high-level male soccer players: a prospective comparative study of arthroscopic second-generation autologous chondrocyte implantation versus microfracture. *Am J Sports Med* 39:2549–2557
- Kreuz PC, Kalkreuth RH, Niemeyer P, Uhl M, Erggelet C (2019) Long-term clinical and MRI results of matrix-assisted autologous chondrocyte implantation for articular cartilage defects of the knee. *Cartilage* 10:305–313
- Kreuz PC, Muller S, Freymann U, Erggelet C, Niemeyer P, Kaps C et al (2011) Repair of focal cartilage defects with scaffold-assisted

- autologous chondrocyte grafts: clinical and biomechanical results 48 months after transplantation. *Am J Sports Med* 39:1697–1705
23. Kreuz PC, Steinwachs M, Erggelet C, Lahm A, Krause S, Ossendorf C et al (2007) Importance of sports in cartilage regeneration after autologous chondrocyte implantation: a prospective study with a 3-year follow-up. *Am J Sports Med* 35:1261–1268
  24. Krych AJ, Pareek A, King AH, Johnson NR, Stuart MJ, Williams RJ 3rd (2017) Return to sport after the surgical management of articular cartilage lesions in the knee: a meta-analysis. *Knee Surg Sports Traumatol Arthrosc* 25:3186–3196
  25. Mandelbaum BR, Browne JE, Fu F, Micheli L, Mosely JB Jr, Erggelet C et al (1998) Articular cartilage lesions of the knee. *Am J Sports Med* 26:853–861
  26. Minas T (1998) Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life. *Am J Orthop (Belle Mead NJ)* 27:739–744
  27. Mithoefer K, Hambly K, Della Villa S, Silvers H, Mandelbaum BR (2009) Return to sports participation after articular cartilage repair in the knee: scientific evidence. *Am J Sports Med* 37(Suppl 1):167s–176s
  28. Mithoefer K, Hambly K, Logerstedt D, Ricci M, Silvers H, Della Villa S (2012) Current concepts for rehabilitation and return to sport after knee articular cartilage repair in the athlete. *J Orthop Sports Phys Ther* 42:254–273
  29. Naal FD, Impellizzeri FM, Leunig M (2009) Which is the best activity rating scale for patients undergoing total joint arthroplasty? *Clin Orthop Relat Res* 467:958–965
  30. Niemeyer P, Albrecht D, Andereya S, Angele P, Ateschrang A, Aurich M et al (2016) Autologous chondrocyte implantation (ACI) for cartilage defects of the knee: A guideline by the working group “Clinical Tissue Regeneration” of the German Society of Orthopaedics and Trauma (DGOU). *Knee* 23:426–435
  31. Niethammer TR, Altmann D, Holzgruber M, Pietschmann MF, Gulecyuz MF, Notohamiprodjo S et al (2020) Patient reported and MRI outcomes of third generation autologous chondrocyte implantation after 10 years. *Arthroscopy*. <https://doi.org/10.1016/j.arthro.2020.03.009>
  32. Niethammer TR, Limbrunner K, Betz OB, Gulecyuz MF, Pietschmann MF, Feist M et al (2016) Analysis of the autologous chondrocyte quality of matrix-based autologous chondrocyte implantation in the knee joint. *Int Orthop* 40:205–212
  33. Niethammer TR, Pietschmann MF, Horng A, Rossbach BP, Ficklscherer A, Jansson V et al (2014) Graft hypertrophy of matrix-based autologous chondrocyte implantation: a two-year follow-up study of NOVOCART 3D implantation in the knee. *Knee Surg Sports Traumatol Arthrosc* 22:1329–1336
  34. Panagopoulos A, van Niekkerk L, Triantafyllou I (2012) Autologous chondrocyte implantation for knee cartilage injuries: moderate functional outcome and performance in patients with high-impact activities. *Orthopedics* 35:e6–14
  35. Pestka JM, Feucht MJ, Porichis S, Bode G, Sudkamp NP, Niemeyer P (2016) Return to sports activity and work after autologous chondrocyte implantation of the knee: which factors influence outcomes? *Am J Sports Med* 44:370–377
  36. Peterson L, Vasiladis HS, Brittberg M, Lindahl A (2010) Autologous chondrocyte implantation: a long-term follow-up. *Am J Sports Med* 38:1117–1124
  37. Riboh JC, Cvetanovich GL, Cole BJ, Yanke AB (2017) Comparative efficacy of cartilage repair procedures in the knee: a network meta-analysis. *Knee Surg Sports Traumatol Arthrosc* 25:3786–3799
  38. Rodriguez-Merchan EC (2012) Knee instruments and rating scales designed to measure outcomes. *J Orthop Traumatol* 13:1–6
  39. Tegner Y, Lysholm J (1985) Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res* 198:43–49
  40. Wondrasch B, Zak L, Welsch GH, Marlovits S (2009) Effect of accelerated weightbearing after matrix-associated autologous chondrocyte implantation on the femoral condyle on radiographic and clinical outcome after 2 years: a prospective, randomized controlled pilot study. *Am J Sports Med* 37(Suppl 1):88S–96S
  41. Zak L, Albrecht C, Wondrasch B, Widhalm H, Veksler G, Trattng S et al (2014) Results 2 years after matrix-associated autologous chondrocyte transplantation using the novocart 3D scaffold: an analysis of clinical and radiological data. *Am J Sports Med* 42:1618–1627

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