Aus der

Klinik für Orthopädie und Unfallchirurgie

Klinik der Universität München

Direktoren: Prof. Dr. Wolfgang Böcker und Prof. Dr. Boris Holzapfel

Matrix-assoziierte autologe Chondrozyten-Transplantation für Knorpeldefekte am Knie - Effekte Hydrogel-basierter Matrizes sowie des Rauchens auf das Outcome

Dissertation

zum Erwerb des Doktorgrades der Medizin

an der Medizinischen Fakultät

der Ludwig-Maximilians-Universität zu München

vorgelegt von

Felix Frank Uhlemann

aus

Berlin

Jahr

2025

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter:	Prof. Dr. Thomas Niethammer
Mitberichterstatter:	Prof. Dr. Marcus Schmitt-Sody
	Prof. Dr. Robert Stahl
Mitbetreuung durch den promovierten Mitarbeiter:	
Dekan:	Prof. Dr. med. Thomas Gudermann
Tag der mündlichen Prüfung:	08.05.2025

1. Inhaltsverzeichnis

1. Inhaltsverzeichnis 3

2. Affidavit 4

3. Abkürzungsverzeichnis 5

4. Publikationsliste 6

5. Einleitung 7

5.1 Fachliche Einordnung 7

5.1.1 Epidemiologische Auswertung 8

5.1.2 Paper I (Hydrogel-based autologous chondrocyte implantation leads to subjective improvement levels comparable to scaffold based autologous chondrocyte implantation.) 9

5.1.3 Paper II (The Effect of Smoking on the Outcome of Matrix-Based Autologous Chondrocyte Implantation: Data from the German Cartilage Registry.) 10

5.2 Eigenanteil an den Publikationen 11

5.2.1 Paper I (Hydrogel-based autologous chondrocyte implantation leads to subjective improvement levels comparable to scaffold based autologous chondrocyte implantation) 11

5.2.2 Paper II (The Effect of Smoking on the Outcome of Matrix-Based Autologous Chondrocyte Implantation: Data from the German Cartilage Registry.) 12

6. Zusammenfassung 13

6.1 Abstract (deutsch) 13

6.2 Abstract (englisch) 14

7. Paper I 15

8. Paper II 23

9. Literaturverzeichnis 31

10. Danksagung 33

2. Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

Eidesstattliche Versicherung

Uhlemann, Felix Frank

Name, Vorname

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

Matrix-assoziierte autologe Chondrozyten-Transplantation für Knorpeldefekte am Knie - Effekte Hydrogel-basierter Matrizes sowie des Rauchens auf das Outcome
(eine kumulative Dissertation)

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 08.05.2025 — Ort, Datum

Felix Uhlemann — Unterschrift Doktorandin bzw. Doktorand

3. Abkürzungsverzeichnis

- ACI: autologous chondrozyte implantation
- ACT: autologe Chondrozyten-Transplantation
- BMI: Body Mass Index
- IKDC: International Knee Documentation Committee Subjective Knee Form
- KOOS: Knee Injury and Osteoarthritis Outcome Score
- NRS: Numeric Rating Scale oder Numerische Rating-Skala
- VAS: Visual Analog Scale oder Visuelle Analog-Skala

4. Publikationsliste

- **Geteilte Erstautorenschaft: Hydrogel-based autologous chondrocyte implantation leads to subjective improvement levels comparable to scaffold based autologous chondrocyte implantation.** - *Niethammer TR, Uhlemann F, Zhang A, Holzgruber M, Wagner F, Müller PE.* Knee Surg Sports Traumatol Arthrosc. 2022 Oct;30(10):3386-3392. doi: 10.1007/s00167-022-06886-8. Epub 2022 Feb 28. PMID: 35226109; PMCID: PMC9464160.
- **Co-Autorenschaft: The Effect of Smoking on the Outcome of Matrix-Based Autologous Chondrocyte Implantation: Data from the German Cartilage Registry.** - *Betz VM, Holzgruber M, Simon J, Uhlemann F, Niemeyer P, Müller PE, Niethammer TR.* J Knee Surg. 2023 Jan;36(2):181-187. doi: 10.1055/s-0041-1731456. Epub 2021 Jul 8. PMID: 34237778.

5. Einleitung

5.1 Fachliche Einordnung

Knorpeldefekte des Kniegelenks sind eine häufige Diagnose. Sie werden in einer von fünf durchgeführten Arthroskopien am Kniegelenk diagnostiziert. [1] Dabei beeinträchtigen die Schädigungen Patient*Innen speziell wegen der dadurch entstehenden Schmerzen. Zum Teil gehen mit den Beschwerden erhebliche Einschränkungen des Alltags und der Lebensqualität einher. [2] Dies gilt nicht nur im Alter, sondern häufig auch bei jüngeren Menschen, ob degenerativ oder posttraumatisch. Das Durchschnittsalter der in unseren Arbeiten untersuchten Patienten lag bei unter 40 Jahren. Die Aufgabe der Medizin ist es, die Therapie solcher Knorpeldefekte weiter zu erforschen, um sie stetig weiter zu verbessern. Bisher bestehende Therapieformen sind vielfältig und umfassen u. a. das Debridement, Mikrofrakturierung, osteochondrale Transplantationen, Knochenmarkstimulation und die autologe Chondrozyten-Transplantation (ACT). [3]

Letztere war der Hauptfokus unserer Arbeit. Erstmals beschrieben wurde sie 1994 von Britberg et. al und wird seitdem stetig weiterentwickelt. [4] Bei der ACT handelt es sich um einen zweizeitigen Eingriff. Das Prinzip dabei ist, in einem ersten Schritt gesunde Knorpelzellen aus weniger belasteten Bereichen des Kniegelenks eines Patienten zu entnehmen. Nachdem diese angezüchtet werden, können sie dann in einem zweiten Schritt in die Defektstellen eingebracht werden, wo sie möglichst hyalin-ähnlichen Knorpel bilden sollen.

Während in der ersten Generation der ACT noch Zellsuspensionen in Kombination mit Periostlappen verwendet wurden, kamen in der 2. Generation erstmals Kollagen-basierte Matrizes zum Einsatz. Die Zellsuspensionen wurden dabei allerdings noch unter die Matrizes appliziert. In der dritten Generation werden die Knorpelzellen dann bereits in vitro mit einer Matrix kombiniert und anschließend gemeinsam in den Defekt eingebracht. [5] Mittlerweile existiert mit der Verwendung sogenannter Sphäroide, kleiner Kügelchen aus Knorpelzellen und ex vivo selbst gebildeter extrazellulärer Matrix, ein weiteres Verfahren für die ACT, das ebenfalls gute Ergebnisse im bisherigen Follow-up liefert. [6]

Speziell für fokale Defekte bei Patient*Innen im Alter von unter 55 Jahren, die die gesamte Knorpelschicht betreffen und eine Größe von > 2,5 cm² haben, ist die ACT die Therapie der Wahl. [7] Von Vorteil ist dabei, dass das Alter an sich keine Kontraindikation für die Durchführung der Therapie darstellt. Die ACT kann somit auch bei älteren Patienten, die bis auf den fokalen Defekt einen guten Gelenkstatus haben, zur Anwendung kommen und liefert dabei auch im Vergleich zur Behandlung jüngerer Patient*Innen gute Ergebnisse. [8] Insbesondere die zweite und dritte Generation der ACT führen nachweislich zu positiven Resultaten. [9-12]

Trotz, oder vielleicht gerade wegen des rasanten Fortschritts der Therapiemöglichkeiten gilt es, Schritt zu halten und die jeweiligen Therapieformen mit ihren Vor- und Nachteilen richtig einzuordnen. Dabei sind sowohl Faktoren, die die Indikationsstellung betreffen, als auch die Wahl der richtigen therapeutischen Methode wichtig, um das bestmögliche Ergebnis zu erzielen. Ziel unserer Forschung ist und war es, genau das zu ermöglichen.

5.1.1 Epidemiologische Auswertung

Durch die Schaffung einer multizentrischen Datenbank für Knorpelerkrankungen im Jahr 2013, dem Deutschen Knorpelregister, an welchem sich mittlerweile über 100 Zentren aus Deutschland, Österreich und der Schweiz in weiterwachsender Zahl beteiligen, eröffneten sich für die Forschungsgemeinschaft Möglichkeiten, mittels großer, gut vergleichbarer Patient*Innenkollektive mehr Erkenntnisse über die Therapie sowie Komplikationen bei Knorpeldefekten und knorpelregenerativen Eingriffen zu gewinnen. In der Anfangszeit meiner Arbeit beschäftigten wir uns dementsprechend viel mit der Zusammenstellung und Auswertung epidemiologischer Daten aus dem Register.

Dabei war für uns insbesondere die Therapie des Patello-Femoral-Gelenkes interessant, da hier signifikant schlechtere Outcomes im Vergleich zur Therapie des Tibio-Femoral-Gelenkes beschrieben sind. [11, 13-15] Am ehesten ist dies auf die komplexe Gelenkmorphologie zurückzuführen. Wir untersuchten die Daten von insgesamt 479 Patient*Innen. und fanden heraus, dass sich die Indikati-

onsstellung am Patello-Femoral-Gelenk nicht wesentlich von empfohlenen Indikationsstellung am Tibio-Femoral-Gelenk unterscheidet. [7] Aus diesem Grund kam es nicht zu einer Veröffentlichung des bis dahin verfassten Manuskripts.

5.1.2 **Paper I** (Hydrogel-based autologous chondrocyte implantation leads to subjective improvement levels comparable to scaffold based autologous chondrocyte implantation.)

Bei der dritten Generation, also der matrix-assoziierten ACT, werden den Patient*Innen wie oben beschrieben in einem ersten Eingriff Knorpelzellen insbesondere aus der intercondylären Notch entnommen, in einem komplexen Verfahren angezüchtet, mit einer bestimmten Matrix zusammengeführt und später in einem zweiten Eingriff in den Defekt eingebracht. Dabei gibt es verschiedene Formen der Matrizes. [5]

Neben der bereits länger bekannten festen Kollagen-basierten Matrix, die in einem offenen operativen Eingriff in den Defekt eingenäht werden muss, besteht die Möglichkeit, die Knorpelzellen in einem flüssigen, Hydrogel-basierten Träger anzuzüchten, der sich arthroskopisch und dadurch minimal-invasiv einbringen lässt. Das Material härtet im Anschluss im Gelenk rasch aus. Wenngleich diese Option vor allem aufgrund der Möglichkeit des schonenderen Eingriffs vielversprechend klingt, gab es bis dato noch keine veröffentlichten Vergleiche beider Methoden. Für uns war das der Grund, die Forschung an genau diesem Vergleich voranzutreiben. Weitere Arbeiten zu der Verwendung von Hydrogel-basierten Matrizes im Vergleich zu anderen Therapiemethoden sind parallel entstanden. [12, 16]

In Hinblick auf die Methodik wählten wir eine Match-Pairing Analyse. Jeweils 25 Patient*Innen mit Hydrogel-ACT wurden 25 passenden Patient*Innen, die eine ACT mit fester Matrix erhalten hatten, zugeordnet. Bei der Analyse ging es uns dabei vor allem um objektivierbare Effekte der Therapie für die Patient*Innen, weshalb wir mit der Visuellen Analog Skala (VAS) und vor allem dem International Knee Documentation Committee Subjective Knee Form (IKDC) Score gut etablierte Items wählten, anhand derer wir das Outcome in den 2 Jahren nach dem Eingriff bewerten konnten. [17, 18]

5.1.3 **Paper II** (The Effect of Smoking on the Outcome of Matrix-Based Autologous Chondrocyte Implantation: Data from the German Cartilage Registry.)

Bei der Frage nach möglichen Faktoren, die das Outcome einer Knorpeltherapie mittels ACT begünstigen oder verschlechtern, beschäftigten wir uns insbesondere mit dem Nikotinkonsum. Rauchen ist trotz eingeführter gesetzlicher Einschränkungen im öffentlichen Raum in der Gesellschaft mit einer Prävalenz von 28,9 % immer noch weit verbreitet [19]. Laut dem aktuellen WHO-Report von 2023 sterben jährlich ca. 8,7 Millionen Menschen weltweit an den Folgen von Tabakexposition, 1,3 Millionen davon durch Passivrauch-Belastung. [20]

Zu den negativen Auswirkungen des Rauchens gehört auch eine schlechtere Knochen- und Weichteilheilung, die in multiplen Studien beschrieben ist. [21-26] Bezüglich der Knorpelheilung gibt es jedoch Hinweise darauf, dass diese Korrelation u. a. aufgrund der Avaskularität des betroffenen Gewebes nicht zutrifft. [27-30] Da es zum Effekt des Rauchens bei ACT in der bisherigen Literatur gegensätzliche Ergebnisse gab, wollten wir dies genauer untersuchen. [31, 32]

Anhand von Patient*Innen-Daten aus den Jahren 2015-2018 untersuchten wir ein Kollektiv von insgesamt 281 Studienteilnehmer*Innen, die eine matrixassoziierte ACT erhalten hatten. Wir teilten die Patient*Innen in Nicht-Raucher, Ex-Raucher und Raucher auf und verglichen die Teilgruppen auf Unterschiede in Hinblick auf das Outcome. Dazu nutzten wir mit der Visuellen Analog Skala (VAS) und dem Knee Injury and Osteoarthritis Outcome Score (KOOS) gut validierte und häufig verwendete Messinstrumente. [17, 18, 33]

5.2 Eigenanteil an den Publikationen

5.2.1 **Paper I** (Hydrogel-based autologous chondrocyte implantation leads to subjective improvement levels comparable to scaffold based autologous chondrocyte implantation)

Wie in der Einleitung beschrieben war unser Ziel, einen Vergleich zwischen Hydrogel- und festen Matrizes bei ACT zu ziehen. Dabei wirkte ich zunächst in der Konzeption der Studie mit. Herr Prof. Niethammer und ich entschieden uns hierbei für eine Match-Pairing-Analyse. Zunächst war deshalb wichtig, eine für eine wissenschaftliche Arbeit geeignete Patientenzahl zu erreichen. Hierbei kümmerte ich mich in Zusammenarbeit mit den behandelnden Ärzt*Innen um die Aufklärung der Patient*Innen über die Studie sowie darum, insbesondere im postoperativen Verlauf die Datenerhebung zu überwachen, Patient*Innen an das Ausfüllen der Fragebogen zu erinnern, die Fragebögen wenn nötig zu verschicken und in unser System zu übertragen.

Als wir 25 Patient*Innen für mindestens 2 Jahre nach dem Eingriff beobachtet hatten und deren Follow-up-Daten vollständig waren, war ich für das Match-Pairing mit der deutlich größeren Population von Patient*Innen nach ACT mit fester Matrix zuständig. Hierbei ließen sich jeweils gut geeignete Paare finden. Anschließend führte ich die statistische Arbeit durch, die für das Paper notwendig war, das heißt sowohl die Zusammenstellung der epidemiologischen Daten als auch die jeweiligen Vergleiche zwischen den Patient*Innengruppen. Auch die graphische Aufbereitung der Ergebnisse lag in meinem Aufgabenbereich.

Gleichzeitig führte ich während des gesamten Zeitraums die Literaturrecherche zu unserem Thema durch und verfasste gemeinsam mit Herrn Prof. Dr. Niethammer das Paper.

5.2.2 **Paper II** (The Effect of Smoking on the Outcome of Matrix-Based Autologous Chondrocyte Implantation: Data from the German Cartilage Registry.)

Die Hauptaufgabe zur Arbeit an diesem Paper lag in der Patientenakquise und der Datenerhebung im Rahmen der Deutschen Knorpelregisters. In Zusammenarbeit mit den in unserem Zentrum behandelnden Ärzt*Innen klärte ich die Patient*Innen über das Register auf, überwachte den Follow-up und stellte sicher, dass die Patient*Innen zeitgerecht ihre Rückmeldungen gaben. Falls die Studienteilnehmer*Innen keine Möglichkeit zur elektronischen Dateneingabe hatten, führte ich diese händisch gemeinsam mit den Patient*Innen bzw. über telefonischen oder postalischen Kontakt aus. Bei Fragen unsererseits unterhielt ich Kontakt zum Studienzentrum in Freiburg.

Unser Ziel war es zunächst, mit der großen Breite an epidemiologischen Daten aus dem Register für die Wissenschaft relevante Erkenntnisse zu finden und für weitere Studien aufzubereiten. Dabei führte ich die statistische Auswertung der Daten durch. Aufgrund wenig richtungsweisender Ergebnisse stellten wir dieses Projekt allerdings ein und entschieden, uns bei der Auswertung der Daten aus dem Knorpelregister zunächst auf ein Thema – das Rauchen – zu fokussieren, wobei das zweite Paper dieser Dissertation entstand.

6. Zusammenfassung

6.1 Abstract (deutsch)

Hintergrund/Zielsetzung:
Viele Menschen weltweit leiden aufgrund von fokalen Knorpeldefekten unter großen Einschränkungen, insbesondere hinsichtlich ihrer Lebensqualität. Zur Therapie dieser Defekte hat sich u. a. die matrix-basierte autologe Chondrozyten-Transplantation etabliert.
Das Ziel unserer Arbeit war es, die aktuelle Therapie besser einordnen zu können. Hierfür ging es uns zum einen darum, Faktoren zu identifizieren, die Hinweise auf den weiteren post-operativen Verlauf geben können, wobei wir uns im Verlauf auf das Rauchen fokussierten, da die Auswirkung des Rauchens auf die Knorpelheilung bisher nicht eindeutig geklärt ist. Zum anderen wollten wir die aktuell nebeneinander bestehenden Therapieformen mit Verwendung der schon länger bekannten festen Matrizes auf der einen Seite und der relativ neuen Hydrogel-basierten, flüssigen Matrizes auf der anderen Seite auf Unterschiede bezüglich des Outcomes untersuchen.

Material und Methoden:
Für die Untersuchung verschiedener Einflussfaktoren auf das Outcome nach autologer Chondrozyten-Transplantation verwendeten wir Daten von insgesamt 281 Patient*Innen aus dem Deutschen Knorpelregister, einer multizentrisch geführten Datenbank. Die Patienten wurden in drei bzgl. Parametern wie Alter, BMI, Geschlecht, Defektgröße- und Lokalisation, notwendiger Begleitoperationen und Voroperationen am betreffenden Gelenk vergleichbare Gruppen (Nicht-Raucher, Ex-Raucher und Raucher) geteilt. Untersucht wurden die postoperativen Ergebnisse anhand des KOOS, der NRS und der subjektiven Zufriedenheit der Patient*Innen nach 6, 12 und 24 Monaten.
Zum Vergleich der festen und Hydrogel-basierten Matrizes bildeten wir insgesamt 25 anhand von Defektanzahl und Geschlecht (sowie bei mehreren bestehenden Optionen auch Defektlokalisation, Alter, Defektgröße, Voroperationen und Begleitoperationen) passende Paare aus 50 Patient*Innen, die an der Ludwig-Maximilians-Universität München operiert wurden. Diese wurden im Anschluss bezüglich des IKDC-Scores und der VAS 6, 12 und 24 Monate nach der Operation miteinander verglichen.
Zur statistischen Analyse verwendeten wir jeweils IBM SPSS Statistics in der jeweils aktuellen Version (21 bzw. 26)

Ergebnisse:
Das postoperative Outcome nach autologer Chondrozyten-Transplantation bei Rauchern und Ex-Rauchern zeigt in den ersten 24 Monaten keine signifikanten Unterschiede im Vergleich zu dem Outcome bei Nicht-Rauchern. Sowohl bei der festen als auch der Hydrogel-basierten Variante zeigen sich postoperativ signifikante Verbesserungen bzgl. IKDC-Scores und VAS. Bei dem Hydrogel-basierten Vorgehen ließ sich der Fortschritt anhand der IKDC-Scores schon nach 6, bei der festen Matrix nach 12 Monaten statistisch nachweisen.

Schlussfolgerung:
Hydrogel-basierte und feste Matrizes zur Verwendung bei autologer Chondrozyten-Transplantation liefern in der ersten 24 Monaten nach dem Eingriff vergleichbare Ergebnisse. Das Rauchen spielt für den postoperativen Verlauf innerhalb der ersten 2 Jahre keine Rolle.

6.2 Abstract (englisch)

Background/Purpose:
Many people around the world suffer from severe limitations due to focal cartilage defects, especially with regard to their quality of life. Matrix-based autologous chondrocyte implantation has been established as a treatment for those defects over the last decades.
The main goal of our project was being able to better classify current therapy. On the one hand, we wanted to identify factors that can provide clues to the further outcome. We were therefore focusing on smoking in the course of the study, as the influence of smoking on healing of cartilage has not yet been clearly clarified. On the other hand, we aimed to analyze the currently coexisting forms of therapy with the use of the longer-known scaffold matrices and the relatively new hydrogel-based, liquid matrices for differences in outcomes.

Materials and methods:
To investigate various factors influencing the outcome after autologous chondrocyte implantation, we used data of 281 patients included in the German Cartilage Registry, a multicenter database. The patients were split into groups of non-smokers, ex-smokers and smokers that were comparable in terms of parameters such as age, BMI, gender, defect size and location, necessary concomitant surgeries and previous surgery on the affected joint. The postoperative outcomes were examined using the KOOS, the NRS as well as the subjective satisfaction of patients at 6 months, one and two years after surgery.
To compare scaffold and hydrogel-based matrices, we formed a total of 25 matching pairs from 50 patients who underwent surgery at Ludwig-Maximilians-University of Munich. As criteria for match-pairing we used the number of defects and gender (as well as defect location, age, defect size, previous surgeries and concomitant surgeries in the case of several existing options). The groups were then compared based on IKDC scores and VAS 6, 12 and 24 months after surgery. For statistical analysis, IBM SPSS Statistics versions 21 and 26 were used.

Results:
The post-surgery outcome after autologous chondrocyte implantation of smokers and ex-smokers shows no significant differences in the first 24 months compared to the outcome of non-smokers. Both the scaffold and the hydrogel-based variants showed significant post-surgery improvements in IKDC scores and VAS. In the hydrogel-based approach, progress in IKDC scores can be statistically demonstrated after half a year, in case of scaffold-based matrices, it can be shown after a full year.

Conclusion:
Hydrogel-based and scaffold matrices provide comparable results over the course of 24 months when used in autologous chondrocyte implantation. Smoking has not significantly affected the post-surgery results during the first two years.

7. Paper I

Knee Surgery, Sports Traumatology, Arthroscopy (2022) 30:3386–3392
https://doi.org/10.1007/s00167-022-06886-8

KNEE

Hydrogel-based autologous chondrocyte implantation leads to subjective improvement levels comparable to scaffold based autologous chondrocyte implantation

Thomas Richard Niethammer[1] · Felix Uhlemann[1] · Anja Zhang[1] · Martin Holzgruber[1] · Ferdinand Wagner[1] · Peter Ernst Müller[1]

Received: 20 October 2021 / Accepted: 12 January 2022 / Published online: 28 February 2022

Abstract

Purpose Scaffold-based autologous chondrocyte implantation is a well-established treatment for cartilage defects in the knee joint. Hydrogel-based autologous chondrocyte implantation using an in situ polymerizable biomaterial is a relatively new treatment option for arthroscopic cartilage defects. It is therefore important to determine if there are significant differences in the outcomes. The aim of this study is to compare the outcomes (using subjective parameters) of hydrogel-based autologous chondrocyte implantation (NOVOCART® Inject) with the outcomes of scaffold based autologous chondrocyte Implantation (NOVOCART® 3D) using biphasic collagen scaffold.

Methods The data of 50 patients, which were paired with 25 patients in each treatment group, was analyzed. The main parameters used for matching were gender, number of defects and localization. Both groups were compared based on Visual Analogue Scale (VAS) and subjective IKDC scores, both of which were examined pre-operatively and after 6, 12 and 24 months.

Results Significant benefits in both VAS and IKDC scores after 2 years of follow-up in both groups were found. Comparing the groups, the results showed that in the hydrogel-based autologous chondrocyte implantation group, significant changes in IKDC scores are measurable after 6 months, while it takes 12 months until they are seen in the scaffold based autologous chondrocyte group.

Conclusion Hydrogel-based autologous chondrocyte and scaffold based autologous chondrocyte show comparable improvements and significant benefits to the patients' subjective well-being after a 2-year-follow-up.

Level of evidence III.

Keywords Cartilage defect · ACI · Hydrogel · Scaffold

Introduction

Focal cartilage defects of the knee are a common diagnosis that often leads to severe problems in quality of life and pain. The treatment of these defects is challenging and over the last decades, the recommended course of therapy has changed a lot. Since autologous chondrocyte implantation

Thomas Richard Niethammer and Felix Uhlemann have contributed equally to this article and share first authorship.

Thomas Richard Niethammer and Peter Ernst Müller are members of the working group "Tissue Regeneration" of the German Society for Orthopaedic and Trauma Surgery.

✉ Thomas Richard Niethammer
thomas.niethammer@med.uni-muenchen.de

Felix Uhlemann
Uhlemann.f@gmx.de

Anja Zhang
anja.zhang@med.uni-muenchen.de

Martin Holzgruber
Dominic.simon@med.uni-muenchen.de

Ferdinand Wagner
Ferdinand.wagner@med.uni-muenchen.de

Peter Ernst Müller
Peter.mueller@med.uni-muenchen.de

[1] Department of Orthopaedics and Trauma Surgery, Musculoskeletal University Center Munich (MUM), University Hospital, LMU Munich, Marchioninistraße 15, 81377 Munich, Germany

was introduced clinically in 1994 by Brittberg et al. [4], this technique has been established and according to different studies, it is by now the preferred therapy especially for full-thickness focal cartilage defects over 2.5 cm^2 of the knee [5, 7, 11].

Over the years, autologous chondrocyte implantation (ACI) has been further developed [6]. By now, according to recent literature, especially second and third generation ACI leads to satisfying outcomes [7, 9, 15]. While collagen-based scaffold-ACI is clearly established as a good option for focal cartilage knee defects, hydrogel-based ACI (hydrogel-ACI) has been more recently developed and used as a potentially effective treatment. Reliable data on the outcomes of this procedure is not yet available, but because of the possibility of an arthroscopic implantation, promising results are expected.

For scaffold-ACI, the cultivated chondrocytes were seeded on a collagen-based membrane and implanted in an open surgery. For using a hydrogel, the cultivated chondrocytes were applied in an injectable suspension that combines a gel with a crosslinker in situ. Another difference between the two procedures is the base material. While collagen-based membranes are used commonly, there are fewer studies about hyaluronic-acid-based scaffold or hydrogel.

By now, although there are many studies on ACI, comparisons regarding outcomes of scaffold- and hydrogel-ACI in recent literature could not be found. This is probably due to the novelty of hydrogel-ACI procedure. The aim of this study is to see if there are significant differences in the subjective outcomes of these two procedures over the first 2 years after treatment. The hypothesis was that both scaffold- and hydrogel-ACI lead to good comparable results after 2 years. If hydrogel-ACI leads to comparable clinical results we recommend to use hydrogel-ACI because of its possibility to applicate it less invasive or arthroscopic.

Materials and methods

This study was performed with an IRB (institutional review board, ID 344-12) approval from Ludwig-Maximilians-Universität München. A total of 50 patients were included consecutively in this monocentric study. The inclusion criteria were: symptomatic cartilage defects ICRS grade III-IV of the femorotibial and patellofemoral joint with a minimum defect size of 2.5 cm^2. Exclusion criteria were: malalignment > 3–5 degrees mechanical axis deviation, osteoarthritis (Kellgren Lawrence > 2), subtotally resected meniscus in the affected compartment, rheumatoid arthritis with relevant synovitis, haemophilia-associated arthropathy and corresponding bipolar cartilage defects.

First, the scaffold-ACI group of 25 patients were treated and afterwards the hydrogel-ACI group ($n = 25$) were treated. Surgery was performed by three experienced surgeons at our clinic. After harvesting the osteochondral biopsies after 3–4 weeks, ACI surgery was performed with a knee arthrotomy in both groups. After careful debridement of the cartilage defect and measuring of the defect size scaffold-ACI (NOVOCART® 3D, TETEC GmbH, Reutlingen, Germany), hydrogel-ACI (NOVOCART® Inject, TETEC GmbH, Reutlingen, Germany) was injected with a syringe directly in the cartilage defect. A dual chamber syringe was used to inject a suspension of autologous cell in a solution of modified human albumin, isotonic sodium hyaluronate, human serum, and cell culture media with a cross-linker into the prepared site of the defect.

In both groups, there were 14 patients with a single defect and 11 patients with two defects that needed to be treated. Also, there were 13 men and 12 women in each of the respected treatment groups. The mean age in the hydrogel-ACI group (SD 12.8) at the time of treatment was 37.0 years, while patients treated with scaffold-ACI had a mean age of 33.9 years (SD 11.6). The mean defect size was 4.4 cm^2 (SD 3.1) in the hydrogel-ACI group, and 5.5 cm^2 (SD 2.8) in the scaffold-ACI group. More epidemiologic data such as etiology of the defect can be seen in Table 1.

For match pairing, gender and number of defects as the main parameters were used. When there was more than one option, defect localization, patient age, defect size, former surgical treatments and contemporary treatments were taken in that order as further comparison parameters to find the optimal pairs.

Signed informed consent from the patients were required. The follow-up was over 24 months after treatment with both scaffold-ACI and hydrogel-ACI. All patients treated with any form of ACI are surveyed before treatment, after 6 months, 12 months and 24 months with standardized questionnaires. The two groups were compared regarding the pain level on Visual Analogue Scale (VAS) in movement and International Knee Documentation Committee (IKDC) subjective score. Both scoring systems are well established for the evaluation of knee symptoms. A complete follow-up in both tested items (VAS and IKDC score) after 2 years was given in both cases.

Statistical analysis

Statistical analysis and graphics were performed with IBM SPSS Statistics Version 26. For samples size calculation G*Power 3.1 was used. A total sample size of 46 were calculated. Normal distribution was tested with Kolmogorov–Smirnov and Shapiro–Wilk tests. After normal distribution was declined, group comparisons were done with

Table 1 Comparison of epidemiologic data of patients in both treatment groups

	Hydrogel-ACI ($n=25$)	Scaffold-ACI ($n=25$)
Age at time of treatment		
Mean	37.0	33.9
Median	38.0	32.0
Min	14	13
Max	55	51
Defect size		
Mean	4.4	5.5
Median	3.0	5.0
Min	1.0	0.8
Max	12.0	12.0
Body mass index		
Mean	27.2	26.3
Median	26.3	25.6
Min	18.7	20.9
Max	39.1	35.3
Number of defects		
1	14	14
2	11	11
Localization		
Medial femoral condyle	12	9
Lateral femoral condyle	1	3
Patellar	11	12
Trochlear	1	1
Tibial	0	0
Aetiology		
Osteochondrosis dissecans	0	2
Traumatic (< 1 year)	1	3
Post-traumatic (> 1 year)	6	8
Unknown	18	11
Earlier surgical treatments		
Total	4	9
Bone marrow stimulation	4	7
Autologous chondrocyte implantation	0	1
Flake refixation	0	1
Simultaneous treatments		
Total	3	8
Osteotomy	1	0
Bone grafting	0	1
Medial patellofemoral ligament reconstruction	0	2
Collagen meniscus implantation	0	2
Anterior crucial ligament reconstruction	2	3

Wilcoxon-test. p-Values smaller than 0.05 were taken as significant.

Table 2 Development of VAS and IKDC scores in both treatment groups

	Median	Max	Min	SD
IKDC before surgery				
Hydrogel-ACI ($n=25$)	41.4	89.7	18.4	18.1
Scaffold-ACI ($n=25$)	36.5	94.3	2.3	25.3
IKDC 6 months post-surgery				
Hydrogel-ACI ($n=25$)	51.7	80.5	6.9	18.2
Scaffold-ACI ($n=25$)	44.8	98.9	9.8	21.4
IKDC 12 months post-surgery				
Hydrogel-ACI ($n=25$)	59.8	100.0	9.2	20.9
Scaffold-ACI ($n=25$)	60.9	100.0	32.8	17.2
IKDC 24 months post-surgery				
Hydrogel-ACI ($n=25$)	66.7	100.0	17.2	21.7
Scaffold-ACI ($n=25$)	67.8	100.0	18.4	18.4
VAS before surgery				
Hydrogel-ACI ($n=25$)	4.0	8.0	0.0	2.6
Scaffold-ACI ($n=25$)	7.0	10.0	0.0	3.4
VAS 6 months post-surgery				
Hydrogel-ACI ($n=25$)	3.6	9.0	0.0	2.4
Scaffold-ACI ($n=25$)	2.6	9.0	0.0	2.7
VAS 12 months post-surgery				
Hydrogel-ACI ($n=25$)	2.0	9.0	0.0	2.6
Scaffold-ACI ($n=25$)	1.7	7.0	0.0	2.4
VAS 24 months post-surgery				
Hydrogel-ACI ($n=25$)	2.0	8.0	0.0	2.3
Scaffold-ACI ($n=25$)	2.0	8.2	0.0	2.1

Results

In both groups, statistical tests showed significant improvements in both VAS and IKDC scores after a follow-up of 2 years. Hydrogel-based ACI leads to an earlier improvement in the IKDC score (Table 2).

The median IKDC score improved comparable from 41.4 to 66.7 points in the Hydrogel-ACI group and from 36.5 to 67.8 points in the scaffold-ACI group ($p < 0.001$) (Fig. 1). In the hydrogel-ACI group, the median VAS score improved from 4.0 preoperatively to a score of 2.0 after 2 years, while in the scaffold-ACI group it improved from a level of 7.0 preoperatively to 2.0 ($p < 0.001$) (Fig. 2).

Regarding the IKDC scores, significant improvements were found after 6 months in the hydrogel-ACI group, while the first improvements found in the scaffold-ACI group were after 12 months ($p < 0.05$) (Fig. 3). In comparison, VAS Scores showed an earlier significant improvement in the scaffold-ACI group. The same applies for the measurement after 12 months. These developments can be seen in Fig. 4.

Another finding of this study was that VAS did not improve further from 12 to 24 months. Even though there

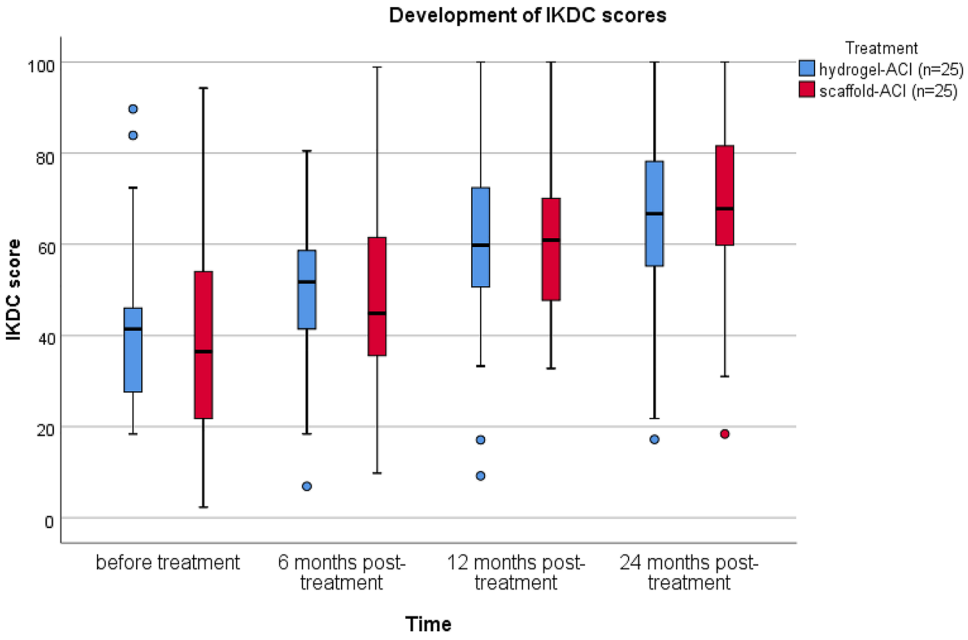

Fig. 1 Development of IKDC score in both treatment groups. Tests have shown significant improvements in IKDC score after a follow-up of 2 years ($p < 0.001$)

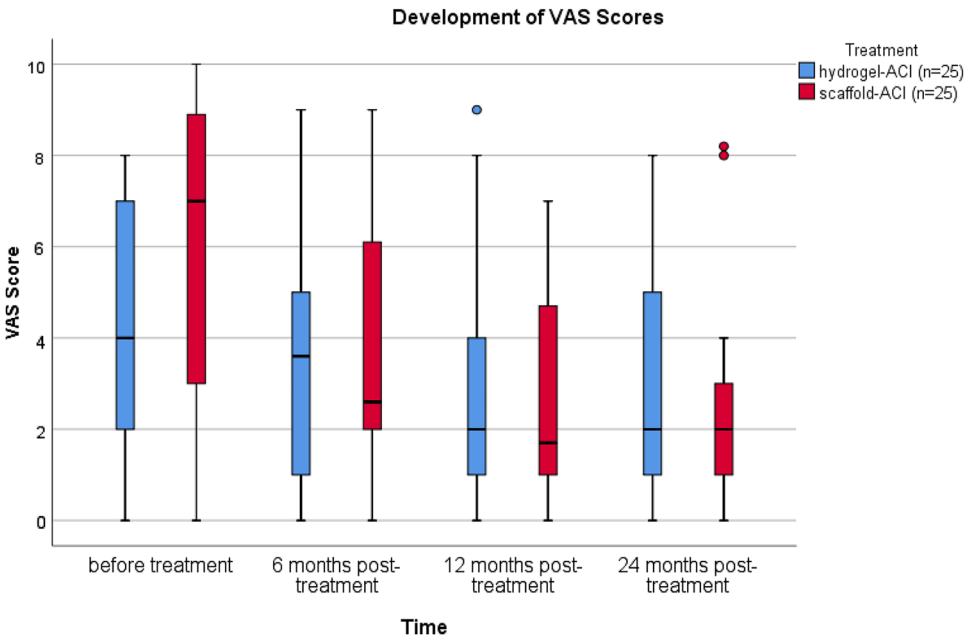

Fig. 2 Development of VAS score in both treatment groups. Tests have shown significant improvements in VAS score after a follow-up of 2 years ($p < 0.001$)

were no significant findings, the tendency in the scaffold-ACI group showed a rising median VAS score (from 1.7 to 2.0), while in the Hydrogel-ACI group, the median score stayed at 2.0 (Fig. 4).

Discussion

The major findings of this study are that both scaffold-based ACI using a biphasic collagen scaffold and hydrogel-based ACI using an in situ polymerizable biomaterial lead to comparable subjective improvements after a follow-up of 2 years. Neither one of the two delivered significantly better results after 2 years, but there were differences in the progress over time. Hydrogel-based ACI leads to an earlier improvement in the IKDC score.

There are multiple studies on scaffold-ACI. Promising results were shown in a recent study regarding the hydrogel-ACI [3, 17, 19]. As there are several papers about first generation up to third generation ACI [1, 2, 12] and few comparisons between different generations [2, 16], there is

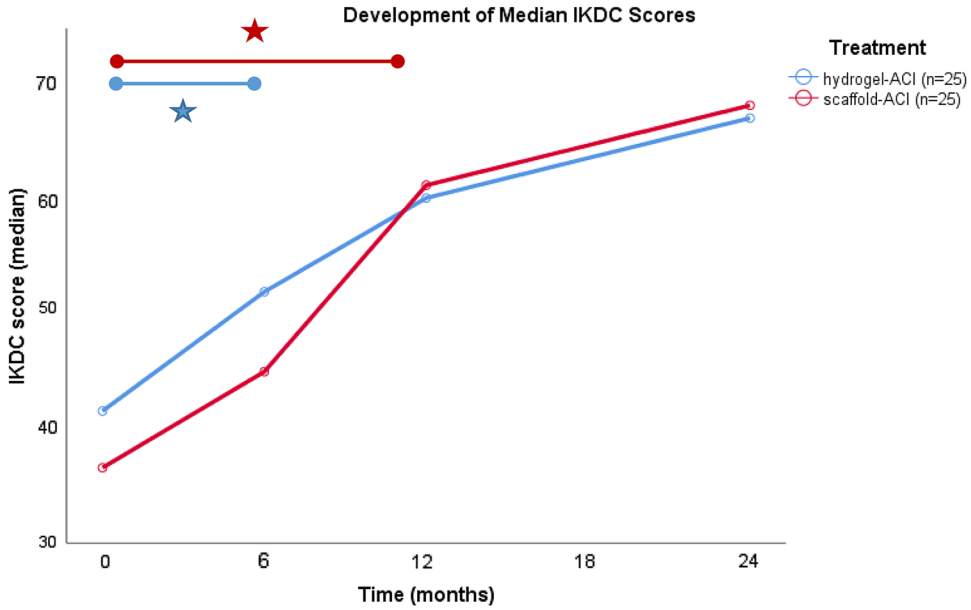

Fig. 3 Comparison of the development of median IKDC score in both treatment groups. Significances already showed after 6 months in the Hydrogel-ACI group, while the first time significances showed in the scaffold-ACI group was after 12 months ($p < 0.05$)

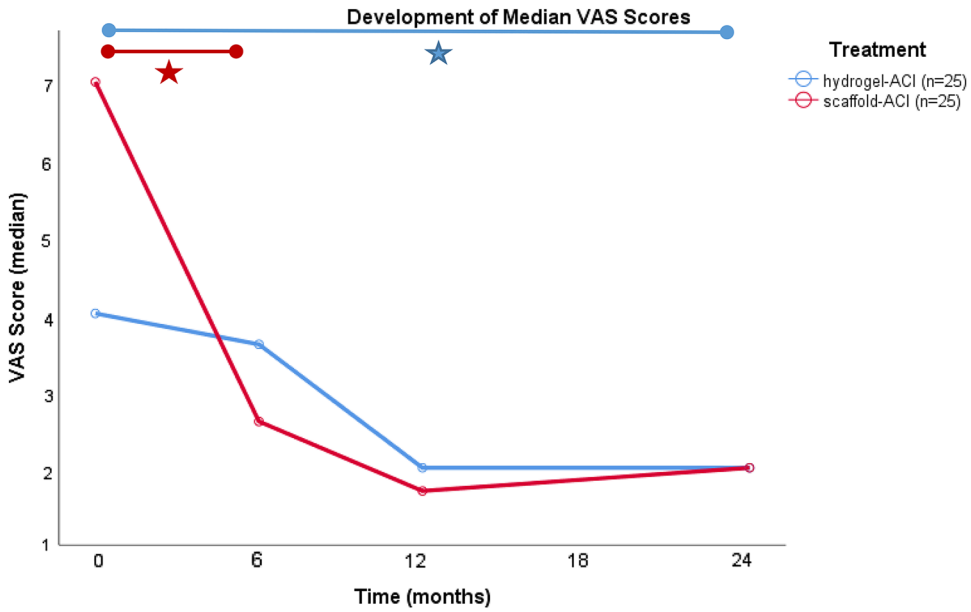

Fig. 4 Comparison of the development of median VAS score in both treatment groups. While the improvement was significant after 6 months in the scaffold-ACI-group, the first significant improvement in the Hydrogel-ACI-group was after 24 months ($p < 0.05$)

no comparison between hydrogel-based and scaffold-based ACI.

It has been described in earlier studies that collagen-based scaffolds lead to satisfying subjective outcomes for patients when they are used in scaffold-ACI [13, 14, 18]. Similar results were found in our study. Both VAS and IKDC showed clear improvements in the comparison surveys before and after treatment. In addition, analogical results for the treatment with hyaluronic-based hydrogel were found. This suggests that neither of the two procedures is superior to the other when it comes to subjective parameters.

Regarding the scaffold-ACI, there is evidence that hyaluronic based scaffolds can lead to significant improvements. Studies showed that its use—also after a follow-up period of up to more than 10 years—delivered significant improvements and satisfying outcomes [1, 8]. Welsch et al. have compared hyaluronic based and collagen-based scaffolds in their study [21]. While the clinical results of both groups were similar and MOCART scores did not significantly vary between both groups after a follow-up of 24 months, the surface of the repair tissue was found to be in significantly better condition in the group treated with the collagen based scaffold.

Up until now, there were very few studies on hydrogel-ACI. Although there have been different reports about the clinical outcomes of hydrogel-ACI already, none of them

focus on the treatment of the knee. Thier et al. as well as Krueger et al. both reported good clinical outcomes for the use in the hip joint after a follow up of one to 3 years [10, 20]. Both papers show significant improvements in subjective scores. Blanke et al. examined the short-term results of hydrogel-ACI for the knee and reported significant improvements in clinical and radiological scores 2 years after treatment [3]. Their findings were supported by the results of the present study.

In the present study, a match-paired analysis was used with two patient groups to compare patients treated with either hydrogel- or scaffold-ACI regarding their subjective outcomes after a follow-up of 2 years. Significant improvements in the first review 6 months after treatment were shown. IKDC scores seem to improve faster in the hydrogel-ACI group.

The biggest limitation of our study is the number of patients treated. A larger group of patients would lead to more conclusive results. In addition, the scores used were both subjective. Another potentially limiting factor of this study could be the novelty of the use of hyaluronic-based cell-suspensions as physicians could improve with more experience so that the quality of the outcome could also improve over the course of multiple years.

This study shows that both scaffold-ACI and hydrogel-ACI lead to comparable results at this time. Regarding the clinical scores, clinical improvements were seen earlier after the hydrogel-based ACI compared with the scaffold based ACI. Hydrogel-ACI is a less invasive procedure and can be performed all-arthroscopically, which might be the reason for the earlier clinical improvement in the IKDC score.

Conclusion

This study showed, that both groups demonstrated a significant improvement after 2 years with neither of the two groups showing significantly better results than the other. Both scaffold based ACI and hydrogel-based ACI with a minimum incision lead to good and comparable clinical results after 2 years. Hydrogel-based ACI leads to an earlier improvement in the IKDC score.

Acknowledgements Thomas Richard Niethammer and Felix Uhlemann have contributed equally to this article and share first authorship.

Funding Open Access funding enabled and organized by Projekt DEAL. No external source of funding was used.

Declarations

Conflict of interest The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Andriolo L, Reale D, Di Martino A, De Filippis R, Sessa A, Zaffagnini S et al (2020) Long-term results of arthroscopic matrix-assisted autologous chondrocyte transplantation: a prospective follow-up at 15 years. Am J Sports Med 48:2994–3001
2. Barie A, Kruck P, Sorbi R, Rehnitz C, Oberle D, Walker T et al (2020) Prospective long-term follow-up of autologous chondrocyte implantation with periosteum versus matrix-associated autologous chondrocyte implantation: a randomized clinical trial. Am J Sports Med 48:2230–2241
3. Blanke F, Oehler N, Haenle M, Lenz R, Vogt S, Tischer T (2021) All-arthroscopic hydrogel-based autologous chondrocyte transplantation in the knee joint: good clinical and magnetic resonance imaging outcome after 24 months. Arthroscopy 37:1892–1899
4. 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
5. Calcei JG, Ray T, Sherman SL, Farr J (2020) Management of large focal chondral and osteochondral defects in the knee. J Knee Surg 33:1187–1200
6. Davies RL, Kuiper NJ (2019) Regenerative medicine: a review of the evolution of autologous chondrocyte implantation (ACI) therapy. Bioengineering (Basel) 6(1):22
7. Hoburg A, Loer I, Korsmeier K, Siebold R, Niemeyer P, Fickert S et al (2019) Matrix-associated autologous chondrocyte implantation is an effective treatment at midterm follow-up in adolescents and young adults. Orthop J Sports Med 7:2325967119841077
8. Kon E, Filardo G, Gobbi A, Berruto M, Andriolo L, Ferrua P et al (2016) Long-term results after hyaluronan-based MACT for the treatment of cartilage lesions of the patellofemoral joint. Am J Sports Med 44:602–608
9. 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
10. Krueger DR, Gesslein M, Schuetz M, Perka C, Schroeder JH (2018) Injectable autologous chondrocyte implantation (ACI) in acetabular cartilage defects-three-year results. J Hip Preserv Surg 5:386–392
11. Medvedeva EV, Grebenik EA, Gornostaeva SN, Telpuhov VI, Lychagin AV, Timashev PS et al (2018) Repair of damaged articular cartilage: current approaches and future directions. Int J Mol Sci 19(8):2366

12. Muller PE, Gallik D, Hammerschmid F, Baur-Melnyk A, Pietschmann MF, Zhang A et al (2020) Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results. Knee Surg Sports Traumatol Arthrosc 28:470–477
13. Niethammer TR, Altmann D, Holzgruber M, Gulecyuz MF, Notohamiprodjo S, Baur-Melnyk A et al (2020) Patient-reported and magnetic resonance imaging outcomes of third-generation autologous chondrocyte implantation after 10 years. Arthroscopy 36:1928–1938
14. Ogura T, Bryant T, Mosier BA, Minas T (2018) Autologous chondrocyte implantation for bipolar chondral lesions in the tibiofemoral compartment. Am J Sports Med 46:1371–1381
15. 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
16. Samsudin EZ, Kamarul T (2016) The comparison between the different generations of autologous chondrocyte implantation with other treatment modalities: a systematic review of clinical trials. Knee Surg Sports Traumatol Arthrosc 24:3912–3926
17. Schlumberger M, Schuster P, Bulow HJ, Mayer P, Eichinger M, Richter J (2019) Arthroscopic autologous chondrocyte implantation in the knee with an in situ crosslinking matrix: minimum 4-year clinical results of 15 cases and 1 histological evaluation. Arch Orthop Trauma Surg 139:1607–1615
18. Schuette HB, Kraeutler MJ, Schrock JB, McCarty EC (2021) Primary autologous chondrocyte implantation of the knee versus autologous chondrocyte implantation after failed marrow stimulation: a systematic review. Am J Sports Med 49:2536–2541
19. Siebold R, Suezer F, Schmitt B, Trattnig S, Essig M (2018) Good clinical and MRI outcome after arthroscopic autologous chondrocyte implantation for cartilage repair in the knee. Knee Surg Sports Traumatol Arthrosc 26:831–839
20. Thier S, Baumann F, Weiss C, Fickert S (2018) Feasibility of arthroscopic autologous chondrocyte implantation in the hip using an injectable hydrogel. Hip Int 28:442–449
21. Welsch GH, Mamisch TC, Zak L, Blanke M, Olk A, Marlovits S et al (2010) Evaluation of cartilage repair tissue after matrix-associated autologous chondrocyte transplantation using a hyaluronic-based or a collagen-based scaffold with morphological MOCART scoring and biochemical T2 mapping: preliminary results. Am J Sports Med 38:934–942

8. Paper II

The Effect of Smoking on the Outcome of Matrix-Based Autologous Chondrocyte Implantation: Data from the German Cartilage Registry

Volker M. Betz, MD[1] Martin Holzgruber, MD[1] Johanna Simon, MD[1] Felix Uhlemann, MD[1] Philipp Niemeyer, MD[2,3] Peter E. Müller, MD[1] Thomas R. Niethammer, MD[1]

[1] Department of Orthopaedics, Physical Medicine and Rehabilitation, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany
[2] Department of Orthopaedic Surgery and Traumatology, Freiburg University Hospital, Freiburg, Germany
[3] Department of Orthopaedic Surgery, Orthopädische Chirurgie München Clinic, Munich, Germany

Address for correspondence Volker M. Betz, MD, Department of Orthopaedics, Physical Medicine and Rehabilitation, University Hospital, Ludwig-Maximilians-University Munich, Marchioninistr. 15, Munich 81377, Germany (e-mail: volker.betz@yahoo.com).

J Knee Surg 2023;36:181–187.

Abstract

Smoking is known to have various deleterious effects on health. However, it is not clear whether smoking negatively affects the postoperative outcome following matrix-based autologous cartilage implantation (MACI) in the knee. The purpose of this study was to evaluate the effect of smoking on the outcome of MACI in the knee. A total of 281 patients receiving MACI in the knee between 2015 and 2018 were registered in the German Cartilage Database. The cohort was divided into ex-smokers, smokers, and nonsmokers. Data regarding the Knee Injury and Osteoarthritis Outcome Score (KOOS), the numeric rating scale (NRS) for pain, and satisfaction with the outcome were analyzed and compared. Follow-ups were performed at 6, 12, and 24 months after surgery. Of the 281 patients, 225 (80.1%) were nonsmokers, 43 (15.3%) were smokers, and 13 (4.6%) were ex-smokers. The three groups were comparable with respect to age, sex, body mass index (BMI), height, defect size, the need for additional reconstruction of the subchondral bone defect, number of previous knee surgeries, and defect location. However, nonsmokers had a significantly lower weight as compared with smokers. Besides a significantly lower preoperative NRS of nonsmokers as compared with smokers, there were no significant differences between the three groups with respect to KOOS, NRS, and satisfaction at 6, 12, and 24 months of follow-ups. The present study of data retrieved from the German Cartilage Registry suggests that the smoking status does not influence the outcome of MACI in the knee.

Keywords
- smoking
- autologous cartilage implantation
- cartilage repair
- knee
- German Cartilage Registry

Focal cartilage defects can severely impact the quality of patient's lives due to severe pain and impaired function. These patients are also at a higher risk to develop osteoarthritis which leads to further destruction of the joint and may lead to long-term disability. Even partial thickness focal defects under 1 cm increase the risk of further cartilage damage in persons who have or are at high risk to develop osteoarthritis.[1] Current treatment options of focal cartilage defects of the knee joint include microfracture,[2] osteochondral autograft transfer,[3] osteochondral allograft transplantation,[4] and autologous chondrocyte implantation (ACI).[5] The third-generation ACI method comprises of autologous cartilage cells seeded on a three-

received
October 15, 2020
accepted after revision
May 1, 2021
article published online
July 8, 2021

Thieme Medical Publishers, Inc.,
333 Seventh Avenue, 18th Floor,
New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0041-1731456.
ISSN 1538-8506.

dimensional collagen scaffold. This approach requires the harvest of cartilage from the patient, isolation, and expansion of chondrocytes in vitro over several weeks, seeding of the cells on the matrix, and subsequently the implantation of the cell-scaffold construct into the patient's focal cartilage defect.[6] Third-generation ACI is applied for full-thickness cartilage defects of a size of at least 2.5 cm^2, while patients are typically up to approximately 55 years without certain concomitant pathologies, including advanced arthritis, rheumatoid arthritis, or subtotal resected meniscus in an impacted compartment.[7]

Since 2004, in many countries complete national smoking bans in public places were adopted due to the well-known deleterious effects of first-hand and second-hand smoke exposure.[8] It is estimated that smoking is responsible for approximately 6 million deaths worldwide per year.[9] Despite this fact, the prevalence of smoking in Germany remains high with 28%.[10] The estimated global prevalence of daily tobacco smoking among the adult population was 15.2% in 2015.[11]

Several investigations have demonstrated that smoking has adverse effects on the musculoskeletal system.[12] In particular, it was reported that smoking is associated with poorer outcomes following orthopaedic surgical procedures, while most of these reports are derived from studies on bone healing.[13–17] Another research work demonstrated that smoking increases the risk of early meniscus repair failure.[18] In this retrospective study, significantly more smokers than nonsmokers needed revision surgery after meniscus repair leading to the conclusion that smoking status should be added to the list of factors influencing the decision between meniscus repair and meniscectomy.[18] The authors explained the poorer outcome with the detrimental effects of smoking on tissue perfusion causing vasoconstriction and platelet aggregation. Similarly, it was found that smoking has a negative effect on rotator cuff repair, leading to impaired healing and poorer clinical outcomes.[19] The authors concluded that smoking cessation would benefit patients improving clinical outcome.

Interestingly, the relationship between smoking and osteoarthritis is controversial.[12] Cartilage is an avascular tissue receiving oxygen and nutrients from the synovial fluid by diffusion. Therefore, cartilage may not be as negatively affected by smoking as other tissues.

Table 1 The patient cohort investigated in the present study was divided into three groups: ex-smokers, nonsmokers, and smokers

Demographics	Ex-smokers	Smokers	Nonsmokers	*p*-Value
Age (y)	40.5 ± 11.2	36.8 ± 10.1	34.6 ± 10.5	0.089
Sex				0.309
Female	30.8%	34.9%	45.1%	
Male	69.2%	65.1%	54.9%	
Body mass index (kg/m^2)	27.5 ± 4.2	26.5 ± 3.6	25.4 ± 3.8	0.054
Weight (kg)	85.2 ± 15.4	83.5 ± 13.6	79.1 ± 13.5	0.055
Height (cm)	175.4 ± 6.6	176.4 ± 9.5	175.3 ± 9.2	0.755
Defect size (mm^2)	429.9 ± 170.2	410.7 ± 192.5	426.7 ± 201.3	0.888
Repair of subchondral bone	15.4%	9.3%	11.6%	0.054
Number of previous knee surgeries				0.599
0	46.2%	37.2%	44.9%	
1	15.4%	37.2%	35.6%	
2	7.7%	11.6%	11.1%	
3	23.1%	4.7%	6.2%	
4	0%	9.3%	1.3%	
5	7.7%	0%	0.9%	
Defect localization				0.688
Patella	30.8%	32.6%	39.1%	
Trochlea	7.7%	7.0%	12.9%	
Medial femoral condyle	38.5%	44.2%	35.1%	
Lateral femoral condyle	23.1%	16.3%	9.8%	
Medial tibial plateau	0%	0%	1.3%	
Lateral tibial plateau	0%	0%	1.8%	

Notes: Recorded parameters were age, sex, body mass index, weight, height, defect size, the need for additional reconstruction of the subchondral bone defect, number of previous knee surgeries, and defect location.
The weight of nonsmokers was significantly lower than that of smokers ($p = 0.032$).
There was no statistically significant difference between the three groups with respect to all other parameters.

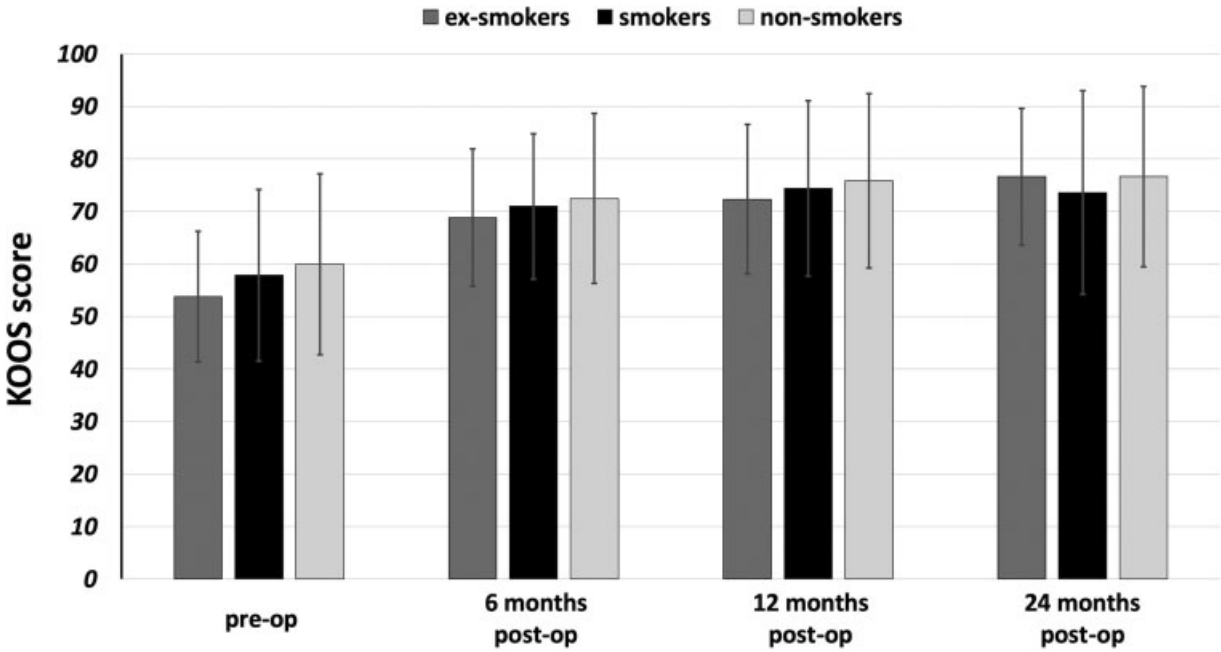

Fig. 1 Clinical outcomes of ex-smokers, non-smokers and smokers analyzed by means of the Knee Injury and Osteoarthritis Outcome Score (KOOS). There were no significant differences detected between the three groups at 6, 12, and 24 months follow-ups. Post-op, postoperative; Pre-op, preoperative.

The purpose of this study was to investigate whether smoking influences the outcome following treatment of focal cartilage defects in the knee by third-generation ACI. Due to the well-known general deleterious health effects of smoking, we hypothesized that smokers show worse outcomes after third-generation ACI.

Methods

Patients and German Cartilage Registry

Data were obtained from the German Cartilage Registry.[20] A total of 281 patients assigned for third-generation ACI between 2015 and 2018 were included in this study. Surgeons

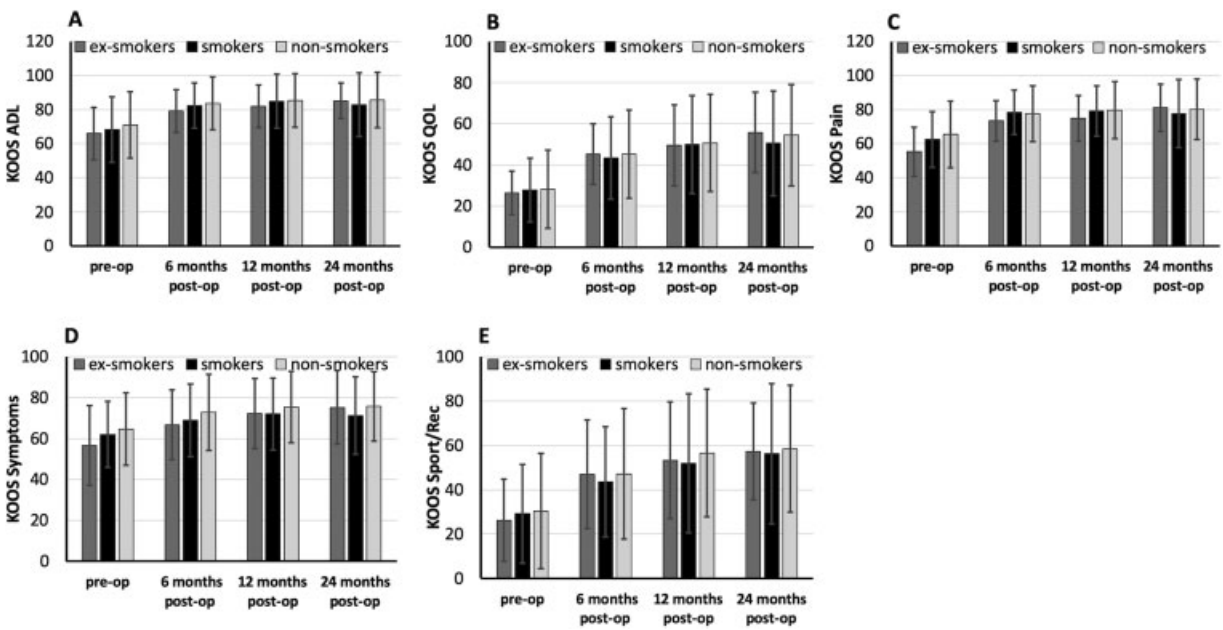

Fig. 2 Outcomes of ex-smokers, non-smokers and smokers analyzed by the five KOOS subscores. (**A**) The Knee Injury and Osteoarthritis Outcome Score (KOOS) ADL (function in daily living), (**B**) KOOS QOL (knee-related quality of live), (**C**) KOOS pain, (**D**) KOOS symptoms, (**E**) KOOS sport/recreation. There were no significant differences detected between the three groups at 6, 12, and 24 months follow-ups. ADL, activity of daily living; Post-op, postoperative; Pre-op, preoperative; QOL, quality of life.

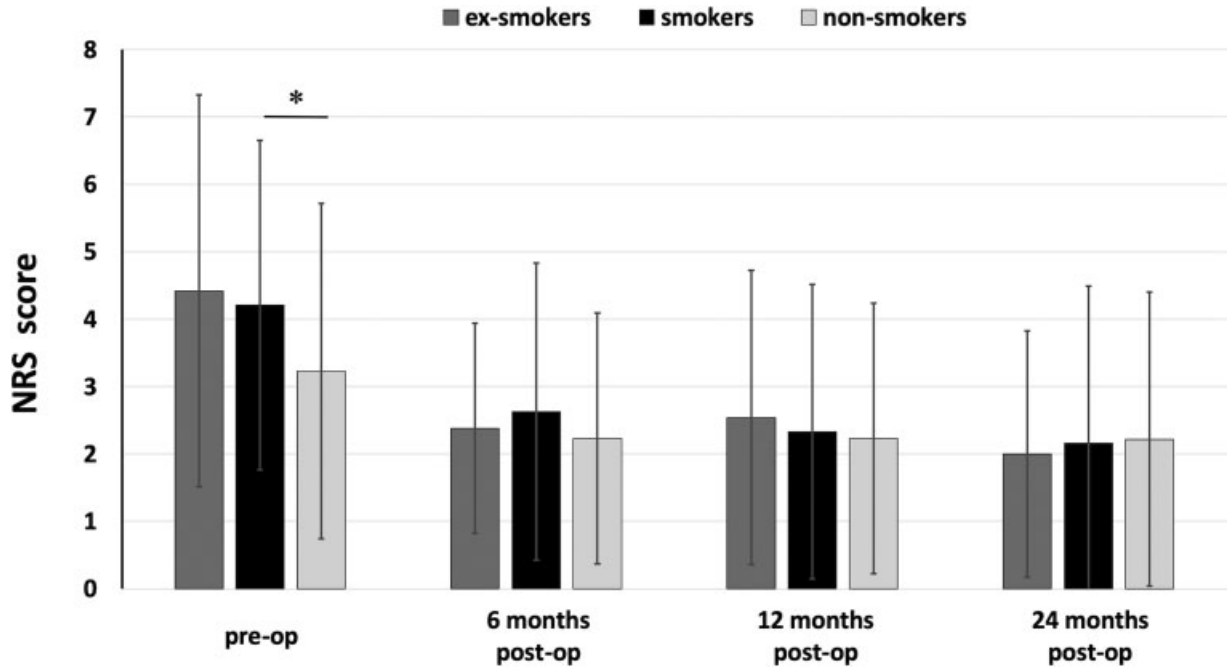

Fig. 3 Clinical outcomes of ex-smokers, nonsmokers and smokers analyzed by means of the numeric rating scale (NRS). Only the preoperative NRS of nonsmokers as compared with smokers was significantly lower ($p = 0.013$). No significant differences between the three groups were detected at 6, 12, and 24 months follow-ups. Post-op, postoperative; Pre-op, preoperative.

have entered datasets of their patients in this international (Germany, Austria, and Switzerland) and longitudinal multicenter registry preoperatively, as well as at 6, 12, and 24 months of follow-ups. Patients who are at least 18 years old, have a personal e-mail address, have given written informed consent, and had surgical treatment of cartilage defects in the knee, hip, or ankle are eligible to take part in the German Cartilage Registry. The study was approved by the local ethical committee (approval number: 105/13) and registered at the DRKS web site (DRKS00005617). Data were collected applying a web-based remote data entry system. Patient- and defect-specific parameters were evaluated. The patient cohort investigated in the present study was divided into three groups: ex-smokers, nonsmokers, and smokers.

Evaluated Parameters

Recorded parameters were age, sex, body mass index (BMI), weight, height, defect size, the need for additional reconstruction of the subchondral bone defect, number of previous knee surgeries, and defect location.

Clinical outcomes were analyzed by means of the Knee Injury and Osteoarthritis Outcome Score (KOOS) and a numeric rating scale (NRS) for pain description. The KOOS is a well-established patient-reported questionnaire comprising the five subscales KOOS pain, KOOS symptoms, KOOS ADL (activity of daily living), KOOS sports/recreation, and KOOS QOL (knee-related quality of live).

Also, patient satisfaction was evaluated. Original data were given as categorical variables. To perform additional statistical analysis of nominally scaled parameters, a patient satisfaction score was applied as follows: "excellent" = 1, "good" = 2, "fair" = 3, and "poor" = 4.

Statistical Analysis

Descriptive cohort data are presented as means ± standard deviations or percentages. SPSS (version 21, IBM Corp.) was employed to conduct statistical analysis. Analysis of variance (ANOVA) was applied to analyze nominally scaled parameters of KOOS, KOOS subscores, NRS, and patient satisfaction score. Relationships between categorical variables of patient satisfaction were tested using a Chi-square test. An error probability <5% ($p < 0.05$) was considered statistically significant.

Results

Of the 281 patients, 225 (80.1%) were nonsmokers, 43 (15.3%) were smokers, and 13 (4.6%) were ex-smokers. Age, sex, BMI, height, defect size, the need for additional reconstruction of the subchondral bone defect, number of previous knee surgeries, and defect location were not significantly different between groups. Interestingly, nonsmokers had a significantly lower weight as compared with smokers ($p = 0.032$; ►**Table 1**).

In the group of ex-smokers, 92.3% of patients responded to the KOOS questionnaire at 6, 12, and 24 months of follow-ups, respectively. In the group of smokers, there were 93% KOOS responders at all three follow-up time points, and 96.4% of nonsmokers entered their KOOS scores in the web-based data collection system at 6, 12, and 24 months.

No significant differences between the three groups with respect to KOOS, KOOS subscores, and NRS at 6, 12, and 24 months of follow-ups were detected (►**Figs. 1–3**). Only the preoperative NRS of nonsmokers as compared with smokers was significantly lower ($p = 0.013$). The groups showed the following increase of the KOOS over time:

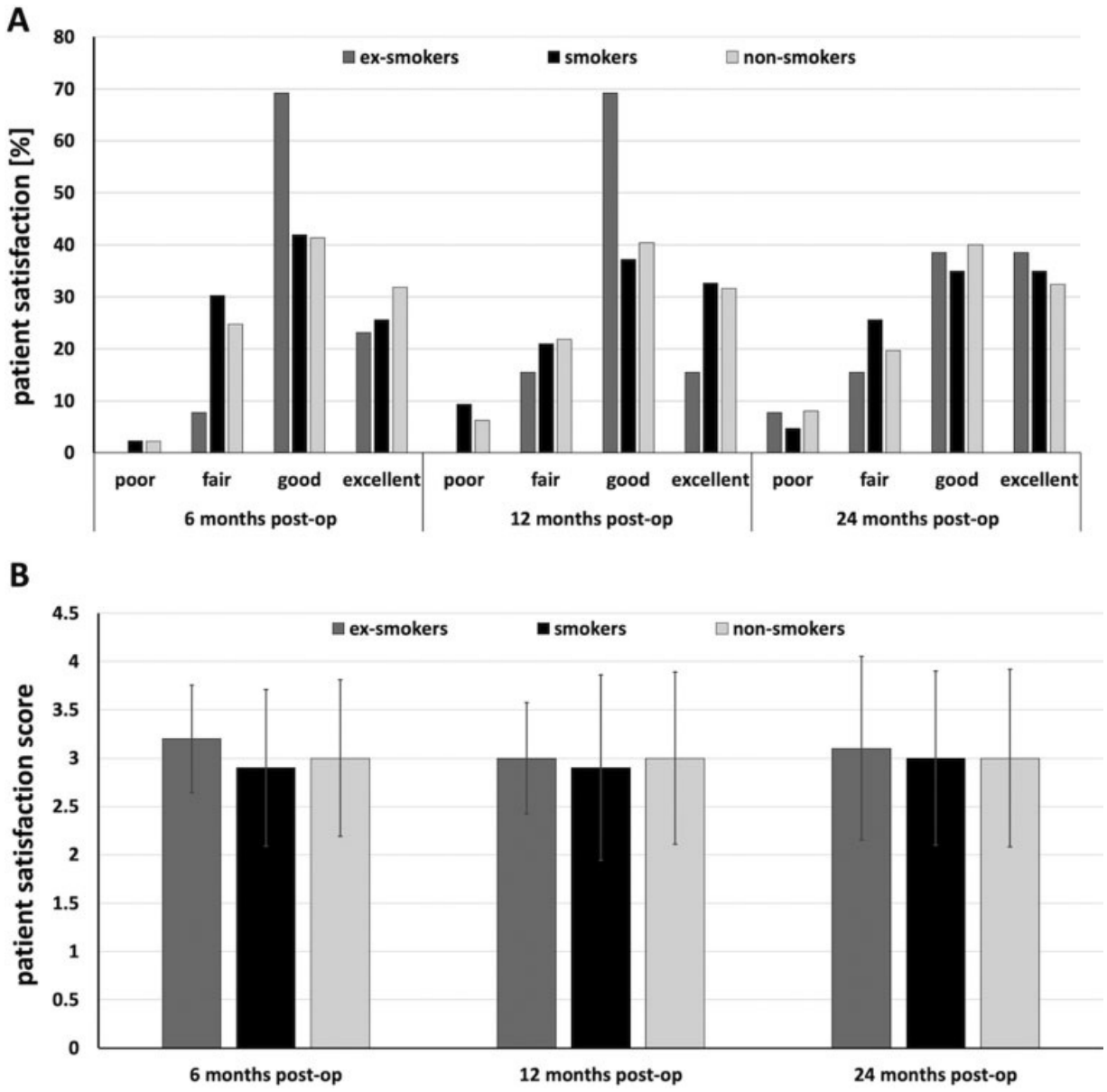

Fig. 4 Patients satisfaction with the outcome was evaluated. Patients were able to choose from "excellent," "good," "fair" or "poor," as shown in (**A**). To perform additional statistical analysis of patient satisfaction a score was applied as follows: "excellent" = 1, "good" = 2, "fair" = 3, and "poor" = 4 (**B**). There were no significant differences detected between the three groups at 6, 12, and 24 months follow-ups.

ex-smokers: preoperative = 53.8 ± 12.4, 6 months = 68.8 ± 13.1, 12 months = 72.3 ± 14.2, and 24 months = 76.6 ± 13.1; smokers: preoperative = 57.9 ± 16.3, 6 months = 71.0 ± 13.8, 12 months = 74.4 ± 16.7, and 24 months = 73.6 ± 19.4; nonsmokers: preoperative = 59.9 ± 17.2, 6 months = 72.5 ± 16.2, 12 months = 75.8 ± 16.6, and 24 months = 76.6 ± 17.2.

Pain analyzed using the NRS decreased from preoperative to 24 months: ex-smokers: preoperative = 4.4 ± 2.9, 6 months = 2.4 ± 1.6, 12 months = 2.5 ± 2.2, and 24 months = 2.0 ± 1.8; smokers: preoperative = 4.2 ± 2.5, 6 months = 2.6 ± 2.2, 12 months = 2.3 ± 2.2, and 24 months = 2.2 ± 2.3; nonsmokers: preoperative = 3.2 ± 2.5, 6 months = 2.2 ± 1.9, 12 months = 2.2 ± 2.0, and 24 months = 2.2 ± 2.2.

Patient satisfaction was also not significantly different between groups (►**Fig. 4A, B**). None of the ex-smokers voted "poor" at 6 and 12 months. Instead, 69.2% of ex-smokers voted "good" at 6 and 12 months. Smokers and nonsmokers gave very similar answers regarding their satisfaction at 6, 12, and 24 months. At 24 months, all three groups voted very similar. Patient satisfaction score was not significantly different between groups and ranged between 2.9 and 3.2. At 6 months, the score was 3.2 ± 1.0 for ex-smokers, 2.9 ± 0.8 for smokers, and 3 ± 0.8 for nonsmokers; at 12 months, 3.0 ± 1.0 for ex-smokers, 2.9 ± 1.0 for smokers, and 3.0 ± 0.9 for nonsmokers; and at 24 months, 3.1 ± 1.0 for ex-smokers, 3.0 ± 0.9 for smokers, and 3.0 ± 0.9 for nonsmokers.

Discussion

In the present study, we did not find evidence that the smoking behavior affects the outcome of third-generation ACI in the knee until 24 months following surgery. This finding is compatible with results from an earlier investigation demonstrating that there is no influence of smoking on the risk of reintervention after ACI.[21] However, our conclusion stands in contrast to a study that was published a decade ago reporting poorer results in smokers than in nonsmokers after ACI in the knee.[22] In this single-center, case-controlled study, smokers showed a significantly lower Modified Cincinnati Knee Score pre- and postoperatively as compared with nonsmokers, and smokers demonstrated significantly less improvement after 2 years than nonsmokers. While our study included a larger number of patients with data collected from multiple study centers, we decided to employ the Knee Injury and Osteoarthritis Outcome Score (KOOS) instead of the Modified Cincinnati Knee Score. The KOOS subscores were recommended by the International Cartilage Repair Society (ICRS) as basic assessment tools to investigate articular cartilage repair since they show good psychometric properties and provide relevant and quantitative data including pain and joint function.[23] The KOOS has been validated as reliable and responsive for patients suffering from focal cartilage lesions.[24–26]

The outcome of our study is supported by findings of several previous investigations. A recent meta-analysis suggests that there is an inverse association between smoking and osteoarthritis in the knee, meaning that smoking protects from this cartilage degeneration.[27] A clinical study in healthy patients showed that smoking is associated with increased tibial cartilage volume.[28] Moreover, in vitro studies demonstrated that nicotine has a positive effect on chondrocyte metabolism.[29,30] Hence, we believe it is likely that smoking does not negatively affect cartilage repair procedures. On the other side, it has been concluded that smoking impairs healing of several musculoskeletal tissues.[12] In particular, there is evidence that smoking is associated with delayed bone healing.[13–17] Also, it was reported that smokers have a higher risk for impaired regeneration of wounds of the skin and other soft tissues.[31,32]

The negative effects of smoking on healing of bone and soft tissue are caused by multiple mechanisms, including vasoconstriction, decreased oxygen delivery, and reduced fibroblast migration.[33–36] Cartilage, however, is an avascular tissue and the decrease of microperfusion and oxygenation by nicotine and carbon monoxide may not affect cartilage healing as much as bone and soft-tissue healing. Instead, an in vitro experiment demonstrated stimulating effects of nicotine on human chondrocytes derived from healthy patients and osteoarthritis patients leading to enhanced cell proliferation and collagen synthesis.[30] Despite these considerations, in our present study, the group of smokers did not achieve a better outcome after third-generation ACI than nonsmokers or ex-smokers.

The preoperative NRS of smokers was significantly higher than in the group of nonsmokers. This finding is in agreement with other previous studies reporting that smokers experience more musculoskeletal pain than nonsmokers.[37–39] It is thought that elevated levels of proinflammatory mediators can amplify pain in smokers.[40,41]

Strengths and Limitations

Strengths of this study include the way data were collected. We used registry data from a large number of "real world patients" with similar patient- and defect-specific parameters. The reported data may be closer to reality as in contrast to highly selected cartilage defect patients enrolled in randomized clinical trials that are suggested not to be representative of patients in an orthopaedic practice.[24,42] Data from the German Cartilage Registry were collected by multiple international study centers using a web-based remote data entry system.[20]

Limitations are that register studies are subject to selection bias, since it cannot be guaranteed that every single patient receiving ACI will be documented. Also, there might have been unconsidered confounding variables influencing the outcome. Yet, it has been postulated that randomized controlled trials should be supplemented by observational studies with data from multicenter patient registries.[43–45]

Conclusion

Our data suggest that smoking does not affect the outcome within the first 2 years after third-generation ACI. Despite this finding, we recommend that prior to cartilage repair procedures surgeons inform their patients about the various deleterious effects of smoking on health.

Funding
None.

Conflict of Interest
None declared.

References

1 Guermazi A, Hayashi D, Roemer FW, et al. Brief report: partial- and full-thickness focal cartilage defects contribute equally to development of new cartilage damage in knee osteoarthritis: the multicenter osteoarthritis study. Arthritis Rheumatol 2017;69(03):560–564
2 Kim JK, Vaidya R, Lee SK, et al. Clinical and radiological changes after microfracture of knee chondral lesions in middle-aged Asian patients. Clin Orthop Surg 2019;11(03):282–290
3 Wang D, Chang B, Coxe FR, et al. Clinically meaningful improvement after treatment of cartilage defects of the knee with osteochondral grafts. Am J Sports Med 2019;47(01):71–81
4 Zouzias IC, Bugbee WD. Osteochondral allograft transplantation in the knee. Sports Med Arthrosc Rev 2016;24(02):79–84
5 Everhart JS, Jiang EX, Poland SG, Du A, Flanigan DC. Failures, reoperations, and improvement in knee symptoms following matrix-assisted autologous chondrocyte transplantation: a meta-analysis of prospective comparative trials. Cartilage 2019. Doi: 10.1177/1947603519870861

6 Krill M, Early N, Everhart JS, Flanigan DC. Autologous chondrocyte implantation (ACI) for knee cartilage defects: a review of indications, technique, and outcomes. JBJS Rev 2018;6(02):e5
7 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(03): 426–435
8 Fu M, Castellano Y, Tigova O, et al; EUREST-PLUS consortium. Prevalence and correlates of different smoking bans in homes and cars among smokers in six countries of the EUREST-PLUS ITC Europe Surveys. Tob Induc Dis 2019;16:A8
9 Kastaun S, Kotz D, Brown J, Shahab L, Boeckmann M. Public attitudes towards healthcare policies promoting tobacco cessation in Germany: results from the representative German study on tobacco use (DEBRA study). BMJ Open 2019;9(08):e026245
10 Kotz D, Böckmann M, Kastaun S. The use of tobacco, e-cigarettes, and methods to quit smoking in Germany. Dtsch Arztebl Int 2018; 115(14):235–242
11 Peacock A, Leung J, Larney S, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction 2018; 113(10):1905–1926
12 Lee JJ, Patel R, Biermann JS, Dougherty PJ. The musculoskeletal effects of cigarette smoking. J Bone Joint Surg Am 2013;95(09): 850–859
13 McKee MD, DiPasquale DJ, Wild LM, Stephen DJ, Kreder HJ, Schemitsch EH. The effect of smoking on clinical outcome and complication rates following Ilizarov reconstruction. J Orthop Trauma 2003;17(10):663–667
14 Adams CI, Keating JF, Court-Brown CM. Cigarette smoking and open tibial fractures. Injury 2001;32(01):61–65
15 Castillo RC, Bosse MJ, MacKenzie EJ, Patterson BMLEAP Study Group. Impact of smoking on fracture healing and risk of complications in limb-threatening open tibia fractures. J Orthop Trauma 2005;19(03):151–157
16 Harvey EJ, Agel J, Selznick HS, Chapman JR, Henley MB. Deleterious effect of smoking on healing of open tibia-shaft fractures. Am J Orthop 2002;31(09):518–521
17 Schmitz MA, Finnegan M, Natarajan R, Champine J. Effect of smoking on tibial shaft fracture healing. Clin Orthop Relat Res 1999;(365):184–200
18 Blackwell R, Schmitt LC, Flanigan DC, Magnussen RA. Smoking increases the risk of early meniscus repair failure. Knee Surg Sports Traumatol Arthrosc 2016;24(05):1540–1543
19 Santiago-Torres J, Flanigan DC, Butler RB, Bishop JY. The effect of smoking on rotator cuff and glenoid labrum surgery: a systematic review. Am J Sports Med 2015;43(03):745–751
20 Maurer J, Grotejohann B, Jenkner C, et al. A registry for evaluation of efficiency and safety of surgical treatment of cartilage defects: the German Cartilage Registry (KnorpelRegister DGOU). JMIR Res Protoc 2016;5(02):e122
21 Jungmann PM, Salzmann GM, Schmal H, Pestka JM, Südkamp NP, Niemeyer P. Autologous chondrocyte implantation for treatment of cartilage defects of the knee: what predicts the need for reintervention? Am J Sports Med 2012;40(01):58–67
22 Jaiswal PK, Macmull S, Bentley G, Carrington RW, Skinner JA, Briggs TW. Does smoking influence outcome after autologous chondrocyte implantation?: a case-controlled study J Bone Joint Surg Br 2009;91(12):1575–1578
23 Mithoefer K, Saris DB, Farr J, et al. Guidelines for the design and conduct of clinical studies in knee articular cartilage repair: international cartilage repair society recommendations based on current scientific evidence and standards of clinical care. Cartilage 2011;2(02):100–121
24 Hochrein A, Zinser W, Spahn G, et al. What parameters affect knee function in patients with untreated cartilage defects: baseline data from the German Cartilage Registry. Int Orthop 2019;43(05): 1107–1112
25 Bekkers JE, de Windt TS, Raijmakers NJ, Dhert WJ, Saris DB. Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. Osteoarthritis Cartilage 2009;17(11):1434–1439
26 Roos EM, Roos HP, Ekdahl C, Lohmander LS. Knee injury and Osteoarthritis Outcome Score (KOOS)–validation of a Swedish version. Scand J Med Sci Sports 1998;8(06):439–448
27 Kong L, Wang L, Meng F, Cao J, Shen Y. Association between smoking and risk of knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2017;25(06):809–816
28 Racunica TL, Szramka M, Wluka AE, et al. A positive association of smoking and articular knee joint cartilage in healthy people. Osteoarthritis Cartilage 2007;15(05):587–590
29 Gullahorn L, Lippiello L, Karpman R. Smoking and osteoarthritis: differential effect of nicotine on human chondrocyte glycosaminoglycan and collagen synthesis. Osteoarthritis Cartilage 2005;13 (10):942–943
30 Ying X, Cheng S, Shen Y, et al. Nicotine promotes proliferation and collagen synthesis of chondrocytes isolated from normal human and osteoarthritis patients. Mol Cell Biochem 2012;359 (1,2):263–269
31 Sørensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. Arch Surg 2012;147(04):373–383
32 Theocharidis V, Katsaros I, Sgouromallis E, et al. Current evidence on the role of smoking in plastic surgery elective procedures: a systematic review and meta-analysis. J Plast Reconstr Aesthet Surg 2018;71(05):624–636
33 Silverstein P. Smoking and wound healing. Am J Med 1992;93 (1A):22S–24S
34 Hwang K, Son JS, Ryu WK. Smoking and flap survival. Plast Surg (Oakv) 2018;26(04):280–285
35 Wong LS, Martins-Green M. Firsthand cigarette smoke alters fibroblast migration and survival: implications for impaired healing. Wound Repair Regen 2004;12(04):471–484
36 Wong LS, Green HM, Feugate JE, Yadav M, Nothnagel EA, Martins-Green M. Effects of "second-hand" smoke on structure and function of fibroblasts, cells that are critical for tissue repair and remodeling. BMC Cell Biol 2004;5:13
37 Karim A, Pandit H, Murray J, Wandless F, Thomas NP. Smoking and reconstruction of the anterior cruciate ligament. J Bone Joint Surg Br 2006;88(08):1027–1031
38 Mallon WJ, Misamore G, Snead DS, Denton P. The impact of preoperative smoking habits on the results of rotator cuff repair. J Shoulder Elbow Surg 2004;13(02):129–132
39 Amin S, Niu J, Guermazi A, et al. Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. Ann Rheum Dis 2007;66(01):18–22
40 Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. Chest 2007;131(05):1557–1566
41 O'Loughlin J, Lambert M, Karp I, et al. Association between cigarette smoking and C-reactive protein in a representative, population-based sample of adolescents. Nicotine Tob Res 2008;10(03):525–532
42 Engen CN, Engebretsen L, Årøen A. Knee cartilage defect patients enrolled in randomized controlled trials are not representative of patients in orthopedic practice. Cartilage 2010;1(04):312–319
43 Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ 1996;312(7040):1215–1218
44 Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. JACC Cardiovasc Interv 2008;1(03):211–217
45 Silverman SL. From randomized controlled trials to observational studies. Am J Med 2009;122(02):114–120

9. Literaturverzeichnis

1. Hjelle, K., et al., *Articular cartilage defects in 1,000 knee arthroscopies.* Arthroscopy, 2002. **18**(7): p. 730-4.
2. Heir, S., et al., *Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery.* Am J Sports Med, 2010. **38**(2): p. 231-7.
3. Richter, D.L., et al., *Knee Articular Cartilage Repair and Restoration Techniques: A Review of the Literature.* Sports Health, 2016. **8**(2): p. 153-60.
4. 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.
5. 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.
6. Hoburg, A., et al., *Sustained superiority in KOOS subscores after matrix-associated chondrocyte implantation using spheroids compared to microfracture.* Knee Surg Sports Traumatol Arthrosc, 2023. **31**(6): p. 2482-2493.
7. 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.
8. Niemeyer, P., et al., *Autologous chondrocyte implantation for treatment of focal cartilage defects in patients age 40 years and older: A matched-pair analysis with 2-year follow-up.* Am J Sports Med, 2010. **38**(12): p. 2410-6.
9. Niemeyer, P., et al., *First-generation versus second-generation autologous chondrocyte implantation for treatment of cartilage defects of the knee: a matched-pair analysis on long-term clinical outcome.* Int Orthop, 2014. **38**(10): p. 2065-70.
10. Hoburg, A., et al., *Matrix-Associated Autologous Chondrocyte Implantation Is an Effective Treatment at Midterm Follow-up in Adolescents and Young Adults.* Orthop J Sports Med, 2019. **7**(4): p. 2325967119841077.
11. Nawaz, S.Z., et al., *Autologous chondrocyte implantation in the knee: mid-term to long-term results.* J Bone Joint Surg Am, 2014. **96**(10): p. 824-30.
12. Niemeyer, P., et al., *Comparison of Hydrogel-Based Autologous Chondrocyte Implantation Versus Microfracture: A Propensity Score Matched-Pair Analysis.* Orthop J Sports Med, 2023. **11**(8): p. 23259671231193325.
13. Krishnan, S.P., et al., *Who is the ideal candidate for autologous chondrocyte implantation?* J Bone Joint Surg Br, 2006. **88**(1): p. 61-4.
14. Niemeyer, P., et al., *Characteristic complications after autologous chondrocyte implantation for cartilage defects of the knee joint.* Am J Sports Med, 2008. **36**(11): p. 2091-9.
15. Niemeyer, P., et al., *Autologous chondrocyte implantation for the treatment of retropatellar cartilage defects: clinical results referred to defect localisation.* Arch Orthop Trauma Surg, 2008. **128**(11): p. 1223-31.
16. Niemeyer, P., et al., *Treatment of Large Cartilage Defects in the Knee by Hydrogel-Based Autologous Chondrocyte Implantation: Two-Year Results of a Prospective, Multicenter, Single-Arm Phase III Trial.* Cartilage, 2022. **13**(1): p. 19476035221085146.
17. Collins, N.J., et al., *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), 2011. **63 Suppl 11**(0 11): p. S208-28.

18. Mithoefer, K., et al., *Guidelines for the Design and Conduct of Clinical Studies in Knee Articular Cartilage Repair: International Cartilage Repair Society Recommendations Based on Current Scientific Evidence and Standards of Clinical Care.* Cartilage, 2011. **2**(2): p. 100-21.

19. Starker, A., et al., *Smoking behaviour and passive smoke exposure of adults - Results from GEDA 2019/2020-EHIS.* J Health Monit, 2022. **7**(3): p. 6-20.

20. Samarasekera, U., *WHO's ninth report on the global tobacco epidemic.* Lancet Oncol, 2023. **24**(9): p. 957.

21. Adams, C.I., J.F. Keating, and C.M. Court-Brown, *Cigarette smoking and open tibial fractures.* Injury, 2001. **32**(1): p. 61-5.

22. Blackwell, R., et al., *Smoking increases the risk of early meniscus repair failure.* Knee Surg Sports Traumatol Arthrosc, 2016. **24**(5): p. 1540-3.

23. Castillo, R.C., et al., *Impact of smoking on fracture healing and risk of complications in limb-threatening open tibia fractures.* J Orthop Trauma, 2005. **19**(3): p. 151-7.

24. Harvey, E.J., et al., *Deleterious effect of smoking on healing of open tibia-shaft fractures.* Am J Orthop (Belle Mead NJ), 2002. **31**(9): p. 518-21.

25. Lee, J.J., et al., *The musculoskeletal effects of cigarette smoking.* J Bone Joint Surg Am, 2013. **95**(9): p. 850-9.

26. McKee, M.D., et al., *The effect of smoking on clinical outcome and complication rates following Ilizarov reconstruction.* J Orthop Trauma, 2003. **17**(10): p. 663-7.

27. Gullahorn, L., L. Lippiello, and R. Karpman, *Smoking and osteoarthritis: differential effect of nicotine on human chondrocyte glycosaminoglycan and collagen synthesis.* Osteoarthritis Cartilage, 2005. **13**(10): p. 942-3.

28. Kong, L., et al., *Association between smoking and risk of knee osteoarthritis: a systematic review and meta-analysis.* Osteoarthritis Cartilage, 2017. **25**(6): p. 809-816.

29. Racunica, T.L., et al., *A positive association of smoking and articular knee joint cartilage in healthy people.* Osteoarthritis Cartilage, 2007. **15**(5): p. 587-90.

30. Ying, X., et al., *Nicotine promotes proliferation and collagen synthesis of chondrocytes isolated from normal human and osteoarthritis patients.* Mol Cell Biochem, 2012. **359**(1-2): p. 263-9.

31. Jaiswal, P.K., et al., *Does smoking influence outcome after autologous chondrocyte implantation?: A case-controlled study.* J Bone Joint Surg Br, 2009. **91**(12): p. 1575-8.

32. Jungmann, P.M., et al., *Autologous chondrocyte implantation for treatment of cartilage defects of the knee: what predicts the need for reintervention?* Am J Sports Med, 2012. **40**(1): p. 58-67.

33. Bekkers, J.E., et al., *Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions.* Osteoarthritis Cartilage, 2009. **17**(11): p. 1434-9.

10. Danksagung

Diese Doktorarbeit wäre ohne die Unterstützung der folgenden Personen nicht zustande gekommen, weswegen ich mich auch in diesem Rahmen nochmals bei Ihnen bedanken möchte.

Zuallererst gilt mein Dank meinem Doktorvater, Herrn Prof. Dr. Thomas Niethammer, der mich durch das gesamte Projekt begleitet hat, nie ungeduldig wurde und mir dabei stets freundlich mit Rat und Expertise zur Seite stand. Die Gespräche, die wir hatten, waren immer konstruktiv und halfen mir, in meiner Arbeit voranzukommen. Eine bessere Betreuung hätte ich mir persönlich nicht wünschen können.

Außerdem möchte ich mich bei allen Mitarbeitenden der Klinik für Orthopädie und Unfallchirurgie der LMU in München bedanken, die mich in ihren Arbeitsbereichen willkommen hießen, Patient*Innen für die Datenerhebung einbezogen und die für ein gutes Arbeitsklima sorgten.

Auch meinen Vorgesetzten und Kolleg*Innen möchte ich danken. Natürlich ging mein Berufsstart in einem der Doktorarbeit fernen Fach und Klinikum damit einher, dass weniger Zeit für die Dissertation verfügbar war. Dabei wurden mir jedoch immer Unterstützung und Wohlwollen entgegengebracht und nie Steine in den Weg gelegt, die Doktorarbeit zu beenden.

Meiner Familie (insbesondere meinen Eltern) und meiner Freundin gilt ebenfalls großer Dank. Sie halfen mir, die Motivation für die Dissertation auch in schwierigen Phasen nicht zu verlieren und waren trotz des damit einhergehenden Zeitaufwands immer verständnisvoll und unterstützend.