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Autologe Chondrozytenimplantation

Analyse der defektbezogenen Einflussfaktoren bei ACI im Kniegelenk

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

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Inhaltsverzeichnis

Abkürzungsverzeichnis

ACI	autologe Chondrozytenimplantation bzw. autologous chondrocyte implantation
BMI	Body Mass Index bzw. body mass index
DGOU	Deutschen Gesellschaft für Orthopädie und Unfallchirurgie bzw. German Society for Orthopaedics and Trauma
DICOM	Digital Imaging and Communications in Medicine
ICRS	International Cartilage Repair Society
IKDC	International Knee Documentation Commitee Subjective Knee
KOOS	Knee Injury Osteoarthritis Outcome Score
MFX	Mikrofrakturierung bzw. microfracture
MACI	matrixgestützten autologe Chondrozytenimplantation bzw. Matrix supported autologous chondrocyte implantation
MRI	magnetic resonance imaging
MRT	Magnetresonanztomographie
OAT	osteochondrale Autotransplantation bzw. osteochondral autograft transfer
SPSS	Statistical Package for the Social Sciences
VAS	visuelle Analogskala bzw. visual analog scale
Med. FC	medialer Femurkondylus
pat	patella
EZM	extrazelluläre Matrix

Publikationsliste

1. Niethammer TR, **Gallik D**, Chevalier Y, Holzgruber M, Baur-Melnyk A, Müller PE, Pietschmann MF. Effect of the defect localization and size on the success of third-generation autologous chondrocyte implantation in the knee joint. Int Orthop. 2020 Dec 6. doi: 10.1007/s00264-020-04884-4. Epub ahead of print. PMID: 33280063.

2. Müller PE*, **Gallik D***, Hammerschmid F, Baur-Melnyk A, Pietschmann MF, Zhang A, Niethammer TR. Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results. Knee Surg Sports Traumatol Arthrosc. 2020 Feb;28(2):470-477. doi: 10.1007/s00167-019-05661-6. Epub 2019 Aug 12. PMID: 31407047.

* geteilte Erstautorenschaft

1. Mein Beitrag zu den Veröffentlichungen

1.1. Beitrag zu “Effect of the defect localization and size on the success of third-generation autologous chondrocyte implantation in the knee joint”

Die erste Veröffentlichung “Effect of the defect localization and size on the success of third-generation autologous chondrocyte implantation in the knee joint” wurde in dem Journal “International Orthopaedics“ publiziert. Das Thema, die Hypothese und das Konzept der Arbeit legten wir zusammen mit PD Dr. med. T. Niethammer und Prof. Dr. med. M. Pietschmann fest. Anschließend erledigte ich die Terminvereinbarungen und Einladungen zu den Untersuchungen. Nach der Datenerfassung führte ich anhand der MRT-Bilder die darauffolgende Knorpelsegmentation von DICOM-Datensätzen durch. Die Berechnung der relativen Defektgröße erfolgte durch mich im biomechanischen Labor über computer-basierte Bearbeitung. Anhand der Informationen von den Fragebögen berechnete ich die orthopädischen klinischen Scores. Anschließend befasste ich mich eigenständig mit der Verarbeitung der Daten in Excel und Access Software und mit der Auswertung der Daten mittels SPSS. Schließlich erfolgte die Verfassung des Papers.

1.2. Beitrag zu „ Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results “

Die zweite Veröffentlichung „ Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results“ wurde als geteilte Erstautorenschaft in Journal “Knee Surgery, Sports Traumatology, Arthroscopy“ publiziert. Anfangs führte ich die Literaturrecherche durch. Es folgte die Datenerfassung mittels standardisierter Fragebögen, die ich eigenständig versandte und dessen Design ich anpasste. Mit den Informationen von den Fragebögen berechnete ich die klinischen Scores. Die Arbeit mit den gesammelten Daten erfolgte vor allem in Excel und Access. Die statistische Analyse der Daten führte ich in SPSS-Programm durch. Schließlich erfolgte das selbstständige Verfassen des Papers.

2. Einleitung

2.1. Der Gelenkknorpel

Der Knorpel gehört zu dem Stützgewebe und spielt für den Menschen eine wichtige Rolle. Während der Entwicklung werden viele Skelettelemente zunächst knorpelig angelegt und dann weiterentwickelt. Es gibt vier Typen der Knorpel, welche sich in der Zusammensetzung der Matrix unterscheiden: Hyaliner Knorpel, Elastischer Knorpel, Faserknorpel und Fetaler Knorpel. Der Gelenkknorpel ist der hyaline Knorpel. Er ist ein Gewebe ohne vaskulare oder nervale Versorgung. Die Funktion des Knorpels besteht in der Ermöglichung der reibungsarmen Bewegung und der gleichmäßigen Verteilung der einwirkenden Kräfte auf das Gelenk [1].

2.1.1. Aufbau des Gelenkknorpels

Der Gelenkknorpel besteht von extrazellulärer Matrix (EZM), Chondrozyten und Wasser. Die Chondrozyten sind in der EZM fest eingebettet, was ihre Migration innerhalb des Knorpels einschränkt. Sie sind an der Produktion und Abbau der Kollagenen sowie Proteoglykanen beteiligt. Die extrazelluläre Matrix wird vor allem aus Kollagen Typ II, Proteoglykanen und Wasser gebildet [2]. Die Zugfestigkeit als eine wichtige Eigenschaft des Knorpels wird durch die strukturiert angeordneten Kollagenfibrillen gebildet. Die Kollagenfibrillen verankern den Knorpel tief im subchondralen Knochen. Die Proteoglykane sind Makromoleküle, bestehend aus einem Kernprotein und Glykosaminoglykanen. Ihre wasserbindende Fähigkeit ist für die Knorpelelastizität sehr wichtig. Das an den Proteoglykanen gebundene Wasser stellt bis zu 85 % des Knorpelgewichts dar. Das Wasser ist essenziell für die Kraftverteilung sowie reibungsarme Bewegung [3-5]. Die Chondrozyten, Kollagene, Proteoglykane und Wasser sind je nach Tiefe der Knorpelschicht in unterschiedlichen Anteilen zu finden [6]. Dadurch kann man den Gelenkknorpel in 4 verschiedene Zonen unterteilen: Superfiziale Tangentialzone, Transitionalzone, Radiärzone, Kalzifizierungszone (siehe Abbildung 1).

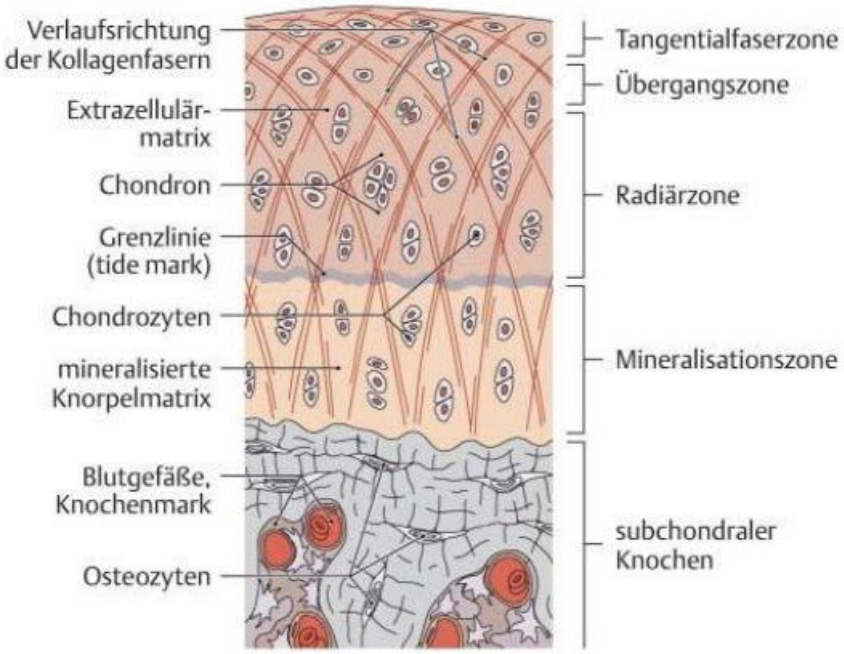

Abbildung 1: Aufbau des Gelenkknorpels [6]

2.1.2. Funktion des Gelenkknorpels

Der Gelenkknorpel hat drei wichtige Funktionen: die Lastenverteilung, die Stoßdämpfung und die reibungsarme Bewegung. Die EZM und die Knorpelzellen sind für die Zugfestigkeit des Knorpels verantwortlich. Das Wasser verleiht wiederum dem Knorpel die Verformbarkeit, die für die Ernährung des Knorpels wichtig ist. Bei der Bewegung strömt das Wasser aus und wieder rein in die EZM. Aufgrund seiner Avaskularität findet die Versorgung des Knorpels mit Nährstoffen lediglich über die Diffusion aus der synovialen Flüssigkeit statt [7]. Somit ist die Bewegung in der Hinsicht auf die Knorpelernährung von großer Bedeutung und gewährleistet die Aufrechterhaltung des funktionsfähigen Knorpels [8, 9]. Im Laufe des Lebens nimmt der Wassergehalt des Knorpels ab, was eine verminderte Gleitfähigkeit sowie einen Verlust der Druckfestigkeit zur Folge hat. Außerdem nimmt die Teilungsfähigkeit der Chondrozyten mit dem Alter ab, was zu einer Verringerung der Gesamtzahl führt. Dies kann die Entstehung der Knorpeldefekte begünstigen.

2.1.3. Fokaler Knorpeldefekt

Der Knorpel stellt ein bradytrophes Gewebe dar, dessen Regenerationsfähigkeit aufgrund der Avaskularität nur sehr gering ist. Die Ursache kann man in der oben beschriebenen morphologischen Zusammensetzung des Knorpels finden. Die Chondrozyten sitzen fest in der extrazellulären Matrix eingebettet, was die Migration in das Defektareal erschwert. Somit ist das Heilen eines Defektes sehr eingeschränkt möglich [10]. Die fokalen Defekte verbreiten sich und enden eventuell in eine Arthrose, was eine generalisierte Schädigung des Gelenkes darstellt [4, 11]. Die vollschichtigen Knorpeldefekte, die als präarthritische Läsionen gelten, verursachen oft erhebliche Schmerzen und vermindern die Lebensqualität der Patienten [4, 12, 13]. Somit liegt der Fokus der Therapie schon die frühen fokalen Defekte zu behandeln.

2.2. Chirurgische Therapieansätze fokaler Defekte

Generell unterscheidet man die knochenmarkstimulierenden und die transplantierenden Techniken. Durch knochenmarkstimulierende Techniken werden mesenchymale Stammzellen in den Defekt rekrutiert, die den Defekt mit einer fibrocartilaginösen Narbe heilen [14]. Diese Verfahren sind kostengünstig und klinisch gut bewiesen. Die Patienten zeigen danach oft reduzierte Schmerzen und eine verbesserte Gelenkfunktion. Daher werden diese Verfahren oft als „first line“ Therapie für fokale Knorpeldefekte angesehen [15-18]. Die Narbe besteht aus einem Faserknorpel, der qualitativ dem hyalinen Knorpel unterlegen ist [19]. Im Vergleich zu dem hyalinen Knorpel hat der Faserknorpel minderwertige mechanische und biochemische Eigenschaften, enthält erhebliche Mengen an Kollagen Typ I und ist anfällig für Verletzungen. Unter Belastung kommt es mit der Zeit zum Abbau dieses minderwertigen Reparaturknorpels was schließlich zu vorzeitiger Arthrose führt [20].

Aktuell ist das Ziel der modernen chirurgischen Verfahren durch die Transplantation von Chondrozyten einen hyalin-ähnlicheren Reparaturknorpel zu erreichen. Zu diesen Versorgungsmöglichkeiten gehören knorpelersetzenden Methoden wie die osteochondrale Transplantation (OATS) und die autologe Chondrozytenimplantation (ACI). Bei der OATS wird ein Knorpel-Knochenzylinder direkt in gleicher Sitzung in den Defektbereich verpflanzt, wobei der Zylinder aus einer nicht lasttragenden Region des Gelenkes stammt. Im Rahmen der ACI werden die eigenen hyalinen Knorpelzellen entnommen, im Labor für 3-4 Wochen gezüchtet und anschließend in die defekte Stelle implantiert.

Seit der ersten ACI von Brittberg et al im Jahre 1994 hat es viele Verbesserungen in diesem Verfahren gegeben und aktuell ist es ein etabliertes und anerkanntes Verfahren zur

Behandlung von Knorpeldefekten im Knie [21-24]. Die ACI der ersten Generation benutzte noch ein Periostlappen, unter den die kultivierten Zellen implantiert wurden. Eine Weiterentwicklung des Verfahrens im Sinne der 2. Generation stellte dann eine Kollagenmembran dar [25]. Mittlerweile ist ACI der dritten Generation verbreitet, wo als Trägermedium der gezüchteten Chondrozyten eine resorbierbare Matrix benutzt wird (MACI). Dies vereinfachte das operative Verfahren eindeutig. Die Wirksamkeit dieses Verfahrens wurde in mehreren Studien mit erhöhter Funktion und Schmerzreduktion nachgewiesen [26-29].

2.3. ACI und ihre Einflussfaktoren

Die ACI als ein sehr viel versprechendes Verfahren in der Knorpeltherapie ist das Ziel vieler Studien. Um diese Methode weiterentwickeln zu können und damit noch bessere Ergebnisse zu erzielen, sollten alle Einflussfaktoren, die das klinische Ergebnis beeinflussen, so klar wie möglich sein und gut erforscht werden. Es gibt patientenbezogene (Geschlecht, Alter, BMI, körperliche Aktivität) und defektbezogene (Läsionsgröße, Lokalisation, Voroperationen, Ätiologie) Aspekte, die die Behandlungsergebnisse der ACI beeinflussen können. Die Studien, die diese Faktoren untersuchten, zeigten heterogene Ergebnisse. Es wurde beschrieben, dass weibliches Geschlecht und chronische Ätiologie mit minderwertigem Ergebnis verbunden sind [30, 31]. Was das Alter und den BMI betrifft, so wiesen einige Studien negative Auswirkungen eines höheren Patientenalters und des BMI auf das klinische Ergebnis nach [32, 33]. Auf der anderen Seite, Vasiliadis et al beschrieb keinen Zusammenhang zwischen dem klinischen Ergebnis und dem Alter [34]. Filardo et al in einer großen Matrix assoziierten ACI Kohorte stellte einen Nachteil des höheren Alters mit degenerativer Ätiologie und einen Vorteil des männlichen Geschlechts mit höherer körperlicher Aktivität fest [30].

Wir konzentrierten uns in unserer Studie auf die Analyse der defektbezogenen Einflussfaktoren wie die relative Defektgröße und die Voroperation mit Mikrofrakturierung (MFx).

2.3.1. Einfluss der Lokalisation

Der Einfluss der Lokalisation auf das klinische Ergebnis wurde bisher von vielen Autoren untersucht. Die patellar lokalisierten Läsionen wurden seit Anfang der ACI mit einem schlechteren klinischen Ergebnis in Verbindung gebracht [33, 35]. Die patellaren Ergebnisse

verbesserten sich mit der Entwicklung der ACI Technik [36-39]. Meyerkort et al. beschrieb eine gute klinische Verbesserung mit KOOS-Score >70 5 Jahre nach patellarer ACI der dritten Generation [39]. Es gibt wenige Studien, die sich auf die Lokalisation der ACI der dritten Generation konzentrieren. Gigante et al. sah keinen signifikanten Unterschied zwischen verschiedenen Lokalisationen des Defekts in seiner kleinen Patientenprobe [40]. Filardo et al verglich die dritte Generation ACI in patellarer vs. trochlearer Region mit signifikanter Überlegenheit der trochlearen Läsionen. In einer anderen Studie von dieser Gruppe wurden kondyläre und trochleare Läsionen verglichen und leicht bessere Ergebnisse für die Trochlea beschrieben [41]. In der Studie von Gobi et al zeigten Patienten mit trochlearen Läsionen bessere Ergebnisse als die Patienten mit patellaren Läsionen [42]. Welsch untersuchte die ACI der dritten Generation an der Patella und am medialen Femurkondylus ohne signifikante Differenz aus der radiologischen Sicht ohne klinische Beurteilung [43]. Ebert et al zeigte einen signifikanten Unterschied zwischen femorotibialen und patellofemoralen KOOS- Scores [44]. In einer neuen Studie präsentierte Niemeyer et al nicht signifikant bessere Ergebnisse patellar im Vergleich zu femoral bei Verwendung der ACI der dritten Generation mit Sphäroid-Technologie [45].

2.3.2. Einfluss der Defektgröße

Die Defektgröße spielt bei der Indikation der Therapie des fokalen Knorpelschadens eine wichtige Rolle. Die ACI wurde bei der Defektgröße von 2,5-3 cm2 und größer empfohlen [20]. Diese Empfehlung differenziert nicht zwischen den einzelnen Kniekompartimenten wie die Patella oder Kondylen. In allen verfügbaren Studien und auch in den empfohlenen Leitlinien handelt es sich um intraoperativ gemessene absolute Defektgröße. Ein erhöhtes Versagensrisiko wurde bei der Behandlung großer Defekte beschrieben [17]. Auf der anderen Seite gibt es andere Studien, die keinen Zusammenhang zwischen Outcome und absoluter Defektgröße finden konnten [34, 46, 47]. Es gibt keine Studie, die die relative Defektgröße untersucht. Die relative Defektgröße repräsentiert den Anteil des Defekts an der gesamten Knorpelschicht des bestimmten Kniekompartiments. Daher haben wir in unserer Studie nicht nur die absolute, sondern auch die relative Defektgröße analysiert.

2.3.3. Einfluss der Mikrofrakturierung als Voroperation

Die Patienten Allgemein kann man unter den ACI Patienten zwei Gruppen unterscheiden. Die Patienten ohne Voroperation, also mit primär durchgeführter ACI, und die Patienten mit sekundärer ACI nach fehlgeschlagener Voroperation am Knorpel. In der Studie von Zaslav et al. ohne Kontrollgruppe wurde gezeigt, dass Patienten mit sekundärer ACI nach fehlgeschlagenen Knorpelbehandlungen eine klinisch signifikante und langanhaltende Verbesserung der Schmerzen und der Kniefunktion erwarten können [48]. Ein Vergleich mit Patienten mit primär durchgeführter ACI wurde nicht durchgeführt.

Minas et al berichtete über eine erhöhte Versagensrate der sekundären ACI nach der Vorbehandlung mit den vorherigen Knochenmarkstimulationstechniken (BMS) [49]. Die Versagensraten der sekundären ACI betrugen nach Pridie Bohrungen 28%, Abrasionsplastik 27% und Mikrofrakturierung 20%. Die Studie untersuchte das Ergebnis der ACI nach allen Knochenmarkstimulationstechniken mit der Mehrheit der Pridie Bohrung und Abrasionsplastik wobei die Mikrofrakturierung (MFx) nur eine Minderheit darstellte. Keine weitere Beurteilung der klinischen Kniefunktion mittels Scores wurde in der Studie untersucht. In der Studie von Pestka et al wurden 28 Patienten mit der sekundären ACI nach fehlgeschlagener Mikrofrakturierung mit Matched-Pair-Analyse analysiert [50]. Sie beobachteten eine erhöhte Versagensrate und einen signifikant reduzierten klinischen Score in der sekundären ACI Gruppe. Jungmann et al. zeigte, dass Patienten mit sekundärer ACI nach vorheriger BMS, in der Mehrheit nach der Mikrofrakturierung, ein erhöhtes Versagensrisiko haben [47]. In der weiteren Studie beschrieb Minas et al das Überleben der ersten Generation von ACI und potenzielle Prädiktoren für das Versagen in einer großen Patientenkohorte über zehn Jahre [51]. Das Überleben von ACI der ersten Generation sank bei Patienten mit vorheriger Mikrofrakturierung signifikant (44%) im Vergleich zu Patienten mit primärer ACI (77%).

3. Fragestellung

Wir konzentrierten uns in unserer Studie auf die Analyse der defektbezogenen Einflussfaktoren auf die klinischen Ergebnisse nach ACI im Knie. Das Ziel war es zu quantifizieren, wie die Lokalisation, die relative Defektgröße und die Voroperation mit Mikrofrakturierung (MFx) das Outcome der ACI beeinflussen.

In der ersten Veröffentlichung „Effect of the defect localization and size on the success of third-generation autologous chondrocyte implantation in the knee joint“ analysieren wir den Einfluss der Lokalisation und der relativen Defektgröße auf die ACI. Unsere Hypothese war, dass Defekte an der Patella und Defekte mit einem größeren Anteil an der gesamten Knorpelschicht des bestimmten Kniekompartiments, ein schlechteres Ergebnis liefern.

Die zweite Publikation „Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results“ vergleicht die klinischen Ergebnisse von der ACI ohne Voroperation am Knorpel (primäre ACI) und der ACI nach vorheriger Mikrofrakturierung (sekundäre ACI). Im Rahmen unserer Arbeitshypothese war zu prüfen, ob die sekundäre ACI nach fehlgeschlagener Mikrofrakturierung zu statistisch signifikant schlechteren Ergebnissen führt.

4. Material und Methoden

4.1. Ablauf der ACI der dritten Generation

4.1.1. Indikationsstellung

Bei der Indikationsstellung zu der ACI berücksichtigten wir die allgemeinen Empfehlungen der „AG Geweberegeneration“ der Deutschen Gesellschaft für Orthopädie und Unfallchirurgie (siehe Abbildung 2) [20]. Es erfolgte vorerst eine klinische-orthopädische Untersuchung, dann eine Kernspinuntersuchung und eine Arthroskopie des betroffenen Gelenkes.

Die Arthroskopie als eine invasive Maßnahme war bei der Indikationsstellung obligatorisch, da es der Einteilung des Knorpeldefektes nach Outerbridge Klassifikation und der Beurteilung des Defektes im Allgemeinen diente [52]. Zu den Kontraindikationen für die Durchführung der ACT gehörten eine Gonarthrose, aktive rheumatoide Arthritis, aktive Autoimmunerkrankung oder Tumorleiden sowie sich Knorpelläsionen an gegenüberliegenden Gelenkflächen (sog. Kissing

lesions). Außerdem mussten die möglichen Komorbiditäten, wie die pathologische Beinachse oder eine Patelladysplasie ausgeschlossen werden. Diesbezüglich erfolgte die Röntgenuntersuchung des Knies mit tangentieller Patellaufnahme, sowie eine Ganzbeinaufnahme.

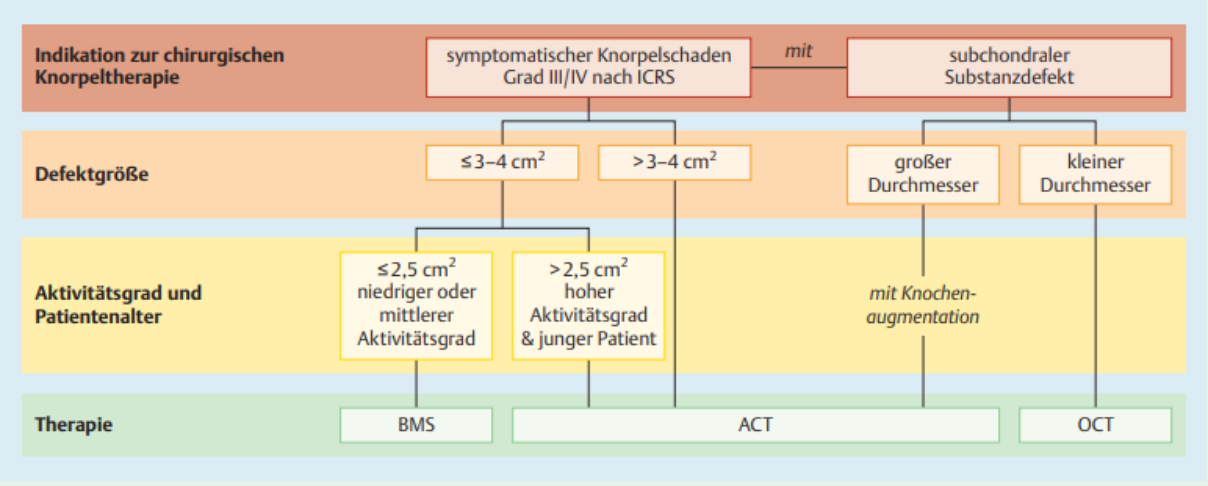

Abbildung 2: Behandlungsempfehlung der AG Geweberegeneration der DGOU [20]

4.1.2. OP-Technik

Alle Patienten wurden mit NOVOCART® 3D (TETEC AG, Reutlingen, Deutschland) einer dritten Generation ACI behandelt. Bei der ersten arthroskopischen Operation des Kniegelenkes, die den vollschichtigen Defekt von ICRS III-IV bestätigte, wurden zwei Knorpel-Knochenzylinder aus dem nichttragenden interkondylären Notch genommen und in einer sterilen Nährstofflösung an den Hersteller geschickt. Diese Zylinder hatten einen Durchmesser von drei Millimetern mit einer Tiefe von etwa fünf bis zehn Millimetern. Anschließend erfolgten die Isolierung und Vermehrung der Chondrozyten im Labor. Die Herstellung des Implantates betrug 3 bis 4 Wochen. Bei der zweiten Operation wurde das ACI-Verfahren mit einer minimalinvasiven parapatellaren Arthrotomie des Kniegelenks durchgeführt. Der Knorpeldefekt wurde gemessen und das Debridement wurde durchgeführt, um die gesunden Knorpelschultern an den Defekträndern zu schaffen. Das Implantat mit den autologen Chondrozyten wurde auf die gewünschte Größe geschnitten und in den Knorpeldefekt gelegt. Danach wurde es mit resorbierbarer Vicryl USP 5-0 Naht fixiert. Die perioperative Antibiotikaprophylaxe wurde mit intravenösem Cefuroxim 1.5g durchgeführt.

4.1.3. Postoperative Nachbehandlung

Die postoperative Rehabilitation wurde mit einem standardisierten Protokoll durchgeführt. Bei Patienten mit femoralen Defekten begann die Rehabilitation mit der Verwendung eines kontinuierlichen passiven Bewegungsgeräts (CPM) nach 24 Stunden Bettruhe und Drainageentfernung. In den ersten 6 Wochen war eine Teilbelastung von 20 kg und Flexion bis 90° erlaubt. Danach erfolgte Belastungsaufbau mit 20-30 kg pro Woche. Bei Patienten mit patellaren Defekten wurde die Flexion auf 30° für 2- 3 Wochen limitiert und in den nächsten Wochen schrittweise erhöht. Die Vollbelastung in Streckung war schon nach Drainagezug erlaubt. Alle Patienten wurden von Physiotherapeuten behandelt. Mäßige körperliche Aktivitäten wie Radfahren, Schwimmen und Nordic Walking waren nicht früher als 3 Monate postoperativ erlaubt. Die Patienten wurden darauf hingewiesen, nicht früher als 12 Monate nach der Operation mit der Durchführung von Hochleistungssportarten (z. B. Fußball, Basketball) zu beginnen.

4.2. Datenerhebung und Auswertung

Die klinische Datenerfassung erfolgte nach einem standardisierten Schema, das sich von Fragebögen und MRT- Untersuchungen zusammensetzte. Die präoperative Erhebung der Daten wurde zusammen bei der Indikationsstellung durchgeführt. Anschließend wurden die klinischen Auswertungen postoperativ mit einem Fragebogen durchgeführt, der nach 6, 12, 24 und 36 Monaten versandt wurde. Die Fragebögen enthielten die subjektive Beurteilung des Knies durch das ICDC Score und eine visuelle Analogskala für Schmerzen (VAS). Darüber hinaus wurden patientenspezifische Parameter wie Alter, Geschlecht und Body-Mass-Index (BMI) abgefragt. Die defektspezifischen Daten wurden durch die Lokalisation und Defektgröße erfasst. Zusätzlich dazu erfolgten die bildgebenden Untersuchungen mittels MRT. Zur Bestimmung der relativen Defektgröße wurde der Knorpel und der Knorpeldefekt des entsprechenden Kniekompartiments anhand der MRT Bilder in einem open source Software 3D Slicer manuell segmentiert. Anschließend wurden die beiden Flächen mittels Paraview (Kitware, Clifton Park, New York, USA) in ein Model gebracht und in Relation gesetzt. Für die statistische Auswertung klinischer Daten wurde das statistische Programm SPSS verwendet. Die einzelnen statistischen Tests und Modelle, die uns entsprechende Ergebnisse brachten, werden in dem jeweiligen Paper erklärt.

5. Zusammenfassung

In der vorliegenden Arbeit stelle ich meine zwei veröffentlichten Publikationen vor. Beide Publikationen handeln von der autologen Chondrozytenimplantation (ACI). In unserer Arbeit konnte der Einfluss der Lokalisation, Defektgröße und der Vorbehandlung mit Mikrofrakturierung (MFx) auf die klinischen Ergebnisse der ACI gezeigt werden.

In unseren beiden Studien analysierten wir die Patienten mit ACI der dritten Generation im Knie. Die Patienten wurden in den Jahren von 2004 bis 2018 mit einer dritten Generation ACI NOVOCART® 3D (TETEC AG, Reutlingen, Deutschland) behandelt. Es erfolgte in beiden Studien eine Matched-Pair-Analyse. Dank dieser Methode konnte man die nicht untersuchten Einflussfaktoren eliminieren. In beiden Arbeiten wurden ähnliche Kriterien für das Matching verwendet. Es waren Variablen wie Alter, Geschlecht, Body-Mass-Index, Anzahl der behandelten Defekte. Das genaue chirurgische und anschließend das rehabilitative Vorgehen der ganzen Prozedere wurde in den vorherigen Kapiteln erklärt. Die Hypothese unseres ersten Papers „Effect of defect size and localization of third generation autologous chondrocyte implantation in the knee joint" war, dass Defekte an der Patella und Defekte mit einem größeren Anteil an der gesamten Knorpelschicht des bestimmten Kniekompartiments, ein schlechteres Ergebnis liefern. Die Analyse wurde von 25 femoralen und 25 patellaren Defekten mit einer Nachbeobachtungszeit von 3 Jahren durchgeführt. Das Durchschnittsalter der femoralen Gruppe betrug 34,6 Jahre (15-53). Es waren 11 Männer und 14 Frauen mit dem mittleren BMI von 27,3 kg/m2 (20-36). Die durchschnittliche intraoperative Defektgröße betrug 4,8 cm2 (2-15). In der gematchten Gruppe mit Patienten mit ACI an der Patella war das Durchschnittsalter 33,3 Jahre (13-56). Es waren 10 Männer und 15 Frauen mit mittlerem BMI 26,3 kg/m2 (19-35) und durchschnittlicher intraoperativer Defektgröße von 4,6 cm2 (2-12). Die MRT-Bilder wurden für die computer-gestützte Segmentierung des Knorpels und des Defektes verwendet. Der Anteil des Defektes im gesamten Knorpelvolumen des entsprechenden Kniekompartiments ergab uns die relative Defektgröße. Das klinische Ergebnis wurde mit dem IKDC-Score und VAS präoperativ und nach 6, 12, 24 und 36 Monaten postoperativ gemessen.

In unseren Ergebnissen zeigten die IKDC und VAS Scores eine signifikante Verbesserung im Vergleich zu dem präoperativen Zustand in beiden Gruppen. In der femoralen Gruppe verbesserte sich die IKDC von 33,9 (SD 18,1) präoperativ auf 71,5 (SD 17,4) nach 3 Jahren und die VAS von 6,9 (SD 2,9) präoperativ auf 2,4 (SD 2,5) nach 3 Jahren. In der patellaren Gruppe stieg IKDC von 36,1 (SD 12,6) auf 54,7 (SD 20,3) nach 3 Jahren. Die VAS verbesserte sich von 6.7 (SD 2.8) auf 3.4 (SD 2) nach 3 Jahren. Beim direkten Vergleich beider Gruppen über einen Zeitraum von 3 Jahren wurde ein signifikanter Unterschied 1-3 Jahre postoperativ ($p < 0.05$) festgestellt. Bei allen postoperativen Zeitpunkten war der IKDC Wert der femoralen

Gruppe besser als der patellaren Gruppe. Nach der Segmentierung der Knorpelschicht und des Defekts in MRT-Daten gefolgt von computergestützter Verarbeitung erhielten wir die relative Defektgröße, indem wir die Defektgröße in die Relation zur Knorpelvolumengröße des medialen Femurkondylus/ Patella stellten. In der femoralen Gruppe war der durchschnittliche relative Defekt 6,7% (1,2-13,9), während in der patellaren Gruppe 18,9% (4,0-47,7). Dies stellte einen signifikanten Unterschied ($p<0.05$) dar. Der Anteil des Defektes an dem gesamten Knorpel des untersuchten Kompartiments zeigte sich somit patellar signifikant größer als femoral, obwohl die absolute Defektgröße identisch war. Bei der Analyse des Einflusses der relativen Defektgröße auf das klinische Ergebnis, gemessen durch IKDC und VAS, wurde jedoch keine signifikante Korrelation gefunden ($p>0,05$). Was die absolute Defektgröße betrifft, so wurde auch keine statistisch signifikante Korrelation zwischen Ergebnis und absoluter Defektgröße gefunden. Dank unserer Arbeit konnten wir bestätigen, dass die autologe Chondrozytenimplantation der dritten Generation klinische Vorteile für femorale und patellare Defekte bietet. Die patellaren Defekte führen dabei zu einem schlechteren klinischen Ergebnis im Vergleich zu den femoralen Defekte. Nach unseren Ergebnissen haben weder die absolute noch die relative Defektgröße einen signifikanten Einfluss auf den Outcome. Unsere Studie war die erste, die sich mit dem Termin der relativen Defektgröße befasste und es wäre wert diese Thematik weiter zu erforschen.

In unserem zweiten veröffentlichten Paper “Autologous chondrocyte implantation after failed bone marrow stimulation leads to worse clinical results” beobachteten wir die klinischen Ergebnisse der Patienten der sekundären ACI nach fehlgeschlagener Mikrofrakturierung im Knie über drei Jahre postoperativ. Die Hypothese lautete, dass die sekundäre ACI nach fehlgeschlagener Mikrofrakturierung schlechtere Ergebnisse als die primäre ACI liefert. Ähnlich wie in dem ersten Paper wurde eine Matched-pair Analyse durchgeführt mit insgesamt 40 Patienten mit der autologen Chondrozytenimplantation der dritten Generation (Novocart® 3D). Die erste Gruppe mit 20 Patienten repräsentierte die primäre ACI ohne Voroperation oder Vorbehandlung des Knorpels. In der „gematchen“ Gruppe war die sekundäre ACI nach fehlgeschlagener Vorbehandlung des Knorpels mittels Mikrofrakturierung. Die durchschnittliche Defektgröße betrug 5,4 cm. Die klinische Datenerfassung erfolgte mittels IKDC-Score und VAS in Ruhe und in der Belastung. Sowohl die erste als auch die zweite Gruppe zeigten eine signifikante Verbesserung von IKDC-Score und VAS-Score im Vergleich zu den präoperativen Befunden. Die erste Gruppe zeigte einen IKDC-Score von 37,0 präoperativ. Der maximale IKDC-Wert wurde nach zwei Jahren mit 77,7 Punkten erreicht. Im Vergleich zu den präoperativen IKDC-Werten wurde zu allen Zeitpunkten eine signifikante Verbesserung festgestellt. Der subjektive IKDC-Score der zweiten Gruppe lag präoperativ bei 29,9 und nach sechs Monaten bei 44,3. Danach beobachteten wir weitere Steigerung auf

einen Maximalwert von 50,1 nach einem Jahr. Eine signifikante Verbesserung des IKDC-Scores im Vergleich zu präoperativen Befunden wurde zu jeder Zeit beobachtet. Ähnlich verhielten sich die Ergebnisse bezüglich der visuellen Analogskala (VAS) in Ruhe und bei Belastung. In der ersten Gruppe lag die präoperative VAS bei Belastung bei 6,4 und in Ruhe bei 1,9. Im weiteren Verlauf verbesserten sich die Werte zu allen Zeitpunkten mit signifikantem Unterschied zu den präoperativen Werten. In der zweiten Gruppe mit sekundärer ACI war die anfängliche VAS 6,8 bei Belastung und 4,4 in Ruhe. Danach wurde eine signifikante Verbesserung der VAS bei Belastung im Vergleich zu den präoperativen Ergebnissen erst nach 6 Monaten und 1 Jahr festgestellt. In VAS in Ruhe war es nach 6 Monaten, 1 Jahr und 3 Jahren. Der beste Wert von VAS wurde nach einem Jahr (3,8 in Bewegung und 1,0 in Ruhe) erzielt. Beim Vergleich der IKDC-Ergebnisse der beiden Gruppen wurde bei allen Follow-ups ein signifikanter Unterschied zugunsten der primären ACI beobachtet. Was die Schmerzen betrifft, beobachteten wir bei VAS bei Belastung einen signifikanten Unterschied in allen Follow-ups. Die VAS in Ruhe zeigte einen signifikanten Unterschied in allen Follow-ups mit Ausnahme nach 6 Monaten. Die Gruppe der primären ACI ohne vorherige Knorpeltherapie war immer der anderen Gruppe mit sekundärer ACI überlegen. Dadurch konnte unsere untersuchte Hypothese bestätigt werden. Sowohl die primäre als auch die sekundäre ACI Gruppe zeigten eine deutliche Verbesserung in unserer Nachbeobachtungszeit. Die autologe Chondrozytenimplantation der dritten Generation bleibt somit ein geeignetes Verfahren zur Behandlung von Knorpeldefekten bei Patienten mit vorheriger Mikrofrakturierung. Allerdings, nach unseren Ergebnissen ist der Outcome der sekundären autologen Chondrozytenimplantation schlechter als der primären autologen Chondrozytenimplantation. In dieser Hinsicht schlussfolgern wir, dass bei grenzwertig großen Defekten die ACI vor Mikrofrakturierung bevorzugt werden sollte.

6. Abstract (English)

6.1. Introduction and Methods

In this document I present my two publications. Both publications are about autologous chondrocyte implantation of the third generation (ACI). This technique of cartilage regeneration has become very popular and showed excellent results in the past years. However, this complex therapy method involves immense costs. In this regard, it is necessary to know all the influencing factors of the ACI, which can be at the indication making benefited of. We concentrated us on the influence of defect localization, defect size and the effect of previous microfracture therapy on the ACI afterwards. In our two studies, we analysed our knee patients with ACI NOVOCART® 3D done between 2004 and 2018. A matched pair analysis was carried out in both of our studies. Thanks to this method, it was possible to eliminate the influencing factors, which we did not look at. The goal of matching was to find for every patient from one group another patient from the second group with similar observable characteristics. The criteria for matching were in both paper similar. The criteria were age, defect localization, body mass index, number of defects treated or in the first paper also the intraoperatively measured absolute defect size. The exact surgical and then the rehabilitative procedures are explained in the publications under "surgical technique and rehabilitation". Clinical data were gathered by a standardized scheme. The preoperative clinical state was carried out together with the indication. Subsequently, the gathering of the clinical data was performed by our questionnaire 6,12,24 and 36 months after the surgery. The questionnaires included the subjective evaluation by the IKDC score as well as the visual analog scale for pain (VAS). Furthermore, the patient-specific and the defect-specific data were documented. The imaging examinations were done by the MRI and for the statistical analysis was SPSS program used. The specific statistical tests and models that brought us to the corresponding results are mentioned individually in the paper.

6.2. Results of Paper 1 ”Effect of defect size and localization of third generation autologous chondrocyte implantation in the knee joint"

The hypothesis of our first paper ”Effect of defect size and localization of third generation autologous chondrocyte implantation in the knee joint" was that defects at the patella and defects with a higher relative defect size lead to worst results. A matched pair analysis was carried out. There were 25 patellar and 25 femoral defects. The follow-up period lasted 3 years.

The mean age in the femoral group was 34.6 years (15-53). The group consisted of 11 men and 14 women. The mean intraoperative absolute defect size was 4.8 cm2 (2-15). The average body mass index (BMI) of 27.3 kg/m2 (20-36) was recorded. In the other group of patellar ACI was it 33.3 years (13-56), BMI of 26.3 kg/m2 (19-35), 10 men and 15 women and intraoperative defect size of 4.6 cm2 (2-12). Initially, MRI images were used to do the computer-assisted segmentation of the defect and of the whole cartilage layer. The clinical result was measured before the surgery and 6, 12, 24 and 36 months after the surgery. As for the clinical assessment there were used the IKDC and VAS scores. In both groups could IKDC and VAS provide a significant difference compared to the preoperative condition. After 3 years we noticed in the femoral group an improvement from 33.9 (SD 18.1) preoperatively to 71.5 (SD 17.4) in IKDC and from 6.9 (SD 2.9) to 2.4 (SD 2.5) in VAS. The second group of the patellar defects showed after 3 years an increase in the IKDC from 36.1 (SD 12.6) to 54.7 (SD 20.3) and an improvement in the VAS from 6.7 (SD 2.8) to 3.4 (SD 2). After 1-3 years postoperatively the femoral IKDC score was significant better ($p < 0.05$) than the patellar group, which confirmed part of our hypothesis. With the data from the MRI segmentation we could calculate the relative defect size. The calculation was done by the ratio between the absolute defect size and the whole cartilage layer of the relevant knee. The result was calculated in percentage. A comparison between the relative defects revealed a significant difference between femoral (6.7%) and patellar group (18.9%). Consequently, it implies that although the absolute defect size in both groups was the same, the share of the defect on the cartilage layer of the patella was higher than femoral. However, according to our data neither the absolute nor the relative defect size has a significant impact on the outcome.

6.3. Conclusion of Paper 1 ”Effect of defect size and localization of third generation autologous chondrocyte implantation in the knee joint"

Thanks to our work, we were able to confirm that third generation of ACI offers benefits to the patients with cartilage defects. The patellar defects lead to a worse clinical result compared to the femoral defects. In terms of influence on the outcome the absolute and relative defect size showed itself as irrelevant. Despite this fact, our study was the first to look at the issue of the relative defect size and it would be worth further exploring this topic.

6.4. Results of Paper 2 “Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results”

In our second published paper “Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results” we observed the outcome of patients of the second line matrix-based ACI after failed microfracture therapy. The observation period was three years postoperatively. The hypothesis was that the second line ACI after unsuccessful microfracture provides inferior results compared to the first line ACI. Similar to the first paper, we did a matched pair analysis. We matched two groups with together 40 ACI patients. The first group of 20 patients represented first line ACI without pre-surgery or pre-treatment of the cartilage. The second matched group represented the second line ACI. It means the patients with a previous unsuccessful microfracture therapy. Clinical data collecting was carried out using IKDC and VAS scores. The first group had preoperatively an IKDC score of 37.0, which increased to 77.7 after two years. The postoperative IKDC increase was always statistically significant, comparing to preoperative values. Analysing the VAS at rest and in motion we noticed a significant improvement at all follow ups as well. In the second group was the subjective IKDC score preoperatively at 29.9 and then after six months at 44.3. After 12 months was it 50.1, as the further increase continued. A significant improvement compared to preoperative findings was observed at all times. The VAS begun at 6.8 in motion and 4.4 at rest. Both VAS scores improved significantly after 6 and 12 months, while the VAS at rest reached significant difference also after 3 years compared to preoperative results. When comparing our two groups in terms of IKDC and VAS in motion, a significant difference in favour of first line ACI was observed in all follow-ups. Similar was it in VAS at rest with only one exception after 6 months. The first line group of patients without previous microfracture treatment was always superior to the group of second line ACI. This confirmed our hypothesis.

6.5. Conclusion of Paper 2 “Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results”

The matrix-based ACI as the third generation of this procedure confirmed itself as an appropriate approach in the therapy of full cartilage defects. The benefits of this method were significantly proven for the patient with and without previous microfracture surgery. However, the ACI therapy after previous failed microfracture procedure was clearly inferior to first line ACI. It implies, that the ACI should be initially preferred instead of microfracture in the larger defects.

7. Veröffentlichungen

Effect of the defect localization and size on the success of third-generation autologous chondrocyte implantation in the knee joint

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Abstract

Introduction Femoral and patellar cartilage defects with a defect size > 2.5 cm^2 are a potential indication for an autologous chondrocyte implantation (ACI). However, the influence of the localization and the absolute and relative defect size on the clinical outcome has not yet been determined. The purpose of this study is to analyze the influence of the localization and the absolute and relative defect size on the clinical outcome after third-generation autologous chondrocyte implantation.

Methods A total of 50 patients with cartilage defects of the knee were treated with third-generation autologous chondrocyte implantation (Novocart® 3D). A match paired analysis was performed of 25 treated femoral and 25 treated patella defects with a follow-up of three years. MRI data was used to do the manual segmentation of the cartilage layer throughout the knee joint. The defect size was determined by taking the defect size measured in the MRI in relation to the whole cartilage area. The clinical outcome was measured by the IKDC score and VAS pre-operatively and after six, 12, 24, and 36 months post-operatively.

Results IKDC and VAS scores showed a significant improvement from the baseline in both groups. Femoral cartilage defects showed significantly superior clinical results in the analyzed scores compared to patellar defects. The femoral group improved IKDC from 33.9 (SD 18.1) pre-operatively to 71.5 (SD 17.4) after three years and the VAS from 6.9 (SD 2.9) pre-operatively to 2.4 (SD 2.5) after three years. In the patellar group, IKDC improved from 36.1 (SD 12.6) pre-operatively to 54.7 (SD 20.3) after three years and the VAS improved from 6.7 (SD 2.8) pre-operatively to 3.4 (SD 2.) after three years. Regarding the defect size, results showed that the same absolute defect size at med FC (4.8, range 2−15) and patella (4.6, range 2−12) has a significantly different share of the total cartilaginous size of the joint compartment (med FC: 6.7, range 1.2−13.9; pat: 18.9, range 4.0−47.0). However, there was no significant influence of the relative defect size on the clinical outcome in either patellar or femoral localization.

Conclusion Third-generation autologous chondrocyte implantation in ACI-treated femoral cartilage defects leads to a superior clinical outcome in a follow-up of three years compared with patellar defects. No significant influence of the defect size was found in either femoral or patellar cartilage defects.

Keywords ACI · Autologous chondrocyte implantation · Defect size · Cartilage defect · Localization

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Introduction

Full-thickness cartilage defects are pre-arthritic lesions and can produce significant pain and disability for patients [1, 2]. The intrinsic regeneration capability of the cartilage is very limited and the healing likelihood of once damaged cartilage is reduced. Many studies have proven that autologous chondrocyte implantation (ACI) represents an appropriate method for treatment of larger full-thickness cartilage defects in knees and leads to significant improvement [3–9].

Since the first-generation ACI, using a periosteal flap, there have been many improvements in this procedure including

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using a collagenous membrane (second-generation ACI) or a 3D collagenous scaffold (third generation) [10]. The available studies researching the possible influencing factors (site, lesion size, etiology, age, location etc.) on the outcome of ACI have shown various results [11–18]. As for the localization, the defects on femoral condyle reached excellent mid-term and long-term clinical outcomes, while patellar-located lesions were associated with less successful clinical outcomes [11–13, 19]. The improvement of the ACI technique and the concomitant correction of the patellofemoral malalignment improved the outcome of the patellar defects [15, 17]. Despite these improvements, using the ACI on the patella remains controversial and with unclear results, which are worth researching.

There are only a few studies analyzing the third generation of the ACI focusing on the localization of the defect and comparing the femoral with patellar defects [20, 21]. According to current recommendations, the defect size of 2.5–3 cm^2 and larger is regarded as a potential indication for the ACI [7, 22]. However, it is not known whether this "critical" limit is identical for the different knee compartments as patella and condyles or whether a differentiated size consideration with relative defect size (damaged area in relation to the total compartment) for these compartments is needed. The correlation between the outcome and the absolute defect size measured intra-operatively was the focus of previous studies showing various results [23, 24]. The relative defect size had not been researched and evaluated until this study.

The aim of our research is to analyze the influence of the localization and the defect size on the clinical outcome following third-generation ACI. Our hypothesis was that patellar defects and defects with a bigger share on the whole cartilage layer of the knee compartment lead to less successful outcomes.

Methods

Our data were captured between 2004 and 2018 with a local Institutional Review Board approval. All patients from our database with femoral and patellar cartilage defects of the knee classified as International Cartilage Repair Society (ICRS) grades III and IV were included in our prospective study and treated with third-generation ACI with intact meniscus and corresponding joint surfaces. We intended to perform a matched pair analysis. The criteria for the pair matching were age, sex, body mass index, numbers of treated defects, and the intra-operatively measured absolute defect size (Table 1). The first group represented 25 patients with medial condyle defects, while the second group consisted of 25 matched patients with patellar defects. All patients were treated with Novocart® 3D (TETEC AG, Reutlingen, Germany), a third-generation ACI.

For precise detection of the absolute defect size, magnetic resonance imaging (MRI) examinations were performed (Magnetom-Sonata; Siemens, Germany) with a conventional circular polarizing 1-channel knee coil three months post-operatively. The following sequences were performed: the fast spin-echo (dual T2-FSE), the fat-saturated gradient echo (3D FS GE), the proton-weighted fat-saturated T1-weighted sequence, and a fast-low-angle shot sequence (FLASH) with selective water excitation, all sequences suitable for the measurement of articular cartilage in the knee joint. DICOM (Digital Imaging and Communications in Medicine) data sets were used in the open source software 3D Slicer to do a manual segmentation of the cartilage layer and of the defect. 3D Slicer is a free software platform for the analysis and visualization of medical images. After the segmentation of the cartilage layer and the cartilage defect, we determined the relative defect size by putting the defect size into relation with the cartilage volume size of the medial femoral condyle/patella, which represented the relative defect size in % (Fig. 1) using the ParaView (Kitware, Clifton Park, New York, USA) and custom-made software [25].

Patient-reported outcomes were measured pre-operatively and at six, 12, 24, and 36 months post-operatively using the clinical scores IKDC (International Knee Documentation Committee) subjective knee form and a visual analog scale (VAS). Additionally, patient-specific parameters such as age, gender, and body mass index (BMI), as well as defect-specific data such as defect size or localization, were collected.

For the statistical analysis of the clinical data, the statistic program SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) was used. For the detection of significant differences between the two groups at the same time of investigation, the Wilcoxon or Friedman test was carried out for paired samples. To compare multiple groups of non-related samples at one point, the Mann–Whitney U test was used. Pearson's correlation models were used to distinguish associations between influencing factors and clinical knee scores. Our primary outcome parameter was the IKDC score, secondary outcome the VAS. A post hoc power analysis was performed with an effect size of 0.916. A statistically significant result of $p < 0.05$ was reported.

Results

There were a total of 50 patients in two matched groups with 25 patients in each study group. As previously explained, all the known influencing factors were removed by matching. The average age of the femoral group was 34.6 years (15–53), 11 male and 14 females, with the mean body mass index (BMI) of 27.3 kg/m^2 (20–36). The mean intra-operative defect size was 4.8 cm^2 (2–15). In the matched pair group with ACI patients, in the patellar group, the average age was 33.3 years

Table 1 Patient characteristics

		Med FC	Patella
Number of patients		25	25
Gender, *n* (%)	Male	11 (44)	10 (40)
	Female	14 (56)	15 (60)
Intraoperative defect size in cm^2 (range; SD)		4.83 (2–15; 2.79)	4.61 (2–12; 2.39)
BMI in kg/m^2 (range; SD)		27.3 (20–36; 4.68)	26.3 (19–35; 4.83)
Age in years (range; SD)		34.6 (15–53; 12.38)	33.2 (13–56; 12.51)

(13–56), ten male and 15 females with a mean BMI of 26.3 kg/m^2 (19–35) and average intra-operative defect size of 4.6 cm^2 (2–12). Patient characteristics are described in Table 1. In 6 (24%) cases in the femoral group, concomitant surgery was carried out (4 cancellous bone grafting and 2 anterior cruciate ligament reconstructions). In the patellar group, nine (36%) concomitant surgery (8 stabilization of the medial retinaculum and 1 high tibial osteotomy) were performed. Previous surgery was performed in nine cases in the patellar group (bone marrow stimulation $n = 7$, cartilage shaving $n = 1$, high tibial osteotomy $n = 1$) and nine cases in the femoral group (bone marrow stimulation $n = 8$, refixation flake fracture $n = 1$).

Localizations

In both groups, a significant IKDC improvement within the group in comparison to pre-operative values (pre-operative vs. 6, 12, 24, 36 months; $p < 0.05$) (Fig. 2) was found at all timepoints. In the femoral group, the IKDC subjective score was 33.9 (3–67) pre-operatively and 56.4 (28–93) after six months. Afterwards, we observed further increasing IKDC score to 66.7 (25–95) after 12 months and 70.2 (48–100) after two years. The maximum value 71.5 (40–100) was reached after three years (Table 2). The patellar group showed an IKDC subjective score of 36.1 (14–65) pre-operatively. Six months pos-toperatively, it was 47.5 (22–78) and the 12-month value was 54.3 (23–81). After two years, the maximum IKDC value was reached with 57.7 (16–93). A slight decrease was seen after three years to 54.7 (22–92).

Comparing the IKDC results of our two groups over a period of three years, we found a significant difference between the two groups. The IKDC score showed a significant difference between the two groups one to three years post-operatively ($p < 0.05$). At all post-operative timepoints, the IKDC value of the femoral group was better than of the patellar group. Only after six months was the difference ($p > 0.05$) statistically not significant. In the following timepoints, significant differences of IKDC score were noticed (after 1 year $p = 0.016$, 2 years $p = 0.030$, and 3 years $p = 0.009$) (Fig. 1; Table 2).

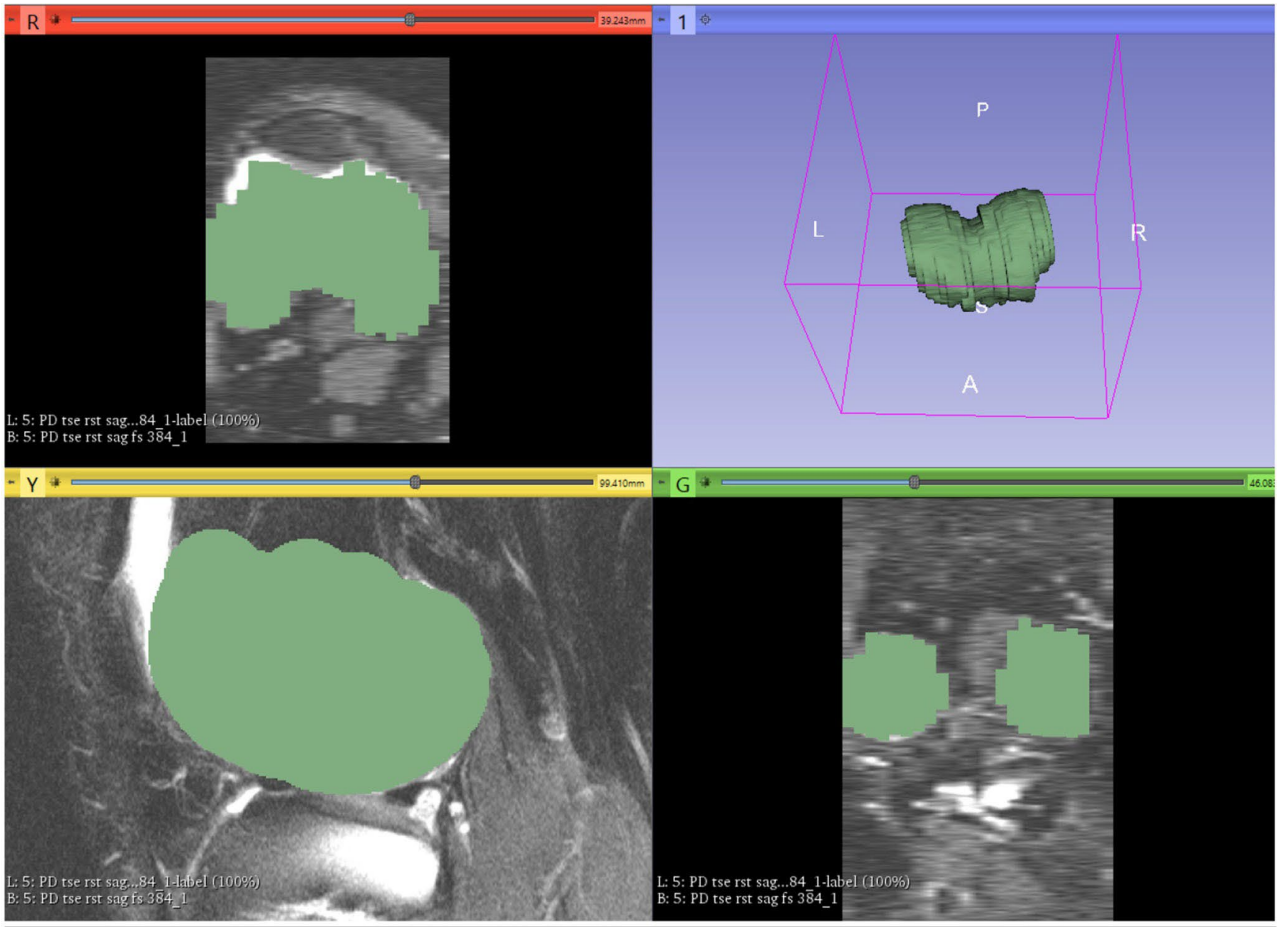
The results of the visual analog scale (VAS) also showed a statistically significant improvement over time. In the femoral group, the patients assessed the VAS at rest pre-operatively with an average of 2.6 (0–8). Post-operatively, the VAS at rest was 0.57 (0–6), 0.87 (0–5), 0.53 (0–4), and 0.78 (0–5) measured 6, 12, 24, and 36 months after ACI, which means a significant improvement at all timepoints (Table 2; Fig. 2). In the patellar group, a significant improvement ($p < 0.05$) of the VAS at rest scale was seen at post-operative measurements after 12 ($p < 0.01$) and 24 months ($p < 0.002$). As for the VAS at movement, there was a significant improvement measured at all times post-operatively in both femoral and patellar groups ($p < 0.02$). The rate of the VAS at movement in the femoral group pre-operatively was 6.9 (0–10) and improved to 1.8 (0–8) at 24 months and to 2.4 (0–9) at 36 months post-operatively. Similarly, in the patellar group, VAS at movement improved from 6.7(0–10) pre-operatively to 3.4 (0–9) after 36 months (Table 2; Fig. 3). Comparing the two groups, a statistically significant difference between the two groups was shown two years post-operatively for VAS at movement ($p = 0.004$) and six months post-op for VAS at rest ($p = 0.005$) (Table 2).

Defect size

The mean relative defect share on the knee was 12.8% (1.2–47.7). In the femoral group, the average relative defect was 6.7% (1.2–13.9), while in the patellar group, it was 18.9% (4.0–47.7) (Fig. 4). Comparing these relative defects sizes, we found a significant difference between the medial femoral condyle and the patella group. This means that the same absolute defect size at medial femoral condyle and patella has a significantly different ($p < 0.05$) share on the total cartilage size of the joint compartment (relative defect size). It is graphically summarized in Fig. 4. In analyzing the influence of the relative defect size on the clinical outcome measured by IKDC and VAS, no statistically significant correlation was found ($p > 0.05$). As for the absolute defect size, no statistically significant correlation between the outcome and the absolute defect size was found.

Discussion

The major findings of this study are that the third-generation ACI in femoral treated cartilage defects leads to a superior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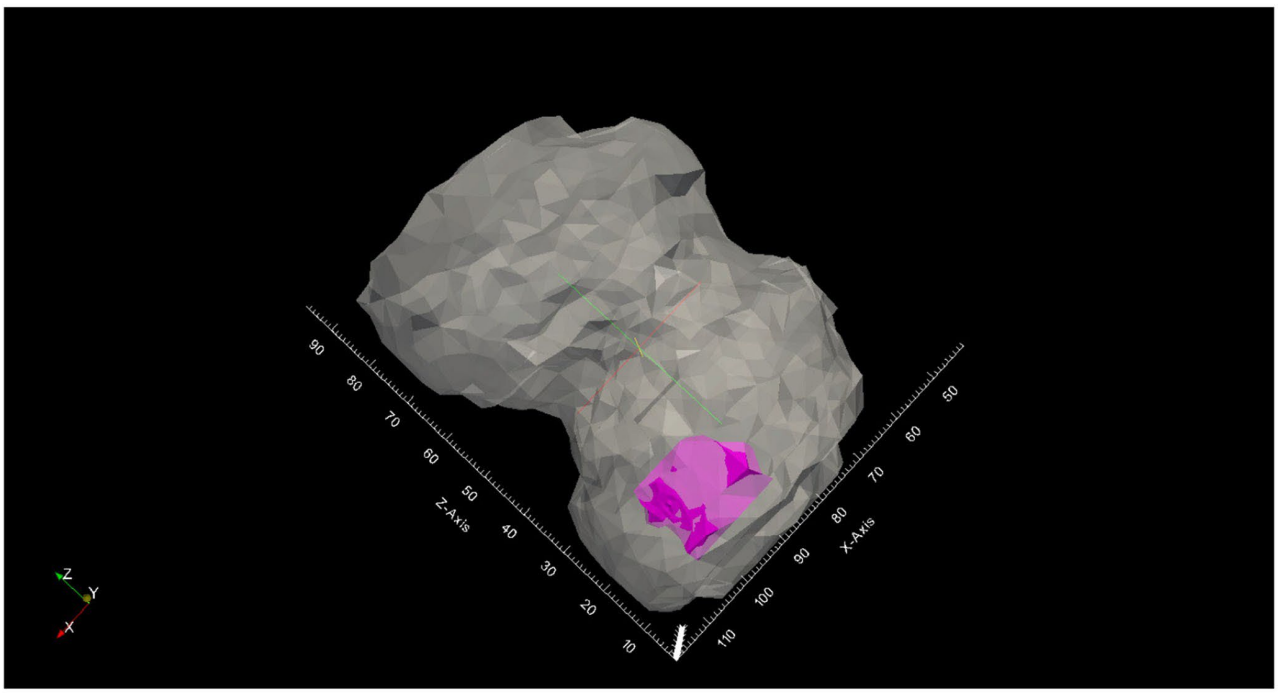
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Fig. 1 The DICOM (Digital Imaging and Communications in Medicine) datasets were used in the open source software 3D Slicer to do the manual segmentation of the cartilage layer and of the defect (a). In the further post-processing using the ParaView and YBones software, the share of the defect on the cartilage layer of the knee compartment, which represented the relative defect size in %, was calculated. The violet part in the picture is the femoral defect, and the white part represents the cartilage layer (b)

clinical outcome in a follow-up of three years compared with ACI-treated patellar cartilage defects and that the relative and absolute defect sizes do not have a significant influence on the outcome.

The third-generation ACI is an established and accepted method for the treatment of full-thickness cartilage defects in the knee as has been proven in many studies [6, 26]. The evidence on the success of the ACI has increased significantly during the past years [27–29]. The efficacy of this procedure has been demonstrated in multiple studies showing a positive effect, with increased function and pain reduction [3–5, 16, 19, 30]. The ACI with its cell expansion in vitro and the whole process is an expensive method of the cartilage therapy [31]. Therefore, the indication for using this procedure should be as clear as possible. All influencing factors are still the focus of many studies.

Since the introduction of ACI, several studies have described factors that influence its clinical outcome. There are patient-related (sex, age, BMI, physical activity) and defect-related (lesion size, location, prior procedures, etiology) aspects that can influence the results of the ACI [32]. The studies investigating the significant correlation of these factors with the outcomes have showed heterogeneous results. Some previous research described that female sex and chronic aetiology are associated with inferior outcomes [18, 33]. Regarding age and BMI as factors, some studies have shown the disadvantageous effects of higher patient age and BMI on the outcome of ACI [33–35].

Filardo et al. in a large matrix-associated ACI cohort presented the disadvantage of higher age with the degenerative aetiology and the benefit of male sex with higher physical activity. On the other hand, Vasiliadis et al. and Kon et al. described no association between clinical outcomes and age, and Gobbi et al. showed no correlation with aetiology [27, 33, 36]. Regarding

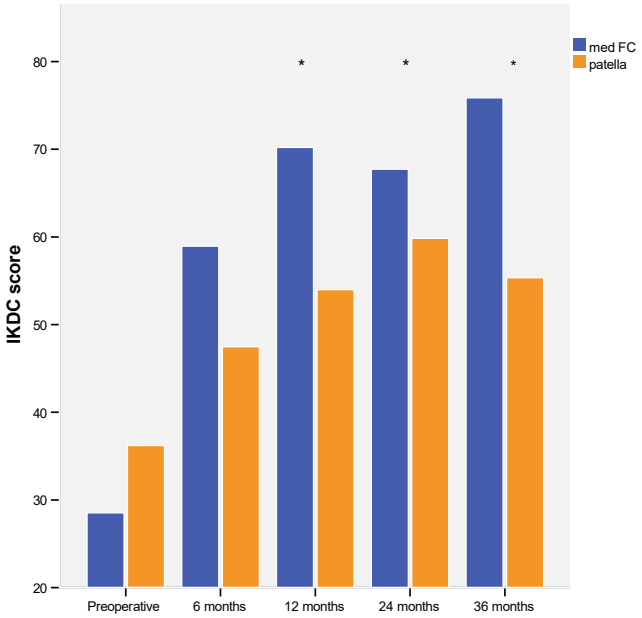

Fig. 2 The evolution of the IKDC results of the two groups over a period of three years. In both groups, there was a significant improvement in comparison to pre-operative values at all timepoints. At 12, 24, and 36 months was the IKDC value of the med FC group significantly better (marked with *) than the patellar group (6 months $p = 0.101$, 1 year $p = 0.0.016$, 2 years $p = 0.030$, and after 3 years $p = 0.009$)

prior procedures, a study regarding the negative influence of prior cartilage procedures has been published [37, 38].

In terms of influencing factors, in our study, we focused on the localization and the defect size. We removed other influencing factors by matching. The patellar-located lesions have been associated with lower clinical outcomes [19, 35], despite the correction of the patellar malalignment showed clinical improvement [17, 39, 40]. In our study, we only analyzed the third-generation ACI. There are few studies focusing on localization analyzing only the third-generation ACI to compare our results with. Gigante et al. did not see a significant difference between various localizations of the defect in his small sample of patients [41]. Filardo et al. compared third-generation ACI in patellar vs. trochlear region, with significant superiority for trochlear lesions. In another study from this group, condyle and trochlear lesions

Table 2 Clinical outcomes of medial femoral condyle (med FC) and patella group over the time

		Pre-operative	6 months	12 months	24 months	36 months
Med FC	IKDC (range; SD)	33.9 (3–67; 18.13)	56.4 (28–93; 17.14)	66.7 (25–95; 19.35)	70.2 (48–100; 14.66)	71.5 (40–100; 17.47)
	VAS at movement (range; SD)	6.90 (0–10; 2.90)	3.60 (0–9; 3.10)	2.81 (0–9; 2.74)	1.83 (0–8; 2.23)	2.40 (0–9; 2.50)
	VAS at rest (range; SD)	2.63 (0–8; 2.69)	0.57 (0–6; 1.36)	0.87 (0–5; 1.44)	0.53 (0–4; 1.04)	0.78 (0–5; 1.48)
Patella	IKDC (range; SD)	36.1 (14–65; 12.59)	47.4 (22–78; 17.46)	54.3 (23–81; 15.48)	57.7 (16–93; 18.59)	54.7 (22–92; 20.31)
	VAS at movement (range; SD)	6.71 (0–10; 2.81)	4.71 (1–10; 2.63)	4.14 (1–9; 2.45)	4.51 (1–10; 3.15)	3.40 (0–9; 2.49)
	VAS at rest (range; SD)	2.66 (0–9; 3.06)	1.8 (0–5.5; 1.92)	0.57 (0–3.7; 0.95)	0.7 (0–3.4; 0.99)	1 (0–3; 1.1)

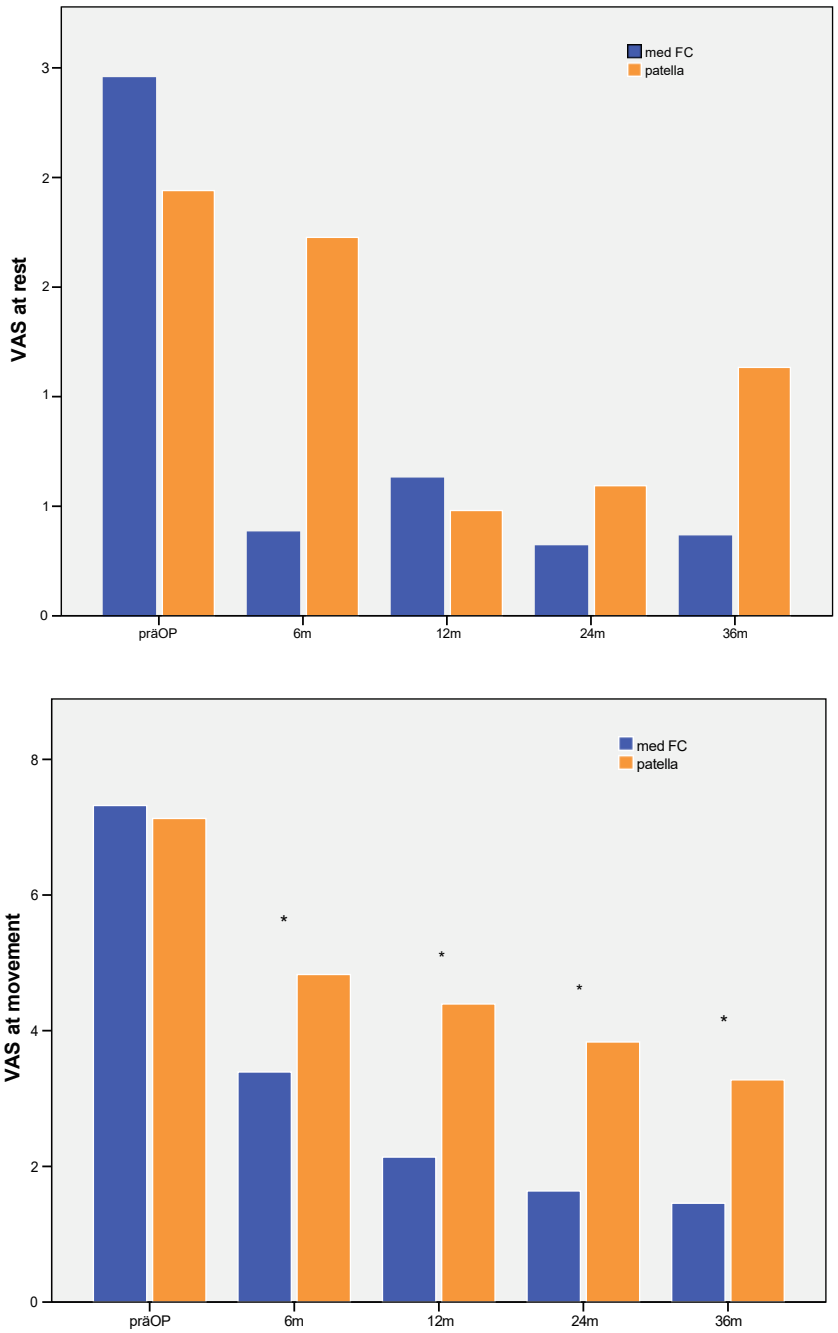

Fig. 3 The comparison of the VAS at rest (a) and at movement (b) in med FC and pat group. The VAS at rest in med FC reached a significant improvement 6, 12, 24, and 36 months after ACI. In the pat group, a significant improvement ($p < 0.05$) of the VAS at rest scale was seen at post-operative measurements after 12 ($p < 0.01$) and 24 months ($p < 0.002$). As for the VAS at movement, there was a significant improvement measured at all times post-operatively in both medial femoral condyle (med FC) and patella groups ($p < 0.02$) (*Stands for significance in both group)

were compared with slightly better results for trochlear [42]. In the study of Gobi et al., ACI patients with trochlear lesions showed better results than those with patellar lesions [43]. We did not analyze the trochlear lesion at all. Meyerkort et al. described good clinical improvement with KOOS score > 70 five years after patellofemoral ACI but did not analyze the femoral localization [40].

Welsch et al. investigated the MACI comparing patella vs. med FC lesions and found no significant difference from the radiological point of view without clinical outcome scores [21]. Kon et al. analyzed the long-term results of the patellar ACI without comparing other localizations, proving no clinical worsening over the time in patellar lesion, despite his previous finding at mid-term results [36]. Ebert et al. showed a significant difference between femorotibial and patellofemoral KOOS scores [44]. In a recent study, Niemeyer et al. presented no significantly better results for patellar defects than femoral using the matrix-associated ACI with spheroid technology [20].

With the increasing number of ACI procedures, there are now many studies focusing attention on the size of the defect. In all of the available studies, the focus of interest is the absolute defect size measured intra-operatively. According to actual recommendations, defect size from 2.5 to 3 cm^2 and larger provides a potential indication for ACI. Previously, it was

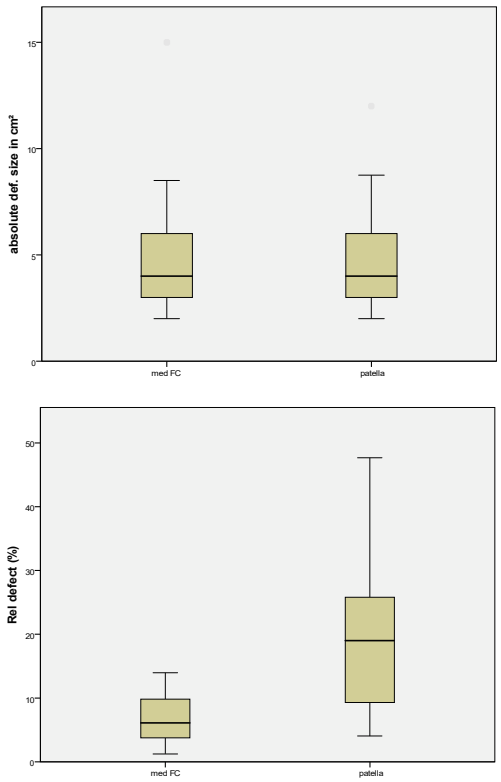

Fig. 4 The same absolute defect size (a) at medial femoral condyle (med FC) and patella has a significantly different ($p < 0.05$) share on the total size of the joint compartment (relative defect size (b))

thought that treatment of large defects was associated with an increased risk of failure [24]. However, there are now many studies that did not find any correlation between outcomes and the absolute defect size [14, 23, 27]. In our study, we also did not find any correlation between outcome and absolute defect size.

To our knowledge, there is no study investigating the relative defect size as the share of the defect on the whole cartilage layer of the knee compartment. Therefore, in our study, we analyzed the absolute and relative defect size, which we obtained by comparing the defect size measured in the MRI in relation to the whole size of the knee compartment. We showed that the same absolute defect size at medial femoral condyle and patella has a significantly different share on the total size of the joint compartment (relative defect size) ($p < 0.05$). Nevertheless, it had not been proven in our further analysis if the relative defect size had no significant influence on the clinical outcome ($p > 0.05$). According to our results, neither the absolute nor the relative defect size has a significant influence on outcomes and could not explain the inferiority of the patellar clinical outcome.

A potential negative effect of the worse clinical outcome in patellar defects is the complexity of the patellofemoral joint. Maltracking or patella instability is causing most of the patellar cartilage defects. Concomitant surgery is often needed. In this study, we could not find negative effects of concomitant surgery in general in both groups. Also, there was no negative effect regarding the treatment of patella instability. In 8 patellar patients, additional stabilization of the patella was performed without worse clinical outcomes ($p > 0.005$).

A limitation of our study is the relatively small number of patients ($n = 50$), with 25 in each group and a relatively short follow-up of three years. A larger study would be helpful to have stronger reliability in our findings and would enable the possibility of getting the significant results for relative defect sizes. Long-term follow-up would also bring us more information about the durability and further development of our results. The next limitation could be the missing matching for aetiology of the defects. When interpreting the results of the present study, lack of randomization should be kept in mind, which reduces the level of evidence from I to III.

Conclusion

Third-generation ACI provides clinical benefits for both patellar and femoral defects. In a follow-up of three years, ACI-treated femoral cartilage defects showed superior clinical outcomes compared with patellar defects. No significant influence of the relative or absolute defect size was found in either femoral or patellar cartilage defects.

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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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Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results

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Abstract

Purpose Third-generation autologous chondrocyte implantation (ACI) is an established and frequently used method and successful method for the treatment of full-thickness cartilage defects in the knee. There are also an increasing number of patients with autologous chondrocyte implantation as a second-line therapy that is used after failed bone marrow stimulation in the patient's history. The purpose of this study is to investigate the effect of previous bone marrow stimulation on subsequent autologous chondrocyte implantation therapy. In this study, the clinical results after the matrix-based autologous chondrocyte implantation in the knee in a follow-up over 3 years postoperatively were analysed.

Methods Forty patients were included in this study. A total of 20 patients with cartilage defects of the knee were treated with third-generation autologous chondrocyte implantation (Novocart® 3D) as first-line therapy. The mean defect size was 5.4 cm^2 (SD 2.6). IKDC subjective score and VAS were used for clinical evaluation after 6, 12, 24 and 36 months postoperatively. The results of these patients were compared with 20 matched patients with autologous chondrocyte implantation as second-line therapy. Matched pair analysis was performed by numbers of treated defects, defect location, defect size, gender, age and BMI.

Results Both the first-line (Group I) and second-line group (Group II) showed significantly better clinical results in IKDC score and VAS score in the follow-up over 3 years compared with the preoperative findings. In addition, Group I showed significantly better results in the IKDC and VAS during the whole postoperative follow-up after 6, 12, 24 and 36 months compared to Group II with second-line autologous chondrocyte implantation (IKDC 6 months $p = 0.015$, 1 year $p = 0.001$, 2 years $p = 0.001$, 3 years $p = 0.011$). Additionally, we found a lower failure rate in Group I. No revision surgery was performed in Group I. The failure rate in the second-line Group II was 30%.

Conclusion This study showed that third-generation autologous chondrocyte implantation is a suitable method for the treatment of full-thickness cartilage defects. Both, Group I and Group II showed significant improvement in our follow-up. However, in comparing the results of the two groups, autologous chondrocyte implantation after failed bone marrow stimulation leads to worse clinical results.

Level of evidence III

Keywords ACI · Second-line therapy · Cartilage

Introduction

Full-thickness cartilage defects, known as pre-arthritic lesions [7], often cause significant pain and disability for the patient [1]. It is well known that the intrinsic regeneration capacity of the cartilage is very limited and the healing likelihood of once damaged cartilage is very small [16]. Surgical medical options in these cases include bone marrow stimulation (BMS) techniques such

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as microfracturing, osteochondral cylinder transplantation and autologous chondrocyte implantation (ACI) [23, 37, 45].

Bone marrow stimulation techniques like microfracture expose the subchondral bone marrow and create a blood clot in the chondral defect, ultimately recruiting mesenchymal stem cells that heal the defect with a fibrocartilaginous scar [41]. Due to the technical simplicity, short surgical times, low cost, and lack of need for additional equipment, BMS has become a popular first-line treatment for chondral defects [28, 45]. Microfracture has historically demonstrated good to excellent results in active patients with small defects at short-term follow-ups [13, 14, 26, 40, 45]. However, the quality of the new regenerated tissue after microfracturing seems to be inferior to that after ACI, as shown by an investigating the histomorphometry and the overall histologic evaluation in the randomised control trial of patients [38].

Autologous chondrocyte implantation, which is a more elaborate and expensive procedure has been proven by several studies to be an appropriate method for treatment of larger full-thickness cartilage defects in knee [10, 21, 29–31, 35]. Since the first ACI, there have been many improvements in this procedure. The third-generation autologous chondrocyte implantation, where the chondrocytes are seeded on an absorbable matrix, simplified the operative procedure and produced comparable clinical results [12].

There are many studies comparing the ACI with BMS options and they have provided various results [3, 18, 42]. There seems to be a general agreement that BMS is appropriate for small defects, while ACI is more suitable for larger defects > 3.5 cm^2 [30]. In selecting the appropriate procedure, a variety of patient-related (sex, age, BMI, activity level) and defect-related (lesion size, location, prior procedures) aspects need to be considered. To date, there has not been much information regarding the results of the subsequent third-generation ACI after the failure of the first-line cartilage therapy.

The aim of this study is the investigation of the clinical results after third-generation autologous chondrocyte implantation as first-line and second-line therapy after failed previous cartilage therapy with bone marrow stimulation technique. This study was focused on investigating the effect of previous BMS on subsequent autologous chondrocyte implantation therapy. The question arises, if autologous chondrocyte implantation is a suitable method for treatment of full-thickness cartilage defects in both situations. The following hypothesis was generated from the questions above: second-line autologous chondrocyte implantation after failed BMS leads to inferior outcomes in comparison to patients with the autologous chondrocyte implantation as first-line therapy.

Materials and methods

In this prospective study, 40 patients with cartilage defects of knee classified as grades III–IV according to the International Cartilage Repair Society (ICRS) were treated with third-generation ACI (NOVOCART® 3D, TETEC AG, Reutlingen, Germany). All patients were treated according to the guidelines of the working group Tissue Regeneration of the German Society for Orthopaedic and Trauma Surgery [30]. A matched pair analysis was performed with 20 patients with ACI after failed previous cartilage therapy with bone marrow stimulation technique (Group II) and 20 patients with ACI without previous cartilage therapy (Group I) was created. The criteria for pair matching were numbers of treated defects and defect location. If there were multiple options, the criteria gender, aetiology, defect size, BMI and age were used for pair matching (Table 1).

The International Knee Documentation Committee (IKDC) Subjective Knee Form and the visual analogue scale (VAS) at rest and during activity were used after 6, 12, 24, and 36 months postoperatively to evaluate the clinical outcomes.

Surgical technique

All patients were treated with NOVOCART® 3D (TETEC AG, Reutlingen, Germany), a third-generation ACI. In the initial arthroscopic procedure of the knee joint, which confirmed the full-thickness cartilage defect of ICRS III–IV, two or three osteochondral cylinders were harvested from the non-weight bearing place at the intercondylar notch and sent in a sterile nutrient solution to the manufacturer. Developing and cultivation time was approximately 3–4 weeks. After cultivation, the cells were seeded on a collagen I/III biphasic scaffold, with a dense membrane and a spongy part of pores. The ACI procedures were performed with a parapatellar arthrotomy of the knee joint, the cartilage defect measured and debrided to create the healthy rim. The ACI scaffolds were cut to the needed size and placed with the cell-seeded spongy part into the debrided cartilage defect. Afterwards the grafts were fixed with absorbable sutures. Perioperative antibiotic prophylaxis was done with intravenous Cefuroxim 1.5 g. In cases with existing deformities or pathologies, additional co-operations were performed.

Rehabilitation

Postoperative rehabilitation was carried out with a standardised protocol. In patients with femoral cartilage defects, rehabilitation began with use of a continuous passive motion (CPM) device after 24 h of bed rest and drain removal.

Table 1 Patients' characteristics

	Group I: ACI without previous BMS	Group II: ACI with previous BMS
Number of patients	20	20
Number of defects *n* (%)		
One treated defect	16 (80)	16 (80)
Two treated defects	4 (20)	4 (20)
Localisation *n* (%)		
Femoral	11 (55)	10 (50)
Patellar	8 (40)	9 (45)
Trochlear	1 (5)	1 (5)
Gender *n* (%)		
Male	8 (40)	6 (30)
Female	12 (60)	14 (70)
Aetiology *n* (%)		
OD	4 (20)	2 (10)
Old trauma > 12 months	3 (15)	3 (15)
Chronic/degenerative	13 (65)	15 (75)
Defect size in $cm^2 \pm SD$ (range)	5.40 ± 2.6 (2–15)	4.82 ± 2.0 (2–10)
BMI in $kg/m^2 \pm SD$ (range)	26.8 ± 4.9 (19.2–34.4)	26.5 ± 3.6 (20.0–34.0)
Age in years ± SD (range)	32.9 ± 11.8 (16–55)	39.1 ± 10 (19–53)
Failure rate (%)	0 of 20 (0)	6 of 20 (30)

During the first 6 weeks post-operation, only a partial load of 20 kg for the femoral cartilage defects was permitted. In patients with patellar defects, a limited knee brace was fitted with flexion to 30° for 2–3 weeks and was gradually increased in the next weeks. Full weight bearing was allowed with full extension after wound healing. All patients were also treated by physical therapists. Moderate physical activities such as cycling, swimming, and Nordic walking were not allowed until 3 months postoperatively. High-impact sports (e.g., soccer, basketball) were not allowed earlier than 12 months after surgery. Institutional review board (IRB) approval was obtained from the ethical committee of the Ludwig Maximilian University (LMU) of Munich (344-12).

Statistical analysis

For the statistical analysis of the clinical data, the statistic program SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) was used. All patients were detected with a failed previous BMS. Accordingly, a matched paired analysis was performed as described above. To calculate the required sample size, power analysis was performed with G*Power (version 3.1) using a *t* test (alpha 0.05, power of 0.95, two-tailed). A minimum total sample size of 57 were calculated (medium effect size of 0.5). For the detection of significant differences between the two groups at the same time of investigation, the Wilcoxon or Friedman test was carried out for paired samples. To compare multiple groups of non-related samples at one point, the Mann–Whitney *U* test was used. A statistically significant result of $p < 0.05$ was reported.

Results

Patient characteristics are described in Table 1.

Group I with first-line ACI showed an IKDC subjective score of 37.0 (SD 13.7) preoperatively. The maximum IKDC value was reached after 2 years with 77.7 (SD 19.7) points. Compared to the preoperative IKDC values, a significant improvement at all timepoints was detected (preoperative vs. 6 months $p = 0.001$, vs 12 months $p = 0.000$, vs 24 months $p = 0.002$, vs 36 months $p = 0.003$).

In Group II with second-line ACI patients, a significant increase of the subjective IKDC score was found. The IKDC subjective score was 29.9 (SD 17.0) preoperatively and 44.3 (SD 19.5) after 6 months. Afterwards we observed an increasing IKDC subjective score to a maximum value of 50.1 (SD 20.4) after 1 year. After 3 years, the average IKDC subjective score was 49.1 (SD 21.2) (Table 2). A significant improvement of the IKDC subjective score was seen at all times compared to preoperative findings (preoperative vs. 6 months $p = 0.05$, vs 12 months $p = 0.002$, vs 24 months $p = 0.009$, vs 36 months $p = 0.011$).

Comparing the IKDC results of the two groups over a period of 3 years, a significant difference between the groups was found. In all follow-ups, a significant difference between the IKDC results of both groups was seen. At all time points,

Table 2 Results of the clinical scores

	Group I: ACI without previous BMS	SD	Group II: ACI with previous BMS	SD	*P* value
Preoperative					
Average IKDC score	37.0	13.7	29.9	17.0	
Average VAS score in motion	6.4	2.2	6.8	2.6	
Average VAS score at rest	1.9	2.5	4.4	3.8	
6 months					
Average IKDC score	57.6	14.3	44.3	19.5	0.015
Average VAS score in motion	2.7	2.4	4.8	3.2	0.043
Average VAS score at rest	0.8	2.3	1.9	2.5	n.s
12 months					
Average IKDC score in	72.5	14.8	50.1	20.4	0.001
Average VAS score in motion	1.2	1.3	3.8	2.5	0.003
Average VAS score at rest	0.1	0.3	1.0	1.2	0.010
24 months					
Average IKDC score	77.7	19.7	48.6	21.8	0.001
Average VAS score in motion	1.4	1.9	5.0	3.1	0.002
Average VAS score at rest	0.2	0.5	2.0	2.9	0.014
36 months					
Average IKDC score	74.7	22.6	49.1	21.2	0.011
Average VAS score in motion	1.4	1.9	4.5	2.8	0.005
Average VAS score at rest	0.4	1.1	1.5	1.7	0.028

Significant p values < 0.005 are underlined

the IKDC value of Group I was better than in Group II. After 6 months, the difference was significant: $p = 0.015$. The significant differences of IKDC subjective scores continued after 1 year $p = 0.001$, 2 years $p = 0.001$ and after 3 years $p = 0.011$ (Table 2) (Fig. 1).

The VAS for pain in Group I was preoperatively at 6.4, and at rest 1.9. A significant improvement in motion and at rest was shown at all time points postoperatively with significant differences of $p = 0.002$ (VAS in motion 6 months), $p = 0.001$ (VAS in motion after 1 year), $p = 0.002$(VAS in motion after 2 years), $p = 0.002$ (VAS in motion after 3 years) and $p = 0.049$ (VAS at rest 6 months), $p = 0.007$ (VAS at rest after 1 year), $p = 0.008$ (VAS at rest after 2 years), $p = 0.029$ (VAS at rest after 3 years) compared to the preoperative values.

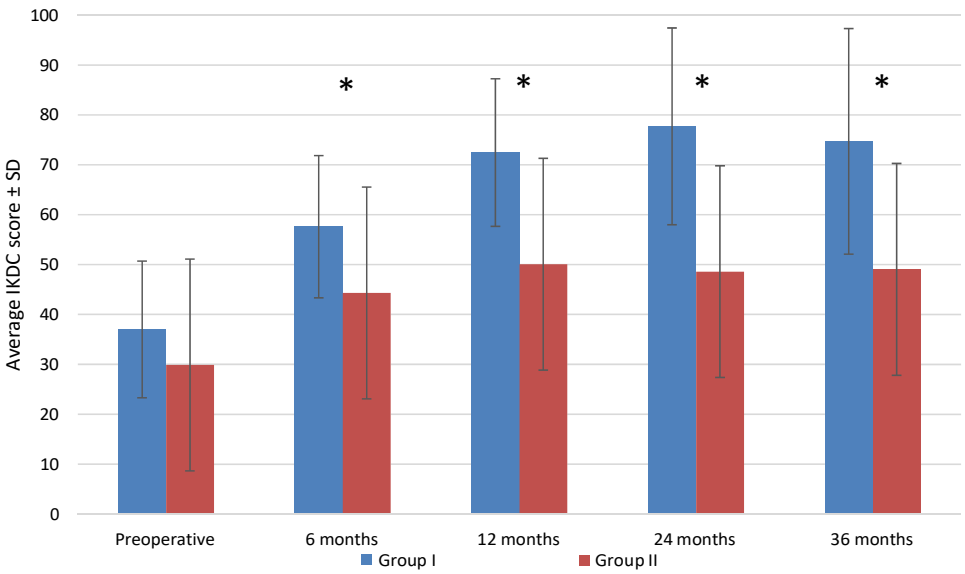

Fig. 1 In Group I and Group II, significantly increased IKDC values compared with the preoperative findings were shown. The outcome of ACI as second-line therapy after previous failed cartilage therapy with bone marrow stimulation is worse than ACI as first-line therapy. At all time points, the IKDC value of Group I is better than the Group II (6 months $p = 0.015$, 1 year $p = 0.001$, 2 years $p = 0.001$ and after 3 years $p = 0.011$) (*$p < 0.05$)

In the Group II, a significant improvement in visual analogue scale (VAS) for pain in motion and at rest was observed. The initial VAS pain was 6.8 in motion and 4.4 at rest. Afterwards, a significant improvement in VAS in motion was found only after 6 months and 1 year. In VAS for pain at rest was it after 6 months, 1 year and 3 years compared to the preoperative results. The best value of VAS was achieved after 1 year (3.8 in motion and 1.0 at rest).

The VAS score in motion showed a significant difference between these groups also in all follow-ups. Group I with first-line ACI patients without previous cartilage therapy had less pain in motion and at rest (Fig. 2). The VAS score at rest showed a significant difference between the two groups in all follow-ups except for after 6 months.

Failure was determined by the need of another revision surgery. The failure rate in Group II was 30% (6 of 20). In three cases, microfracturing was performed, because of partial graft insufficiency, which were treated with microfracturing. In two cases, revision surgery was performed with high tibial osteotomy ($n = 1$) and knee arthroplasty ($n = 1$), because of osteoarthritis. In one case, a symptomatic bone marrow edema occurred, what was treated with retrograde drilling. In Group I, no revision surgery was performed.

Discussion

The major finding of this study is that third-generation of autologous chondrocyte implantation represents a suitable method and has satisfactory results as first-line and as second-line therapy in treating full-thickness cartilage defects. However, the outcome of ACI as second-line therapy after previous failed cartilage therapy with bone marrow stimulation is worse than ACI as first-line therapy. Our data demonstrate that bone marrow stimulation (BMS) (e.g. microfracturing) has a negative effect on subsequent cartilage repair with ACI.

BMS is one of the most commonly used surgical techniques for the treatment of cartilage defects in the knee. Many studies have reported statistically significant improvements in clinical outcomes after microfracture [26, 40, 45]. Due to its low costs and, compared with other cartilage therapies, less demanding surgical procedure, bone marrow stimulation was performed in cases with small and large cartilage defects.

The evidence regarding ACI procedure has significantly increased over the past years [43, 44]. The efficacy of this procedure has been demonstrated in multiple studies showing a positive effect, with increased functionality and pain reduction [5, 10, 31, 34, 35]. As the use of ACI has been increasing over time, there are also more patients with prior cartilage procedures with bone marrow stimulation as the microfracturing in their patient history. Since the introduction of ACI, several studies have described factors that influence its clinical outcome. Studies have shown the disadvantageous effects of defect chronicity and patient age on the outcome of ACI [19, 42]. To date, there have been only a few studies investigating the outcome of ACI as the second-line therapy after previous cartilage treatment.

As a result, a matched pair analysis of first-line vs. second-line ACI in a follow-up over 3 years was performed. Matched pair analysis is a well-established method allowing the scientific statements, often used in similar types of studies [32]. International Knee Documentation Committee (IKDC) Subjective Knee Form and the visual analogue scale (VAS) at rest and during activity were used. Both scores are valid, reliable [6, 15] and have been frequently applied in various studies analysing autologous chondrocyte implantation in the knee joint with ACI [27, 32, 33].

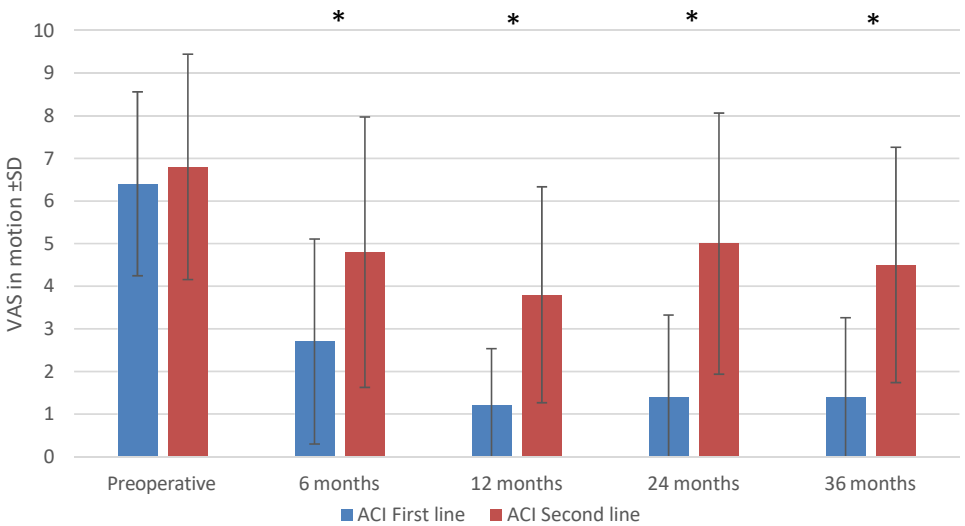

Fig. 2 This diagram shows the comparison of the VAS score in motion of the two groups over a period of 3 years. The VAS score in motion showed a significant difference between these groups in all follow-ups (6 months $p = 0.043$, 1 year $p = 0.003$, 2 years $p = 0.002$ and after 3 years $p = 0.005$) (*$p < 0.05$)

Several studies address the second-generation ACI in the knee joint [36]. These studies have shown an increased failure rate in the second-line ACI group. In the study by Pestka et al., 28 patients with second-line ACI were analysed after failed microfracturing [36] with matched pair analysis. They also observed an increased failure rate and significant reduced clinical scores in the second-line ACI group. Jungmann et al. [17] shows that patients with second-line ACI after previous BMS, for the most part with microfracturing, have an increased failure risk. There were no specific data about the third-generation ACI mentioned. In the present study, we also found a significantly higher rate of failure in the second-line ACI Group II of 30% in cases with third-generation ACI.

In the study by Zaslav et al., first-generation ACI was analysed without a control group. They showed that patients with second-line ACI after failed prior cartilage treatments can expect significant clinical and long-lasting improvements in pain and knee function [46]. A comparison between patients with ACI as first-line therapy was not performed in this study. Minas et al. [24] reported an increased failure rate of second-line ACI after treatment with the previous bone marrow stimulation (BMS) techniques in cases with first-generation ACI. The failure rates of second-line ACI after drilling was 28%, abrasion arthroplasty 27% and microfracture 20%. No further assessment regarding clinical knee function after ACI was investigated in this study.

In a further study, Minas et al. described the survivorship of first-generation ACI in a large patient cohort over 10 years [25]. The survivorship of first-generation ACI grafts was significantly decreased in patients with prior microfracturing (44%) in comparison to patients with first-line ACI (77%). Interestingly, there was no significant difference in clinical outcome scores between second-line ACI after failed marrow stimulation and first-line ACI with periosteal flap.

In the present study, it could be demonstrated that bone marrow stimulation (BMS) (e.g. microfracturing) has a negative effect on subsequent cartilage repair with third-generation ACI. A possible explanation for these findings can be a thickening and alteration of the subchondral plate after microfracturing. Microfracturing and microcracks could be responsible for initiating the secondary ossification centre [8]. With regard to that, the overlying articular cartilage becomes more vulnerable to damage from shear forces [4, 11, 22]. This mechanism results in thickening of the subchondral bone and corresponding thinning of the overlying cartilage, which is then more susceptible to damage and further degeneration [2]. Similar changes are found in osteoarthritis and chronic chondral defects, which have demonstrated worse outcomes with cartilage repair procedures [9].

A deterioration of the regenerated cartilage which appears several years after BMS techniques [20] was observed. The reason for this could be that the new regenerated fibrocartilage tissue induced by bone marrow-stimulating techniques seems to be inferior in its histological-structural quality in direct comparison with hyaline articular cartilage [39]. Although the mechanism of this degeneration has not been conclusively proven, changes in the subchondral bone could be potentially seen as an explanation for the deterioration of BMS and subsequent second-line ACI therapy.

Limitations of the present study are the relatively small number of patients—40, with 20 in each group and the relatively short follow-up of 3 years. A larger study population would be helpful for analysing the subgroups to identify the risk factors for the poorer outcomes of the group with previous BMS therapy. Additional research is needed to identify the exact cause of worse outcomes in cases with second-line ACI. A possible explanation is the influence of the damaged subchondral plate with increased mechanical stiffness. Therefore, an extensive analysis of the subchondral plate in patients with cartilage therapy is needed.

Based on the results of this study, the autologous chondrocyte implantation provides clinical benefits in both first-line cartilage therapy and second-line therapy. In addition, our data demonstrate that BMS has a negative effect on subsequent cartilage repair with autologous chondrocyte implantation in the knee joint. Therefore, the choice of which primary cartilage therapy to perform should be made very carefully. This study has shown that first-line ACI leads to superior clinical results compared with the results after second-line ACI.

Conclusion

This matched pair study analysed the effect of previous bone marrow stimulation on subsequent second-line third-generation ACI. This study showed that third-generation autologous chondrocyte implantation is a suitable method for treatment of full-thickness cartilage defects, including for patients with prior BMS. However, the outcome of ACI patients as second-line therapy was worse than that of the first-line ACI. These results should be considered when choosing the appropriate therapy in cases with large full-thickness cartilage defects.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures were performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1864 Helsinki declaration and its later amendments or comparable ethical standards.

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