**Aus der Klinik für Orthopädie und Unfallchirurgie**

**der Heinrich-Heine-Universität Düsseldorf**

Direktor: Univ.-Prof. Dr. med. Joachim Windolf

# Muskelgesundheit und Prähabilitation in der Kniegelenksendoprothetik:

*Einfluss der Blood-Flow-Restriction Trainingstherapie als prähabilitativer Ansatz im klinisch-randomisierten Studiensetting auf die postoperative Regeneration von Muskelmasse, -kraft und Funktionalität nach elektiver Kniegelenksendoprothetik*

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Alexander Franz, B.Sc.

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Erstgutachter: PD Dr. med. Bernd Bittersohl

Zweitgutachter: Prof. Dr. med. Christoph Zilkens

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## Zusammenfassung

Die endoprothetische Versorgung des Kniegelenks (engl. Total-Knee-Arthroplasty, TKA) ist eine der erfolgreichsten Eingriffe bei Gonarthrose zur Verbesserung der Mobilität und Minderung chronischer Schmerzen. Allerdings führt die Operation zu langanhaltenden muskulären Atrophien sowie Defiziten in der Muskelaktivierung und Kraftgenerierung. Ein neuer Ansatz zur Verbesserung des postoperativen klinischen Ergebnisses ist die Anwendung präoperativer Trainingsprogramme (Prähabilitation). In diesem Zusammenhang kristallisiert sich eine neue Trainingstechnik zunehmend heraus, die für Arthrose-betroffene Patienten einen schmerzfreien Weg zum Muskelaufbau generieren könnte, dass sog. Blood-Flow-Restriction Training (BFR).

Die vorliegende Dissertation bietet eine neue, empirisch-fundierte Analyse und Anwendung des BFR-Trainings als Prähabilitationskonzept vor der endoprothetischer Versorgung des Kniegelenks. Ausgehend von der Beschreibung der Muskelgesundheit der orthopädischen Patientenkohorte mit Gonarthrose, fokussiert die vorliegende Thesis die Genese der prä-, peri- und postoperativen Muskelatrophie, deren Einfluss auf die Rehabilitation und dessen Verbesserung durch eine präoperative Prähabilitationstherapie mit BFR-Training.

Diese Dissertation umfasst insgesamt drei internationale Publikationen. Im Rahmen zweier Übersichtsarbeiten der aktuellen Literatur wurde zunächst die Patientenkohorte der orthopädischen Endoprothetik beschrieben und folgend die aktuellen Prähabilitationsansätze, deren Einfluss auf die postoperative Regeneration sowie die Hypothesenstellung der Einführung des BFR-Trainings thematisiert. Auf Basis dieser Erkenntnisse wurde eine klinisch-prospektive Studie konzipiert, bei der das BFR-Training als Prähabilitation vor einer elektiven TKA angewandt wurde. Die Ergebnisse ermöglichen eine erste Bewertung des Effektes einer BFR-Prähabilitation auf die prä- und postoperative Muskelgesundheit orthopädischer Patienten mit Gonarthrose.

## Summary

Total knee arthroplasty (TKA) is one of the most successful interventions for gonarthrosis to improve mobility and reduce chronic pain. However, the surgical procedure leads to long-lasting muscular atrophy and deficits in muscle activation and strength development. A new approach to improve postoperative clinical outcome is the use of preoperative exercise programs (prehabilitation). In this context, a new training technique is increasingly emerging that could generate a painless pathway to muscle gains for osteoarthritis-affected patients, the blood-flow restriction training (BFR).

This dissertation provides a new, empirically based analysis and application of BFR-training as a prehabilitation concept prior to elective TKA. Based on the description of muscle health of the orthopedic patient cohort with gonarthrosis, this thesis analyzed the genesis of pre-, peri- and postoperative muscle atrophy, its influence on rehabilitation and its improvement by preoperative prehabilitation therapy with BFR-training.

This dissertation includes a total of three international publications. In two reviews of the current literature, the muscle health of the orthopedic patient cohort which received a TKA and the current prehabilitation approaches are described. Furthermore, the impact of current prehabilitation protocols on postoperative regeneration as well as the hypothesis of the beneficial effects of BFR-training were addressed. Based on these findings, a clinical prospective study was designed, where BFR-Training was applied as prehabilitation technique in front of a TKA-surgery to investigate its impact on pre- and postoperative muscle health in orthopedic patients with gonarthrosis.

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**Abkürzungsverzeichnis**

| | | | |
|---|---|---|---|
| **AC** | Active Control Group | **LOP** | Limb Occlusion Pressure |
| **Akt** | Proteinkinase B | **LOS** | Length-of-hospital-stay |
| **AMI** | arthrogenic muscle inhibtion | **MAFbx** | Muskelatrophie-F-Box |
| **AMPK** | AMP-aktivierten Proteinkinase | **mmhg** | Millimeter-Quecksilbersäule |
| **BFR-T** | Blood-Flow-Restriction Training | **MuRF1** | Muskel-RING-Finger 1 |
| **BiBo** | Better in, Better Out | **NMES** | Neuromuscular Electrical Stimulation |
| **CG** | Control Group | **Nrf2** | nuclear factor (erythroid-derived 2)-like 2 |
| **CRF** | Chair-Rising-Test | **PGC-1 α** | Peroxisom-Proliferator-aktivierten Rezeptor-γ-CArthrosektivators-1α |
| **DVT** | Deep-Vein-Thrombosis | **QoL** | Quality of Life |
| **EHR** | exercise heart rate | **ROM** | Range-of-Motion |
| **FoxO3a** | Forkhead-Box O3 | **TKA** | Total Knee Arthroplasty |
| **Gh** | Growth-Hormone | **VAS** | Visuelle Analogskala |
| **HL-RT** | High-Load Resistance Training | **VKB-P** | Vordere Kreuzband-Plastik |
| **IGF-1** | Insulin-like-growth-factor 1 | **Vs.** | Gegen |
| **KOOS** | Knee Injury and Ostearthritis Outcome Score | **1RM** | Ein-Wiederholungs-Maximalkraft |
| **LL-RT** | Low-Load Resistance Training | **6RM** | Sechs-Wiederholungs-Maximalkraft |
| **LL-BFR-T** | Low-Load Blood-Flow-Restriction Training | **6MWT** | Six-Minute-Walking-Test |

# 1. Synopsis

## 1.1 Einführung in das Projekt

Die Arthrose des Kniegelenks ist eine der am häufigsten diagnostizierten Gelenkerkrankungen weltweit und geht bei den betroffenen Patienten mit chronischen Einschränkungen der Mobilität und progredienten Schmerzen einher. Die in erster Linie durch Fehl- oder Überbelastungen entstehende Arthrose ist durch eine fortschreitende Veränderung der Knorpel- und Knochenstruktur gekennzeichnet. Typische radiologische Zeichen für eine Arthrose im Röntgenbild sind eine Verschmälerung des Gelenkspalts, subchondrale Sklerosierung und osteophytäre Randanbauten (2). Auf Grundlage dieser Arthrose -bedingten Veränderungen des Gelenks kann eine radiologische Klassifizierung in fünf Stadien vorgenommen werden, die erstmals von Kellgren und Lawrence veröffentlicht wurde (58). Die Indikation zur konservativen oder chirurgischen Therapie einer radiologisch festgestellten Arthrose des Kniegelenks ist jedoch abhängig von den klinischen Symptomen des Patienten. Typischerweise leiden Arthrose-Patienten unter einer chronischen Reduktion der Mobilität und progredienten Gelenkschmerzen, die zu einer starken Einschränkung des täglichen Lebens und der Lebensqualität (engl. Quality-of-Life, QoL) führen (74).

## 1.2 Arthrose, Endoprothetik und Muskelgesundheit

### 1.2.1 Einfluss der Arthrose des Kniegelenks auf die muskuläre Gesundheit

Neben diesen regelmäßig zur Einschätzung der Schwere der Erkrankung eines Patienten angewendeten klinischen und radiologischen Symptomen sind Arthrose-Patienten auch durch eine stark beeinträchtigte Gesundheit der Skelettmuskulatur charakterisiert. Insbesondere durch die fortschreitende Immobilität ist die Skelettmuskulatur von einer langfristigen Muskelatrophie, einem Verlust der Muskelkraft und einer Verringerung der neuromuskulären Aktivität betroffen (29, 51). Die Muskelatrophie ist durch den Abbau und Entfernung kontraktiler Proteine mit einer damit verbundenen Verringerung der Muskelfasergröße gekennzeichnet (12). Diesbezüglich zeigen Bettruhe-Studien anhand von Muskelbiopsien, dass eine Immobilisierung das Genexpressionsprofil der Skelettmuskulatur verändert, was zu einer Herabregulierung von Genen führt, die an der Energieproduktion und dem Kohlenhydratstoffwechsel beteiligt sind. Zur gleichen Zeit werden Gene hochreguliert, die am

Proteinabbau beteiligt sind (65). Arthrose-Modelle bei Nagetieren haben indirekt gezeigt, dass einer der Hauptregulatoren des anabolen Proteinstoffwechsels, die Proteinkinase B (Akt), bei Arthrose herunterreguliert wird, während gleichzeitig die Expression von nachgeschalteten Produkten der Forkhead-Box O3 (FoxO3a), die am proteasomalen Proteinabbau beteiligt sind (z. B. Muskel-RING-Finger 1 (MuRF1), Muskelatrophie-F-Box (MAFbx)), erhöht wird (5). Neben der Hochregulierung atrophiebezogener Gene sind die Muskeln von Arthrose-Patienten auch durch eine erhöhte Expression von inflammatorischen Zytokinen gekennzeichnet, die als akzessorischer Auslöser für Muskelatrophie-Signale angesehen werden können (69).

Obwohl die Abnahme der Muskelkraft durch den Verlust des Muskelquerschnitts erklärt werden kann (76), ist eine parallele Abnahme der neuromuskulären Aktivierung als sekundäre Ursache für die Verringerung der Muskelkraft und der täglichen Mobilität anzusehen. Vermutlich durch eine gestörte afferente Sensorik verursacht, bedingen arthrotisch- oder chirurgisch-induzierte Veränderungen der Gewebehomöostase (106), Entzündungen (107), Gewebeschädigungen (47) und insbesondere Schmerzen eine negative Auswirkungen auf die neuromuskuläre Aktivierung und führen zum Entstehen einer "arthrogenen Muskelhemmung" (engl. arthrogenic muscle inhibtion, AMI) (57). AMI beschreibt ein Defizit in der neuronalen Muskelaktivierung und der Muskelfaserrekrutierung, ohne dass damit eine strukturelle Schädigung des efferenten Muskels oder des innervierenden Nervs verbunden ist (48). Daher scheinen pathologische Veränderungen der Muskelfunktion sowohl vor als auch nach einer gelenkchirurgischen Intervention in hohem Maße von AMI betroffen zu sein, was in der Folge zu einer beeinträchtigten Kraftentwicklung führt, den Muskelabbau fördert und eine fortschreitende Immobilität unterstützt.

### 1.2.2 Einfluss der endoprothetischen Versorgung des Kniegelenks auf die muskuläre Gesundheit

Aufgrund der fortschreitenden Alterung unserer Bevölkerung und der dabei gleichzeitig steigenden Mobilitätserwartungen im höheren Alter, kommt der Erforschung effizienter Behandlungsmethoden und Präventionsstrategien eine zunehmend wichtige Rolle zuteil. Die derzeit erfolgversprechendste Behandlungsmethode der Arthrose des Kniegelenks im Endstadium ist die chirurgische Versorgung durch eine Kniegelenkstotalendoprothese (engl. Total-Knee-Arthroplasty, TKA), mit steigenden Fallzahlen weltweit (61). Trotz der Optimierung von Prothesendesigns, der Standardisierung von Operationstechniken und der Anwendung von sogenannten Rapid-Recovery-Programmen zur schnelleren postoperativen Rehabilitation weisen Patienten nach TKA im Vergleich zu ihren alters- und geschlechtsgleichen Kontrollpersonen häufig funktionelle Einschränkungen auf (7). Betroffene Patienten berichten dabei über einen fortschreitenden postoperativen Muskelschwund und einem damit verbundenen Kraftverlust der unteren Extremitäten (82, 103). In diesem Zusammenhang berichteten Farquhar und Kollegen (31), dass die funktionelle Gesamtleistung sowie die Muskelkraft des operierten und des nicht-operierten Beins in den ersten drei Jahren nach TKA im Vergleich zu Kontrollgruppen deutlich abnehmen. Doch nicht nur die anhaltende Immobilität verursacht einen fortschreitenden Muskelabbau, auch der chirurgische Eingriff selbst kann als Auslöser der Atrophie angesehen werden (77).

Obwohl mit den modernen chirurgischen Zugangswegen versucht wird direkte Muskelschäden routinemäßig zu vermeiden, haben molekulare Analysen von Muskelbiopsien aus dem *M. vastus lateralis* während einer TKA-Operation ergeben, dass die Proteinbiosynthese herabgesetzt und gleichzeitig die Expression wichtiger Atrophierende hochreguliert wird (8, 104). Speziell bei der Anwendung intraoperativer Blutsperrensysteme, stellt die ischämische Disposition und die anschließende Reperfusion nicht nur ein ernsthaftes Risiko für die Schädigung der Skelettmuskulatur dar (67), sondern führen auch zu einer Dephosphorylierung von Akt, was eine Hemmung des Akt-mTORC-Signalwegs zur Folge hat. Infolgedessen wird die Proteinbiosynthese durch eine geringere Bildung der Translationsinitiationskomplexe blockiert, wobei gleichzeitig die FoxO3a-Produkte (MuRF1, MAFbx) hochreguliert werden, welche den Abbau von Muskelproteinen während und nach der Operation fördern. Darüber hinaus kann die durch eine Blutsperre oder ein chirurgisches Trauma ausgelöste Bildung reaktiver Sauerstoffspezies eine anschließende akute Immunreaktion auslösen, die einen anhaltenden Gewebestress hervorruft, indem sie ebenfalls den Proteinabbau fördert (9, 68).

Obwohl die zugrundeliegenden Mechanismen der chirurgisch-induzierten Veränderungen in der Skelettmuskelphysiologie gut beschrieben sind, wird die ausführliche Diskussion über die Verwendung einer Blutsperre während einer TKA meist von regelmäßig dokumentierten Parametern geleitet (pro: weniger Blutungen, kürzere Operationszeit; contra: erhöhtes Risiko einer tiefen Venenthrombose, verzögerte Erholung). In Bezug auf die Skelettmuskelphysiologie und den perioperativen Einsatz von Blutsperren berichteten Jawhar und Kollegen über eine geringere proteasomabhängige Peptidaseaktivität in Biopsien des *M. vastus medialis* bei Blutsperren-freien Operationen (53). Allerdings zeigten die klinischen Ergebnisse keine statistische Überlegenheit von Operationen ohne Blutsperre in Bezug auf kurzfristige postoperative Schmerzen, Schwellungen oder muskuläre Erholung. Darüber hinaus zeigten Dennis et al. (28) in der langfristigen Nachbeobachtung keine statistisch signifikanten Unterschiede in der Muskelaktivierung und der Regeneration der Muskelkraft zwischen den Operationsvarianten, bei weiterhin bestehender signifikanter Muskelatrophie.

### 1.2.3 Postoperative Rehabilitation und Regeneration der Muskelfunktion

Ähnlich wie die präoperative ist auch die frühe postoperative Phase nach TKA durch Immobilität und Schonhaltung gekennzeichnet und unterstützt daher ebenfalls die katabolen Bedingungen in der Skelettmuskulatur. Diesbezüglich konnte dargestellt werden, dass eine Woche postoperativer Krankenhausaufenthalt, was in mehreren Ländern (z.B. Deutschland, Dänemark) einen durchschnittlichen Hospitalisierungszeitraum darstellt (engl. length-of-hospital-stay, LOS) (49), zu einem signifikanten Muskelschwund nach TKA führt (60). Ratchford und Kollegen (104) konnten diesbezüglich eine signifikante Verringerung der Quadrizeps-Muskelmasse in den ersten zwei Wochen nach der TKA-Operation um 12 % am operierten und um 6 % am nicht-operierten Bein dokumentieren. Darüber hinaus vervollständigen die Abnahme der Muskelkraft und Irritationen bei der Muskelaktivierung die beeinträchtigte Muskelgesundheit der Patienten nach einer TKA (82, 123).

Um die postoperative Rehabilitation zu verbessern, wurden die klinischen Behandlungsabläufe für die TKA-Operation modifiziert, wobei insbesondere das perioperative Schmerzmanagement, die frühe postoperative Mobilisierung und der zeitnahe Übergang in ein spezifisches Rehabilitationsprogramm berücksichtigt wurden (26, 105). Obwohl klinische Ergebnisse wie die LOS und die Rate der Wiedereinweisungen durch diese Modifikationen reduziert werden konnten (11, 115), kann eine schnellere Entlassung aus dem Krankenhaus und der Beginn einer intensiven physiotherapeutischen

Behandlung nur mit kurzfristigen Vorteilen der Rehabilitation in Verbindung gebracht werden. So zeigen die Ergebnisse aus der Literatur, das solche frührehabilitativen Interventionen des Hospitalisierungsablaufes keine langfristigen Verbesserungen bei der funktionellen und muskulären Rehabilitation erbringen (80, 129). Demzufolge weisen Patienten auch zwei Jahre nach TKA eine weiterhin eingeschränkte Muskelgesundheit auf, charakterisiert durch eine fettige Muskelatrophie (97), progrediente Muskelkraftverluste und weiterhin bestehende Irritationen in der neuromuskulären Aktivierung, welche mit damit verbundenen Funktionseinbußen im täglichen Leben einhergehen (46, 103).

Ein entsprechendes Ergebnis liefern systematische Übersichtsarbeiten über die körperliche Aktivität von TKA-Patienten im prä- und postoperativen Vergleich. Dabei kommen diese Arbeiten zu dem Ergebnis, dass Patienten nach elektiver TKA keinen Unterschied in der körperlichen Aktivität zwischen dem Status vor und zwei Jahre nach der Operation aufweisen (4, 43). Auf Basis dieser Ergebnisse scheinen postoperative Maßnahmen nur einen geringen Einfluss auf die muskuläre Rehabilitation nach TKA zu haben, was auf eine multifaktorielle Induktion von Atrophiesignalen zurückzuführen sein könnte, die sowohl prä- und postoperative Immobilität als auch die chirurgische Intervention selbst miteinschließt (86, 130).

Epidemiologische Daten haben gezeigt, dass mehrere physische Faktoren, z. B. eine höhere präoperative Muskelmasse, Muskelkraft, Bewegungsumfang (engl. Range-of-motion, ROM) und die Fähigkeit, funktionelle Aufgaben zu erfüllen, als positive Vorhersagewerte für eine erfolgreiche und schnellere Genesung nach TKA angesehen werden können (81). Dennoch ist eine spezifische Diagnostik zur Bewertung des aktuellen Zustands der Muskelgesundheit der Patienten nicht in die klinische präoperative Routine integriert. Stattdessen wird die elektive Operation ohne Berücksichtigung möglicher präkonditionierender Maßnahmen durchgeführt, obwohl sich der Muskelzustand des Patienten vermutlich auf dem niedrigsten Gesundheitsniveau seines Lebens befindet, ohne Aussicht auf Fortschritte. Daher könnte ein präoperatives Training der Fitness und Muskelgesundheit der Patienten ein vielversprechendes Instrument zur Verbesserung der postoperativen Muskelgesundheit im Rahmen eines „Better in, Better Out“-Ansatzes (BiBo) sein.

### 1.3 Better In, Better Out: Prähabilitation als neuer Therapieansatz?

Das Konzept der Trainingsinterventionen oder der intensiven Physiotherapie zur Verbesserung der Muskelgesundheit und Funktionalität der Patienten vor einer elektiven Operation wird als "Prähabilitation" bezeichnet (16). Die grundlegende Idee der Prähabilitation beruht darin, durch die präoperative Zunahme der Muskelmasse und -kraft und die damit verbundene Verbesserung der Funktionalität als eine Art kompensatorischen "Puffer" aufzubauen, welcher die postoperative Atrophie reduziert und dadurch langfristige die klinische Rehabilitation fördert und eine höhere subjektive Patientenzufriedenheit ermöglicht (121) (Abbildung 1). Bei der TKA konnten mehrere Studien über signifikante Verbesserungen der präoperativen Beinkraft, des ROM und des subjektiven Schmerzempfindens durch die Prähabilitation berichten (79, 113), ohne jedoch positive Auswirkungen auf die postoperative muskuläre und funktionelle Rehabilitation zu zeigen (10). Während routinemäßig kontrollierte klinisch-postoperative Parameter wie LOS, ROM und *Sit-to-Stand*-Zeit sich durch die Prähabilitation positiv beeinflusst zeigten, wiesen Messungen der postoperativen Muskelkraft, Schmerzen und die funktionelle Rehabilitation (z. B. 6-Minuten-Gehtest) keine Verbesserungen auf (20). Aufgrund diverser uneinheitlicher Trainingsprotokolle der publizierten Prähabilitationskonzepte (z. B. Heimtraining vs. Angeleitetes Training), der angewendeten Trainingsintensitäten (z. B. 10 Wiederholungen mit 80% des 1-Wiederholungsmaximums (engl. 1-repetition-maximum, 1RM) vs. Körpergewichtsübungen) oder sogar der Dauer der Prähabilitation (z. B. vier Wochen vs. acht Wochen) ist eine wissenschaftlich fundierte Bewertung des Nutzens der Prähabilitation für die klinische Praxis nicht möglich.

Obwohl die berichteten Prähabilitationskonzepte signifikante Verbesserungen der präoperativen Muskelgesundheit der Patienten zeigen konnten, gibt es keine statistischen Auswirkungen auf die postoperative Rehabilitation. Da eine kürzere Hospitalisierung oder eine kürzere Zeit bis zum Erreichen der 90°-Knieflexion nach TKA als wichtige Faktoren für die Krankenhausvergütung angesehen werden, scheint die funktionelle und muskuläre Erholung durch die derzeit angewandten Prähabilitationsstrategien nicht unterstützt zu werden (20). Daher ergab eine Meta-Analyse mit Systematic Review von Moyer und Kollegen, dass die Gesamtwirkung der Prähabilitation im Rahmen eines BiBo-Ansatzes in der TKA-Therapie nur als gering bis mäßig einzustufen ist (84).

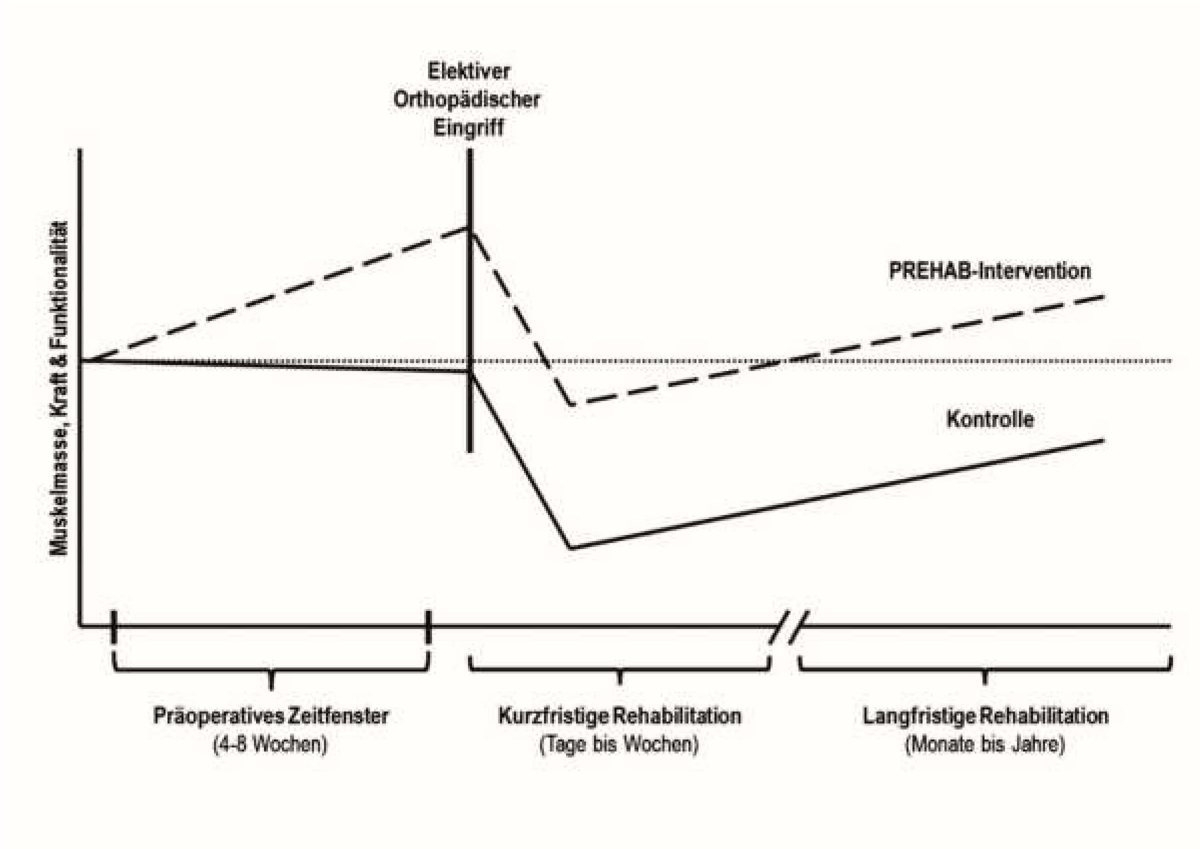


**Abbildung 1** Theoretisches Modell des Einflusses der Prähabilitation auf die postoperativen Rehabilitation von Muskelmasse, -kraft und assoziierter Funktionalität (modifiziert nach Topp et al. (121).

Auch wenn diese Ergebnisse das grundlegende Konzept der Prähabilitation in Frage stellen, ist es doch fraglich, ob die derzeit angewandten Trainingstechniken am besten geeignet sind, die muskuläre Gesundheit in dieser speziellen Patientengruppe zu verbessern. Ausgehend von den beschriebenen Merkmalen der beeinträchtigten Gelenkbeweglichkeit, progredienten Muskelatrophie und chronischen Schmerzen bei Arthrose-Patienten sollten Trainingskonzepte in der klinischen Prähabilitation darauf abzielen, die Muskelmasse und -kraft bei gleichzeitiger Verringerung des AMI zu erhöhen, um eine langfristige Verbesserung der Rehabilitation der Patienten zu gewährleisten. Was die willentliche Muskelaktivierung betrifft, so ist die transkutane elektrische Muskelstimulation (NMES) ein intensiv erforschtes Forschungsgebiet bei Arthrose-Patienten, wobei positive Ergebnisse bei Arthrose- und TKA-induzierter AMI berichtet wurden (98, 102, 116). Bisherige Ansätze haben es jedoch nicht geschafft, die Muskelmasse und -kraft von Arthrose-Patienten durch NMES zu verbessern (40, 93), selbst wenn sie mit einer regelmäßigen Bewegungstherapie kombiniert (30, 64) oder als präoperative

Trainingstherapie angewandt wurde (83, 92). Daher scheint es nach wie vor notwendig zu sein, geeignete Trainingskonzepte für Arthrose-Patienten zu eruieren, um zusätzliche Verbesserungen der Muskelmasse und -kraft zu bewerten.

Aus rein sportwissenschaftlicher Sicht, sind Verbesserungen der Muskelmasse, Kraft und Funktionalität in erster Linie durch die Anwendung hoher mechanischer Belastungen (> 65% 1RM) oder durch die gezielte Auslösung exzentrischer Übungskontraktionen zu erreichen (45, 110). Obwohl diese Belastungsnormative zu positive Resultaten in der Rehabilitation führen (62), ist deren klinische Anwendung durch das Auftreten von Schmerzen während des Trainings und damit verbundener reduzierter Compliance der Patienten zur Trainingstherapie begrenzt (96). Aus diesem Grund hat eine neue Trainingstechnik in den letzten Jahren in der klinischen konservativen Therapie viel Aufmerksamkeit erlangt, da über signifikante Verbesserungen der Muskelgesundheit berichtet wurde, ohne dass hohe mechanische Belastungen eingesetzt werden mussten (124).

## 1.4 Blood-Flow-Restriction Training

Das Blood-Flow-Restriction Training (BFR-T) beschreibt ein Trainingskonzept, das sich durch die Anwendung eines Widerstandstrainings mit geringer mechanischer Belastung (engl. low-load-resistance training, LL-RT, 30% 1RM) in Kombination mit einer externen venösen Okklusion auszeichnet (100). In der Praxis werden spezielle Blutdruckmanschetten proximal der trainierenden Extremität angelegt, um die arterielle Versorgung zu reduzieren und den venösen Rückfluss in der Extremität zu blockieren. Um Weichteilverletzungen zu vermeiden, wird der angewandte Druck zur Auslösung des BFR-T-Effekts anhand des individuellen arteriellen Verschlussdrucks (engl. limb-occlusion-pressure, LOP) berechnet. Der LOP beschreibt den angewandten Druck, bei dem der venöse und arterielle Blutfluss vollständig zum Erliegen kommt. Beim BFR-T wird folgend ein Prozentsatz des individuellen LOP angewandt (z.B. 40% des LOP), um die arterielle Versorgung während des Trainings aufrechtzuerhalten (35). Der Grundgedanke des BFR-T ist der Wechsel von einem primär mechanischen zu einem metabolisch anspruchsvolleren Trainingsreiz, um eine Steigerung der Muskelmasse und -kraft zu erreichen. Zahlreiche wissenschaftliche Studien haben bereits bewiesen, dass LL-BFR-T in der Lage ist, signifikante Muskelmasse- und Kraftzuwächse zu erzielen, die mit hochintensivem Krafttraining mit hohen mechanischen Belastungen (engl. high-load-resistance-training, HL-RT) vergleichbar sind (70).

### 1.4.1 Zugrundeliegende Mechanismen des Blood-Flow-Restriction Trainings

In den letzten Jahren hat sich die Anzahl an Publikationen über die Effekte des BFR-T auf die Muskelmasse, -kraft und andere Leistungsparameter vervielfacht. Die dabei zugrundeliegenden Wirkmechanismen des BFR-T sind jedoch weiterhin unbekannt. Die am häufigsten diskutierten Theorien über die Auswirkungen von BFR auf die Muskelphysiologie sind die "Metabolite-Theory" (72) und die "Cell-Swelling Theory" (71).

In einer kürzlich von unserer Forschungsgruppe veröffentlichten Studie, konnten wir die ersten quantifizierbaren Belege für die oben genannten Theorien erbringen (35). Dabei konnten Anpassungen im Stoffwechsel sowie intravasale Blutdrücke während eines LL-BFR-T der Ellenbogenbeuger mittels invasiver arterieller und venöser Katheter untersucht werden. Wie in der "Metabolite Theory" postuliert, zeigt sich während des LL-BFR-T im Vergleich zur LL-RT ohne externe Okklusion eine hyperkapnische Hypoxie in der trainierenden Extremität. Die sich daraus ergebende Verschiebung der Energiebereitstellung von einer aeroben zur anaeroben Energieversorgung verursacht eine signifikante Laktatazidose während des BFR-T (Abbildung 2). Im Hinblick auf die systemischen Anpassungen an das BFR-T werden nach dieser Theorie die metabolischen Veränderungen von afferenten Nervenfasern (Typ IV-Afferenzen) erkannt (114) und bewirken eine verstärkte neuromuskuläre Aktivierung sowie kardiovaskuläre und endokrine Anpassungen (132). Bereits 20 Minuten nach einem BFR-T kommt es zu einem signifikanten Anstieg der Wachstumshormonsynthese und drei Stunden nach dem Training ist die S6K1-Phosphorylierung, ein Treiber des Muskelanabolismus, sowohl bei jungen als auch bei älteren Patientenpopulationen signifikant im Vergleich zu LL-RT ohne BFR hochreguliert (39), (38).

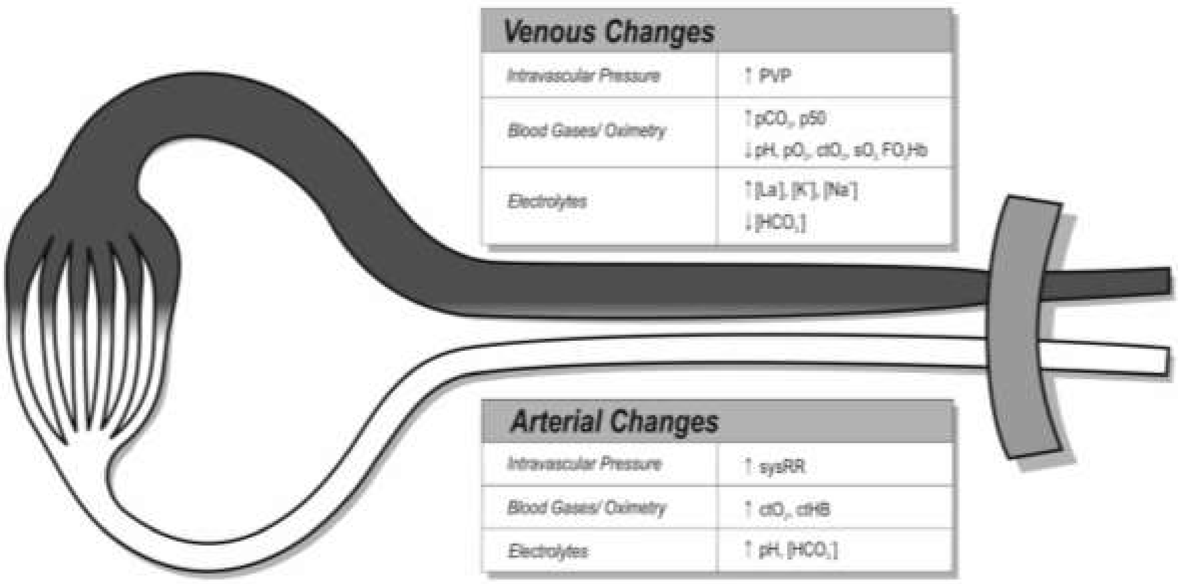


**Abbildung 2** Veranschaulichung signifikanter Veränderungen der metabolischen Homöostase während des BFR-T im Vergleich zu einem LL-RT ($p < 0.05$). Während der weiße Bereich das arterielle System widerspiegelt, beschreibt der dunkle Bereich das venöse System. Die beim BFR-T üblicherweise verwendete Blutsperre befindet sich proximal und ist in grau dargestellt. Änderungen werden durch Pfeile für Anstieg (↑) oder Abfall (↓) gekennzeichnet. SBP, systolischer Blutdruck; PVP, peripherer Venendruck; pCO2, Kohlendioxidpartialdruck; pO2, Sauerstoffpartialdruck; ctO2, Sauerstoffgehalt; FO2Hb, Oxyhämoglobinanteil; ctHb, Hämoglobingehalt; p50, Sauerstoff-Halbsättigungsdruck des Hämoglobins; La-, Laktat; K+, Kalium; Na+, Natrium; HCO3-, Bikarbonat. Quelle: Franz et al. (35)

Die "Cell-Swelling Theory" hingegen geht davon aus, dass der Ursprung des Muskelwachstums durch BFR-T eher mit der lokalen venösen Okklusion zusammenhängt. Intravasale Druckmessungen über arterielle und venöse Katheter zeigten in unserer Studie eine BFR-induzierte arterielle und venöse Hypertonie im Vergleich zum Training ohne BFR (35). Der Anstieg des Venendrucks und die damit verbundene Erhöhung des effektiven Filtrationsdrucks sorgen für eine gesteigerte Filtration von Wasser aus dem Gefäßsystem in das umliegende Gewebe. Durch die gesteigerte Laktatbildung beim BFR-T wird zusätzlich der kolloidosmotische Druck im umgebenden Muskelgewebe erhöht, was eine zusätzliche Wasseraufnahme aus dem Gefäßsystem fördert. Da die durch erhöhte Wasseraufnahme bedingte Zellschwellung auch als Induktor für Hypertrophie-Signale angesehen werden kann (44), unterstützen wissenschaftliche Ergebnisse über eine gesteigerte Gefäßpermeabilität (127) und verringertem Plasmavolumen nach BFR-T (109) die Idee der Hypertrophieinduktion durch Muskelzellschwellung.

Die Anwendung des BFR-T ist in orthopädischen Patientenkohorten vor allem in der Rehabilitation nach Rupturen und operativer Plastik des vorderen Kreuzbandes untersucht. Aktuelle Meta-Analysen bescheinigen der BFR-T Methodik dabei einen signifikanten Einfluss auf die Reduktion postoperativer Muskelatrophie der Quadrizepsmuskulatur (19). Im Zuge degenerativer Gelenkerkrankungen, konnten Bryk et al. (15) bei Arthrose-Patienten durch ein sechswöchiges Trainingsprotokoll mit LL-BFR-T ähnliche Ergebnisse für Zuwächse von Muskelkraft und Funktionalität bei zusätzlicher Schmerzreduktion beschreiben wie bei einem HL-RT. Allerdings verursachte das LL-BFR-T im Vergleich weniger Gelenkschmerzen während der Übungen, was zu einer höheren Compliance der Patienten gegenüber der Trainingsmethode führte (33). Im Gegensatz dazu dokumentierte eine kürzlich veröffentlichte systematische Übersichtsarbeit und Meta-Analyse keine Überlegenheit der BFR-Trainingsmethode gegenüber dem Free-Flow-Training (41). Allerdings wiesen die Autoren in den Einschränkungen ihrer Arbeit darauf hin, dass die geringe Zahl der verfügbaren Daten und die große Vielfalt der publizierten BFR-Übungsprotokolle für dieses Ergebnis verantwortlich sein könnten.

Trotz widersprüchlicher Forschungsergebnisse könnte das BFR-Training als neue Ergänzung zu konservativen therapeutischen Maßnahmen bei degenerativen Gelenkerkrankungen in Betracht gezogen werden. Insbesondere die Verwendung von nur leichten mechanischen Widerständen macht diese Trainingstechnik zu einem potenziellen Kandidaten für eine Prähabilitationsintervention bei Arthrose des Kniegelenks.

### 1.4.2 Hypothetischer Einfluss der Prähabilitation mit Blood-Flow-Restriction auf die postoperative Rehabilitation von Muskelmasse, Kraft und Lebensqualität nach primärer TKA

Obwohl BFR-T positive Ergebnisse bei der postoperativen Rehabilitation nach vorderer Kreuzbandplastik (VKB-Plastik) oder in der konservativen Therapie degenerativer Erkrankungen des Kniegelenks gezeigt hat (19), wurde ihr Einsatz als Prähabilitationsstrategie in der Vorbereitung auf einen endoprothetischen Eingriff bisher nicht untersucht. Dabei könnte nicht nur der präoperative Zugewinn an Muskelmasse und Muskelkraft als kompensatorischer Puffer für die operativ- und rehabilitativ-induzierten katabolen Prozesse dienen, sondern auch molekulare Anpassungen durch das BFR-Training direkt mit einsetzenden Atrophie-Signalen interferieren und diese abschwächen.

Die durch BFR-T induzierten erhöhten Growth-Hormone (GH)- und Insulin-like-Growth-Factor-1- (IGF-1) Spiegel (1, 118) deuten auf eine verstärkte Aktivierung von Akt hin, welche durch einen anschließend verstärkten mTORC1-Pathway die gesteigerte Proteinsynthese und Muskelhypertrophie ermöglichen (39, 131). Neben der unterstützenden Wirkung auf die präoperative Muskelhypertrophie bei Patienten mit Arthrose des Kniegelenks, könnten die langfristigen Erhöhungen der GH- und IGF-1-Konzentrationen (126) und die damit verbundene prolongierte Hochregulierung der Akt-Aktivität in der Lage sein, die katabole Muskelatrophiekaskade perioperativ zu interferieren. Dabei wirkt die verstärkte Induktion von IGF1/Akt-Signalen der chirurgisch-induzierten Atrophie-Signalweg durch eine Unterdrückung der FOXO-Transkriptionsfaktoren entgegen (63). Darüber hinaus konnten Studien einen signifikant-unterstützenden Einfluss erhöhter IGF1-Spiegel auf die Regeneration von Skelettmuskelgewebe nach Muskelbelastung oder -schädigung aufzeigen (85), was darauf schließen lässt, dass auch die postoperative Rehabilitation davon profitieren könnte (Abbildung 3).

Darüber hinaus ist das BFR-Training durch eine laktazide, metabolische Azidose gekennzeichnet (z. B. erhöhte Konzentrationen von Laktat und Adenosinmetaboliten), die zu einer erhöhten Aktivierung der AMP-aktivierten Proteinkinase (AMPK) und in der Folge zu einer erhöhten Expression des Peroxisom-Proliferator-aktivierten Rezeptor-γ-CArthrosektivators-1α (PGC-1α) führt (90, 91). Letzterer fungiert in der physiologischen Reaktion als transkriptioneller Co-Aktivator und Regulator der mitochondrialen Biogenese (6). Eine erhöhte PGC-1α-Aktivität wird in der Regel nach Ausdauertraining beobachtet und führt zu einem erhöhten Gehalt an mitochondrialen Enzymen mit der zusätzlichen Fähigkeit, einen Fasertypwechsel zu Typ-1 Fasern im Muskelgewebe zu unterstützen (66). Ein Wechsel des Fasertyps hin zu einer erhöhten oxidativen Kapazität durch eine präoperative BFR-Prähabilitation könnte die perioperative Muskelbelastung abmildern, indem es die Auswirkungen des durch die Operation induzierten gestörten Ionenhandlings reduziert, was zu weniger Muskelschäden während des chirurgischen Eingriffs führt. Darüber hinaus ist anzunehmen, dass die regelmäßige Durchführung von BFR-Trainings und die damit verbundene Stoffwechselbelastung erhebliche Veränderungen der antioxidativen Kapazität (117) und der peripheren Immunantwort (34) bewirkt. Dies würde eine verbesserte Ausgangslage gegen den perioperativ einsetzenden metabolischen Stress ermöglichen (Abbildung 3) (18).

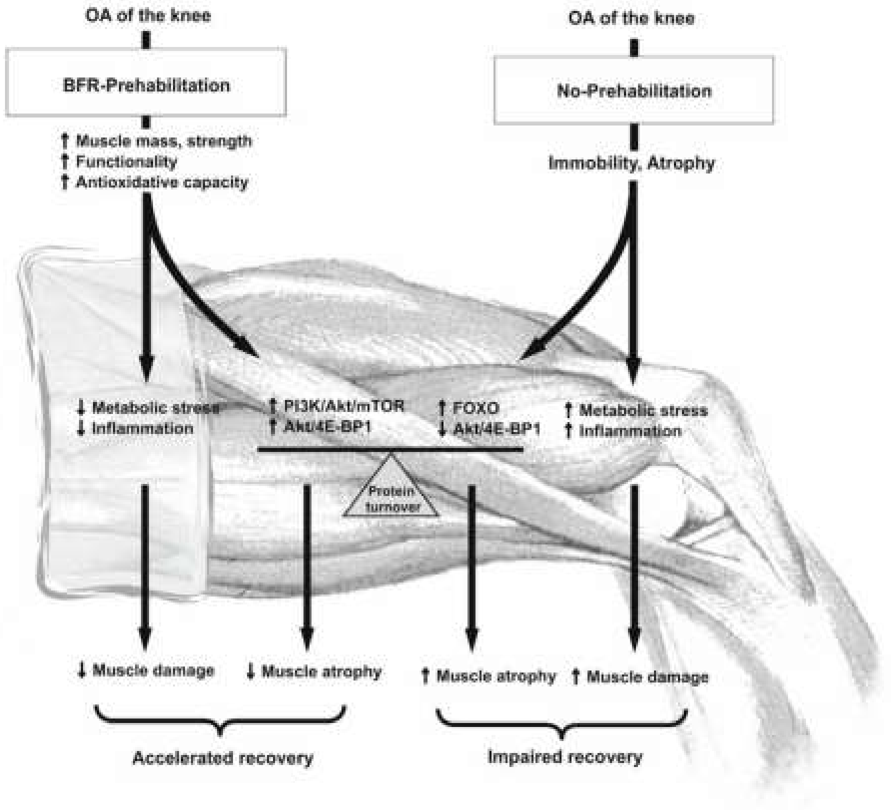


**Abbildung 3** Mögliche Auswirkungen des BFR-Trainings als Prähabilitationskonzept im Vergleich zu TKA-Ergebnissen ohne Prähabilitationsintervention. Quelle: Franz et al. (37)

Unterstützt wird diese Hypothese durch Befunde, wonach metabolischer Stress mit einer erhöhten Langzeitexpressionsrate von Zielgenen des Transkriptionsfaktors nuclear factor (erythroid-derived 2)-like 2 (Nrf2) (z. B. Glutathion, MnSOD, Katalase) einhergeht (91). Während diese Anpassung das antioxidative Abwehrsystem gegen perioperativ einsetzenden metabolischen Stress bei TKA-Patienten unterstützen würde, scheint Nrf2 zusätzlich die Fähigkeit zu besitzen, pro-inflammatorische Signalwege (z. B. NF-κB) zu interferieren (119), was die Regeneration perioperativer Skelettmuskelschädigung (3) und möglicherweise auch nach TKA unterstützen könnte (27). Zweitens konnte gezeigt werden, dass die Überexpression von PGC-1α in transgenen Mäusen die Muskelatrophie durch die damit verbundene geringere Induktion von FOXO-Zielgenen verringert (108). Daher könnten durch die BFR-

Prähabilitation mehrere physiologische Anpassungen induziert werden, die einen besseren Umgang mit operativ bedingten katabolen Konditionen ermöglichen sowie Interferenzeffekte angestoßen werden, die eine postoperative Muskelatrophie reduzieren könnten.

### 1.4.3 Herleitung der Studienfrage

Die in dieser Thesis inkludierten Literaturübersichten über den Zustand der Muskelgesundheit von Arthrose-Patienten und deren Verlauf während der operativen Intervention mittels TKA zeigt deutlich auf, dass die durch Immobilität-gezeichnete Zeit bis zur Operation sowie der Eingriff selbst eine erfolgreiche und zeitnahe Rehabilitation negativ beeinflusst. Während sich der operative Eingriff, die dabei angewendeten Implantate, sowie der postoperative Verlauf stetig weiterentwickeln und versuchen ein Höchstmaß an Perfektion zu generieren, gleitet der klassische Arthrose-Patient weiterhin mit einem signifikant schlechten Muskelzustand, samt anderer Komorbiditäten, in die Operation hinein ohne nachweisliche Aussicht auf eine schnelle Regeneration seiner Muskelgesundheit. Während Trainingsmöglichkeiten zur präoperativen Verbesserung der Muskelmasse, -kraft und/oder neuromuskulären Aktivierung zumeist durch den Faktor Schmerz in Ihrer Häufigkeit, Intensität und Compliance nur eingeschränkt eingesetzt werden können, bietet das BFR-T einen wohlmöglichen neuen Mittelweg. Das dabei am stärksten herausstechende Charakteristikum der Methode, die Anwendung von nur leichten mechanischen Gewichten während des Trainings, könnte es hierbei ermöglichen, Arthrose-Patienten ein schmerzfreies/-reduziertes Training anzubieten, welches durch seine Beeinflussung der Muskelphysiologie dennoch die Intensität erreicht, welche der Muskel für Anpassungen benötigt. Aus diesem Grund wurde im Rahmen dieser wissenschaftlichen Promotionsarbeit eine klinisch-prospektive und randomisierte Studie durchgeführt, welche den Einfluss des BFR-T angewandt als Prähabilitationsstrategie in Arthrose-Patienten vor einer elektiven TKA untersuchte.

## 1.5 Klinisch Prospektive Interventionsstudie:

***Impact of a Six-Week Prehabilitation with Blood-Flow Restriction Training on Pre- and Postoperative Skeletal Muscle Mass and Strength in Patients Receiving Primary Total Knee Arthroplasty***

Auf Basis der Übersichtsarbeiten aus der wissenschaftlich-publizierten Literatur lassen sich fundamentale Forschungsdesiderate bezüglich der Rehabilitation nach endoprothetischem Gelenkersatz ableiten. Während die operative Versorgung der endständigen Arthrose des Kniegelenks die Ursache behandelt, fehlen trotz einer Vielzahl an Rehabilitationsstudien geeignete Interventionen zur Verbesserung der postoperativen Regeneration muskulärer Defizite. Aufbauend auf den Erkenntnissen der Literaturrecherche wurde eine klinisch prospektive Interventionsstudie erstellt, die den Einfluss von BFR-T als Prähabilitationsansatz in der endoprothetischen Versorgung des Kniegelenks untersuchte. Die vorliegende Arbeit zielte darauf ab, den Einfluss der BFR-Technik als Prähabilitationsmethode auf die muskuläre Gesundheit (insbesondere Muskelmasse und Muskelkraft), die Funktionalität und die QoL von Arthrose-Patienten vor-, während- und nach der elektiven Operation zu beschreiben. Indem die bestehende Literatur das Konzept der BiBo durch Prähabilitation in Frage stellt, versuchte dieses Projekt außerdem zu zeigen, dass die präoperative BFR-Prähabilitation einen positiven Effekt auf die postoperative muskuläre und funktionelle Regeneration nach elektiver TKA zeigt. Ein sekundäres Ziel dieser Arbeit ist die Beschreibung und Quantifizierung der muskulären Gesundheit von Patienten mit Arthrose und einer Indikation für eine elektive primäre TKA sowie deren Erholung nach der Operation.

### 1.5.1 Methodik

#### 1.5.1.1 Studiendesign

Für die vorliegende prospektive, klinisch-randomisierte Studie wurden 30 Patienten (Männer = 18, Frauen = 12, Alter = 63,5 ± 8,1 Jahre, Größe = 176,4 ± 7,2 cm, Gewicht = 86,9 ± 16,1 kg) mit der Indikation zum totalen Oberflächenersatz des Kniegelenks mittels Endoprothese bei vorliegender Arthrose des Gelenks (Kellgren & Lawrence III/IV) rekrutiert. Die Patienten wurden nach initialer Aufklärung über die Studiengegebenheiten, Untersuchungen und Risiken mittels doppeltem Losverfahren in drei Gruppen randomisiert. Dabei fungierte eine Gruppe als Kontrollgruppe (CG), welche keine Prähabilitation vor dem elektiven Eingriff durchführte; die zweite Gruppe führte eine Prähabilitation über sechs Wochen auf dem Fahrradergometer bei einer individuellen Intensität durch und erhielt eine zusätzliche BFR-T Belastung während des Trainings (BFR-Gruppe); die dritte Gruppe fungierte als aktive Kontrollgruppe und vollzog ebenfalls ein sechswöchiges Prähabilitationsprotokoll auf dem Fahrradergometer bei einer individuellen Intensität, jedoch mit einer *sham*-BFR Belastung während des Trainings (AC-Gruppe). Die weitere standardisierte Behandlung nach erfolgter Operation bestand aus einem siebentägigen Krankenhausaufenthalt mit täglicher Physiotherapie, an welche sich eine dreiwöchige stationäre Rehabilitation anschloss. Das Projekt wurde durch die Ethikkommission des Universitätsklinikum Düsseldorf positiv bewertet (Studien-Nr.: 5815R).

#### 1.5.1.2 Prähabilitationsprotokoll

Das Prähabilitationsprotokoll bestand aus einem Fahrradergometer-basierenden Trainingsprotokoll, das zweimal pro Woche für 50 Minuten mit einer individuell festgelegten Intensität durchgeführt wurde. Die Intensität des Ergometertrainings wurde auf der Grundlage einer berechneten Belastungsherzfrequenz (engl., EHR) bestimmt (75).

Das zusätzliche BFR-Protokoll wurde während der Ergometerbelastung an beiden unteren Extremitäten periodisch, dreimal pro Bein für eine Dauer von einer Minute (erste Woche) bis sechs Minuten (sechste Woche) angewendet (Abbildung 4). Während die AC-Gruppe eine *sham*-BFR-Belastung mit einem festen Wert von 20 mmHg durchführte, wurde die BFR-Gruppe mit 40% des individuellen LOP belastet (rechts = 88,27 ± 8,46 mmHg, links = 87,32 ± 7,39 mmHg).

Zur Bestimmung des LOP wurden spezielle Blutdruckmanschetten mit einer Breite von 11,5 cm vor der Trainingseinheit proximal an den trainierenden Beinen angelegt (PBFR, Delfi medical Inc., Vancouver, Kanada). Nach einer 10-minütigen Ruhephase wurde der LOP im liegen sonographisch bestimmt, indem die Oberschenkelarterie mit einem Ultraschallgerät dargestellt und der Blutfluss mit einem Doppler beurteilt wurde. Anschließend wurde die Manschette so lange aufgeblasen, bis kein Blutfluss mehr feststellbar war. Dieser Druck wurde als individueller LOP definiert.

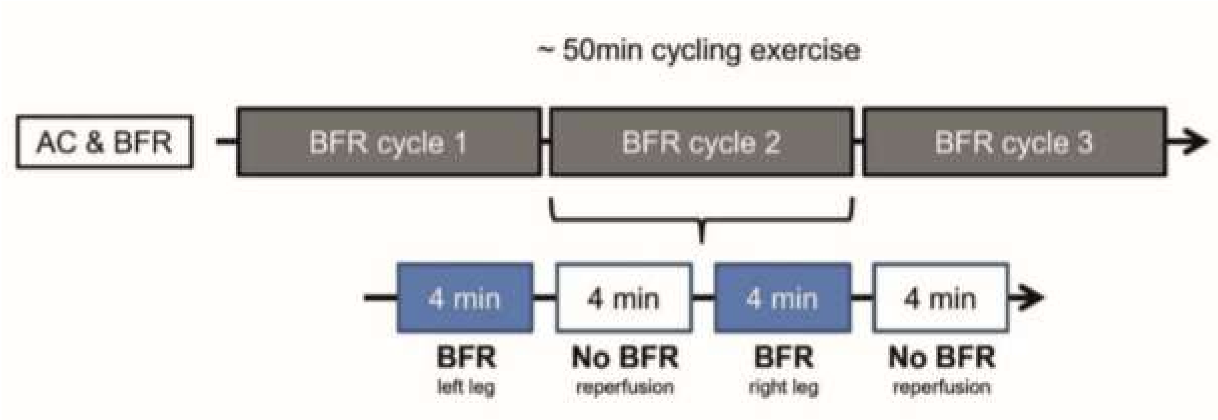


**Abbildung 4** Beispiel für die vierte Rehabilitationswoche für die AC- und BFR-Gruppe. Die 50-minütige Fahrradergometerbelastung ist in drei BFR-Zyklen unterteilt. Jeder Zyklus besteht aus der Anwendung des BFR-T auf beide Beine im Wechsel, gefolgt von einer Pause. Wie hier dargestellt, wird zunächst das linke Bein mit BFR belastet (in Woche vier, vier Minuten lang), gefolgt von einer vierminütigen Pause. Danach wird das rechte Bein mit BFR belastet, mit einer anschließenden Pause. Dieser Zyklus wird insgesamt dreimal wiederholt. Quelle: Franz et al. (36)

#### 1.5.1.3 Untersuchungen

Die Untersuchungen bestanden aus allgemeinen Vital- und anthropometrischen Daten, Muskelfunktionsparametern, Funktionsuntersuchungen und einer fragebogengestützten Datenerhebung. Die Messzeitpunkte waren sechs Wochen (Baseline), drei Wochen (3w-Prehab) und fünf Tage vor der Operation (Pre-OP), sowie drei (3m-Post-OP) und sechs Monate (6m-Post-OP) postoperativ.

Für die Darstellung des Einflusses der Prähabilitation sowie der operativen Intervention auf die Muskelgesundheit wurde zu jedem Zeitpunkt die Muskelmasse beider Ober- und Unterschenkel mittels Umfangsmessungen sowie die Muskelkraft anhand eines unilateralen sechs-Wiederholungs-Maximaltest (6RM) an der Beinstreckermaschine analysiert (Paoli et al., 2013). Die funktionelle Leistungsfähigkeit der Patienten wurde anhand des Chair-Rising-Test (CRT) und 6-Minuten-Gehtest (6MWT) ermittelt. Neben regelmäßiger Abfragung des aktuellen, subjektiven Schmerzniveaus (VAS 0-100 mm) wurde die QoL der Patienten anhand des Knee Injury and Osteoarthritis Outcome Score (KOOS) verwendet. Die statistischen Analysen wurden mit SPSS (SPSS, v.27, Chicago, IL, USA) durchgeführt. Die Normalverteilung und die Homogenität der Varianz wurden mit dem Shapiro-Wilk-Test bzw. dem Levene-Test überprüft. Um die Veränderungen der Messwerte im Laufe der Zeit zwischen den Gruppen zu vergleichen, wurden zweifache ANOVAs mit wiederholten Messungen (rANOVAs; Zeit x Gruppe) durchgeführt. Im Falle signifikanter Wechselwirkungen zwischen Zeit und Gruppe wurden separate einfaktorielle ANOVAs mit wiederholten Messungen verwendet, um die einfachen Haupteffekte für die Zeit innerhalb jeder Gruppe zu analysieren. Wenn die Haupteffekte für Zeit oder Gruppe nachweisbar waren, wurden Post-Hoc-Tests mit Bonferroni-Korrektur durchgeführt, um zu prüfen, welche Faktorstufen sich signifikant voneinander unterscheiden. Für die Interaktions- und Haupteffekte wurde das partielle Eta-Quadrat $\eta p2$ als Effektstärkemaß berechnet und wie folgt interpretiert (Cohen, 1988): ein $\eta p2 \geq 0{,}01$: kleiner Effekt, $\geq 0{,}06$: mittlerer Effekt, und $\geq 0{,}14$: großer Effekt. Für alle Ergebnisse wurde ein Alpha-Niveau von 0,05 als statistisch signifikant interpretiert. Um eine Voreingenommenheit der Untersucher zu verringern, wurde die Datenanalyse für die bewertenden Forscher verblindet.

### 1.5.2 Ergebnisse & Diskussion

#### 1.5.2.1 Arthrose-bedingte Auswirkungen auf die präoperative Muskelmasse und -kraft

Die Ergebnisse der vorliegenden klinisch, randomisierten Studie zeigen, dass die Muskelmasse und -kraft von Arthrose-Patienten zu Beginn der Studie stark beeinträchtigt ist. Zusätzlich zu der subjektiv empfundenen und objektiv messbaren Abnahme der Funktionalität sind die morphologischen und funktionellen Unterschiede zwischen den Extremitäten der Patienten besonders bemerkenswert. Unsere Daten zeigen signifikante Unterschiede zwischen der Muskelmasse sowie der Muskelkraft zwischen dem zu operierenden Bein (OP-Bein) und dem kontralateralen, nicht zu operierenden Bein (Nicht-OP-Bein) bei Studienbeginn (Tabelle 1 und 2). Diese Ergebnisse sind von besonderer Bedeutung da bekannt ist, dass die wichtigsten prädiktiven Parameter für eine erfolgreiche Rehabilitation nach der Operation die präoperative Muskelmasse, die Muskelkraft und die Fähigkeit zur Ausführung funktioneller Aufgaben sind (121). Basierend auf der zuvor durchgeführten Literaturrecherche lässt sich annehmen, dass dieser Zustand durch die präoperative Immobilität und Arthrose-induzierte AMI verursacht wird (77). Da vergleichbare Literaturquellen ähnliche präoperative Defizite aufzeigen (29, 51), könnte dieser Umstand zu der Unzufriedenheitsrate von etwa 20% nach primärer TKA beitragen (14, 17).

**Tabelle 1** Messung der Skelettmuskelmasse der unteren Extremitäten während der prä- und postoperativen Phase. Quelle: Franz et al. (36)

| | CON ($N = 10$) | BFR ($N = 10$) | AC ($N = 10$) | One-Way ANOVA / rANOVA ($p$ / $\eta_p^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Time | | | Group | | | | | Time x Group |
| | | | | CON | BFR | AC | Baseline | 3w-Prehab | Pre-OP | 3m-Post-OP | 6m-Post-OP | |
| **Femoral circumference OP [cm]** | | | | | | | | | | | | |
| Baseline | 58.2 (7.4) | 53.2 (4.2) | 52.0 (7.3) | < 0.001/ 0.728 | < 0.001/ 0.754 | 0.078/ 0.266 | 0.092/ 0.162 | 0.224/ 0.105 | 0.331/ 0.079 | 0.524/ 0.047 | 0.592/ 0.038 | < 0.001/ 0.494 |
| 3w-Prehab | 57.7 (7.5) | 55.6 (4.6) [a] | 52.5 (7.2) | | | | | | | | | |
| Pre-OP | 57.6 (7.6) | 57.0 (5.2) [ab] | 53.4 (7.1) | | | | | | | | | |
| 3m-Post-OP | 55.9 (7.1) [abc] | 55.0 (3.9) [ac] | 52.8 (6.9) | | | | | | | | | |
| 6m-Post-OP | 55.5 (7.6) [abc] | 56.6 (4.0) [ad] | 53.7 (6.4) | | | | | | | | | |
| **Femoral circumference NonOP [cm]** | | | | | | | | | | | | |
| Baseline | 58.5 (7.2) | 55.0 (4.0) | 53.6 (7.3) | 0.001/ 0.627 | < 0.001/ 0.674 | 0.192/ 0.178 | 0.229/ 0.103 | 0.311/ 0.083 | 0.365/ 0.072 | 0.502/ 0.050 | 0.510/ 0.049 | < 0.001/ 0.350 |
| 3w-Prehab | 58.5 (7.2) | 56.8 (4.4) [a] | 54.0 (7.4) | | | | | | | | | |
| Pre-OP | 58.5 (7.2) | 57.6 (4.5) [a] | 54.5 (7.3) | | | | | | | | | |
| 3m-Post-OP | 57.2 (7.2) [abc] | 56.9 (4.3) [a] | 54.2 (6.7) | | | | | | | | | |
| 6m-Post-OP | 57.4 (7.2) [abc] | 58.0 (4.3) [ad] | 55.0 (6.7) | | | | | | | | | |
| **%Difference in femoral circumference NonOP - OP** | | | | | | | | | | | | |
| Baseline | -0.49 (3.24) | -3.44 (1.48) [#] | -3.09 (2.85) | 0.002/ 0.469 | 0.059/ 0.254 | 0.271/ 0.135 | 0.037/ 0.217 | 0.523/ 0.047 | 0.802/ 0.016 | 0.748/ 0.021 | 0.654/ 0.031 | 0.014/ 0.186 |
| 3w-Prehab | -1.43 (3.54) | -2.29 (0.94) | -2.86 (3.16) | | | | | | | | | |
| Pre-OP | -1.64 (3.73) | -1.15 (2.74) | -2.11 (3.17) | | | | | | | | | |
| 3m-Post-OP | -2.27 (4.18) | -3.44 (2.71) | -2.67 (3.44) | | | | | | | | | |
| 6m-Post-OP | -3.44 (3.50) [a] | -2.54 (2.61) | -2.24 (2.80) | | | | | | | | | |

Die Daten werden als Mittelwert (Standardabweichung) angegeben. CON = Kontrollgruppe; BFR = BFR-Trainingsgruppe; AC = aktive Kontrollgruppe; rANOVA = Varianzanalyse mit wiederholten Messungen; OP = operiertes Bein; NonOP = nicht operiertes Bein.

[a] $p < 0.05$, signifikant unterschiedlich zum Ausgangswert innerhalb der jeweiligen Gruppe

[b] $p < 0.05$, signifikant unterschiedlich zu 3w-Prehab innerhalb der jeweiligen Gruppe

[c] $p < 0.05$, signifikanter Unterschied zur Prä-OP in der jeweiligen Gruppe

[d] $p < 0.05$, signifikant unterschiedlich zu 3m-Post-OP innerhalb der jeweiligen Gruppe

[#] $p < 0.05$, signifikanter Unterschied zu CON innerhalb des jeweiligen Zeitpunkts

**Tabelle 2** Messung der Skelettmuskelkraft der unteren Extremitäten während der prä- und postoperativen Phase. Quelle: Franz et al. (36)

| | CON ($N$ = 10) | BFR ($N$ = 10) | AC ($N$ = 10) | One-Way ANOVA / rANOVA ($p$ / $\eta^2_p$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Time | | | Group | | | | | Time x Group |
| | | | | CON | BFR | AC | Baseline | 3w-Prehab | Pre-OP | 3m-Post-OP | 6m-Post-OP | |
| **Leg extension OP [kg]** | | | | | | | | | | | | |
| Baseline | 20.3 (8.1) | 13.8 (9.1) | 11.8 (7.8) | | | | | | | | | |
| 3w-Prehab | 20.3 (7.1) | 21.9 (9.1) [a] | 15.3 (9.8) [a] | | | | | | | | | |
| Pre-OP | 20.3 (7.1) [*] | 31.5 (10.4) [ab] | 16.0 (10.2) [a*] | 0.001/ 0.591 | < 0.001/ 0.863 | 0.014/ 0.392 | 0.077/ 0.173 | 0.230/ 0.103 | 0.003/ 0.351 | 0.033/ 0.223 | 0.002/ 0.364 | < 0.001/ 0.614 |
| 3m-Post-OP | 15.0 (6.3) [abc] | 22.1 (10.4) [ac] | 11.1 (9.5) [*] | | | | | | | | | |
| 6m-Post-OP | 18.5 (7.0) [d*] | 30.8 (11.1) [abd] | 15.3 (9.4) [d*] | | | | | | | | | |
| **Leg extension NonOP [kg]** | | | | | | | | | | | | |
| Baseline | 28.3 (10.4) | 24.3 (7.3) | 17.5 (7.1) [#] | | | | | | | | | |
| 3w-Prehab | 28.5 (10.5) | 31.8 (7.6) [a] | 20.3 (8.1) [a*] | | | | | | | | | |
| Pre-OP | 28.3 (10.7) [*] | 38.4 (9.7) [ab] | 22.0 (8.7) [a*] | 0.018/ 0.404 | < 0.001/ 0.851 | 0.003/ 0.503 | 0.026/ 0.237 | 0.021/ 0.250 | 0.003/ 0.348 | 0.002/ 0.379 | 0.000/ 0.445 | < 0.001/ 0.587 |
| 3m-Post-OP | 22.5 (8.6) [abc*] | 34.1 (8.5) [a] | 18.8 (9.2) [c*] | | | | | | | | | |
| 6m-Post-OP | 27.0 (9.5) [*] | 39.6 (9.7) [abd] | 20.8(8.3) [d*] | | | | | | | | | |
| **%Difference leg extension NonOP - OP** | | | | | | | | | | | | |
| Baseline | -34.4 (36.0) | -64.6 (31.9) | -51.0 (31.3) | | | | | | | | | |
| 3w-Prehab | -33.1 (26.2) | -40.3 (23.2) [a] | -39.6 (35.9) | | | | | | | | | |
| Pre-OP | -31.9 (28.5) | -21.0 (16.2) [ab] | -44.1 (42.5) | | 0.367/ 0.038 | | | | 0.003/ 0.366 | | | 0.063/ 0.150 |
| 3m-Post-OP | -39.5 (34.0) | -46.7 (29.2) [c] | -69.1 (40.7) | | | | | | | | | |
| 6m-Post-OP | -37.0 (28.4) | -27.3 (23.9) [abd] | -38.1 (26.8) | | | | | | | | | |

Die Daten werden als Mittelwert (Standardabweichung) angegeben. CON = Kontrollgruppe; BFR = BFR-Trainingsgruppe; AC = aktive Kontrollgruppe; rANOVA = Varianzanalyse mit wiederholten Messungen; OP = operiertes Bein; NonOP = nicht operiertes Bein.

[a] $p < 0.05$, signifikant unterschiedlich zum Ausgangswert innerhalb der jeweiligen Gruppe

[b] $p < 0.05$, signifikant unterschiedlich zu 3w-Prehab innerhalb der jeweiligen Gruppe

[c] $p < 0.05$, signifikanter Unterschied zur Prä-OP in der jeweiligen Gruppe

[d] $p < 0.05$, signifikant unterschiedlich zu 3m-Post-OP innerhalb der jeweiligen Gruppe

[#] $p < 0.05$, signifikanter Unterschied zu CON innerhalb des jeweiligen Zeitpunkts

* $p < 0.05$, significantly different to BFR-group within the respective time point

#### 1.5.2.2 Auswirkung der Prähabilitation mit Blood-Flow-Restriction Training auf die präoperative Muskelmasse, Kraft und Lebensqualität

Aktuelle Meta-Analysen bescheinigen der Prähabilitation in der Gelenkchirurgie nur einen geringen bis mäßigen Einfluss auf die prä- und postoperativen klinischen Ergebnisse (84, 125). Diese Bewertung wird im Wesentlichen dadurch beeinflusst, dass die bisherigen publizierten Prähabilitationsmaßnahmen zu verstärkten Schmerzen bei den Patienten führten, daher vereinfacht sowie in ihrer Belastung reduziert wurden und dadurch nicht mehr die Intensität besaßen, die für einen Muskelaufbau notwendig ist. Mittels der Anwendung von BFR-T während einer Fahrradergometerbelastung war es das Ziel der durchgeführten Studie dieses Problem zu umgehen, indem wir einen additiven metabolische Stimulus verursachen, um Muskelmasse und -kraft aufzubauen.

Die Ergebnisse der vorliegenden Studie deutet darauf hin, dass die Prähabilitation mit einem sechswöchigen Fahrradergometerprotokoll ausreicht, um die Skelettmuskelmasse und -kraft der unteren Extremitäten sowie das subjektive Schmerzempfinden vor einer TKA-Operation signifikant zu verbessern. Im Vergleich dazu konnte BFR-T bereits nach drei Wochen Prähabilitation die Muskelmasse erhöhen (Tabelle 1), die Muskelkraft steigern (Tabelle 2) und die funktionelle Leistungsfähigkeit gegenüber Patienten der AC verbessern (Abbildung 5).

Diese Ergebnisse stimmen mit der Literatur überein die zeigt, dass ein sechswöchiges, auf der Krafttrainingsübung „Kniestrecker" basierendes Prähabilitationsprotokoll mit BFR-T bei Patienten, die eine Rekonstruktion des vorderen Kreuzband erhalten (VKB-Plastik), signifikante Verbesserungen der Muskelmasse und -kraft bewirkt (55). Auch wenn in der vorliegenden Studie nur ein indirektes Messinstrument zur Darstellung der Muskelmasse gewählt wurde (Bestimmung des Oberschenkelumfangs), lassen diese Ergebnisse die Interpretation zu, dass Veränderungen des Beinumfangs in erster Linie durch Muskelzuwächse erklärt werden können. Darüber hinaus zeigte der Vergleich zwischen dem OP- und Nicht-OP-Bein, dass ein präoperatives BFR-T bestehende muskuläre Dysbalancen erfolgreich ausgleichen kann (Tabelle 1 und 2). Neben der Wahl der Trainingstechnik scheint auch die Dauer der Prähabilitation von großer Bedeutung zu sein. In einer Studie von Grapar Zargi et al. (42) konnte ein fünfmaliges BFR-T innerhalb von 10 Tagen vor einer elektiven VKB-Plastik keinen Einfluss auf die Muskelmasse und Muskelkraft zeigen. In Anbetracht der vorliegenden Ergebnisse scheint eine Prähabilitationsdauer zwischen drei und sechs Wochen mit Kraft- oder Ausdauer-BFR-T in der Lage zu sein, signifikante muskuläre Effekte vor einer elektiven Gelenkoperation zu induzieren.

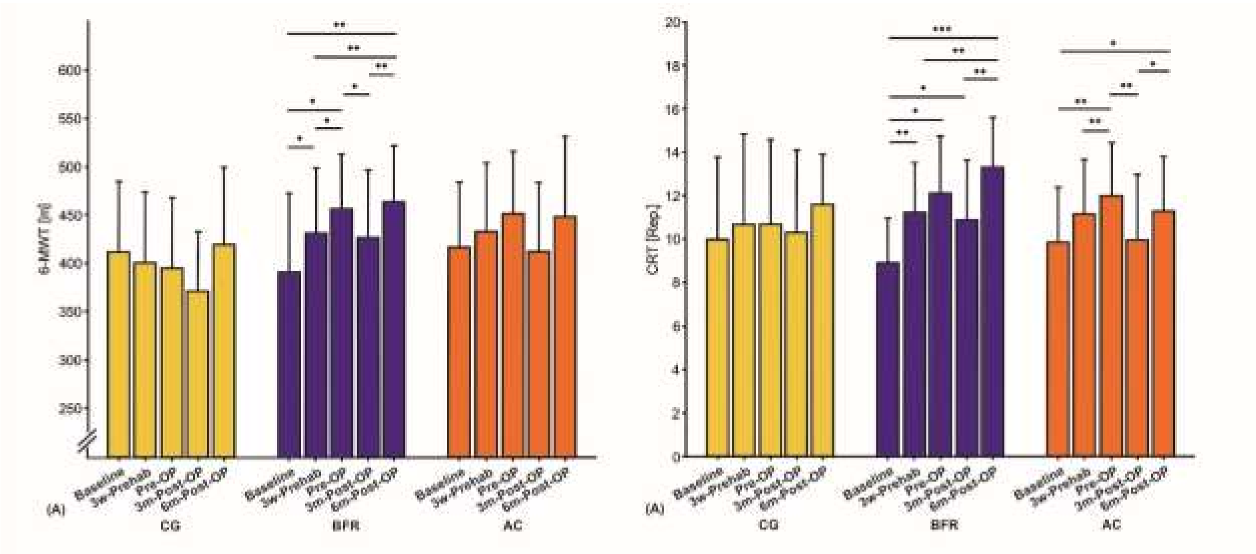


**Abbildung 5** Darstellung der Ergebnisse des 6-Minuten-Gehtest (6-MWT; A) und des Chair-Rising-Test (CRT; B) während der prä- und postoperativen Phase. Die Daten sind als Mittelwert (Standardabweichung) angegeben. CON = Kontrollgruppe; BFR = BFR-Trainingsgruppe; AC = aktive Kontrollgruppe. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, signifikanter Unterschied innerhalb der jeweiligen Gruppe. Quelle: Franz et al. (36)

Die Verbesserungen der Skelettmuskelmasse und -kraft der BFR-Gruppe während und nach der Prähabilitationsphase waren mit einer gleichmäßigen Verbesserung aller fünf Subparameter des KOOS-Scores verbunden (Abbildung 6). Diese Ergebnisse stehen ebenfalls im Einklang mit der bisherigen Literatur, in der über den positiven Einfluss einer erhöhten Muskelmasse und -kraft auf das subjektive Schmerzempfinden und die Lebensqualität von Patienten mit Arthrose berichtet wurde (25, 59). Eine Meta-Analyse von Ferlito und Kollegen (32) kam zu dem Schluss, dass BFR-T zu einer ähnlichen Zunahme der Muskelmasse und -kraft bei gleichzeitiger Verringerung des Schmerzempfindens führt wie ein HL-Training. Obwohl es in der aktuellen Studie keine HL-Vergleichsgruppe gibt, stimmen die vorliegenden Ergebnisse mit den publizierten Daten überein, die zeigen dass ein LL-Training mit BFR dem LL-Training allein überlegen ist (112).

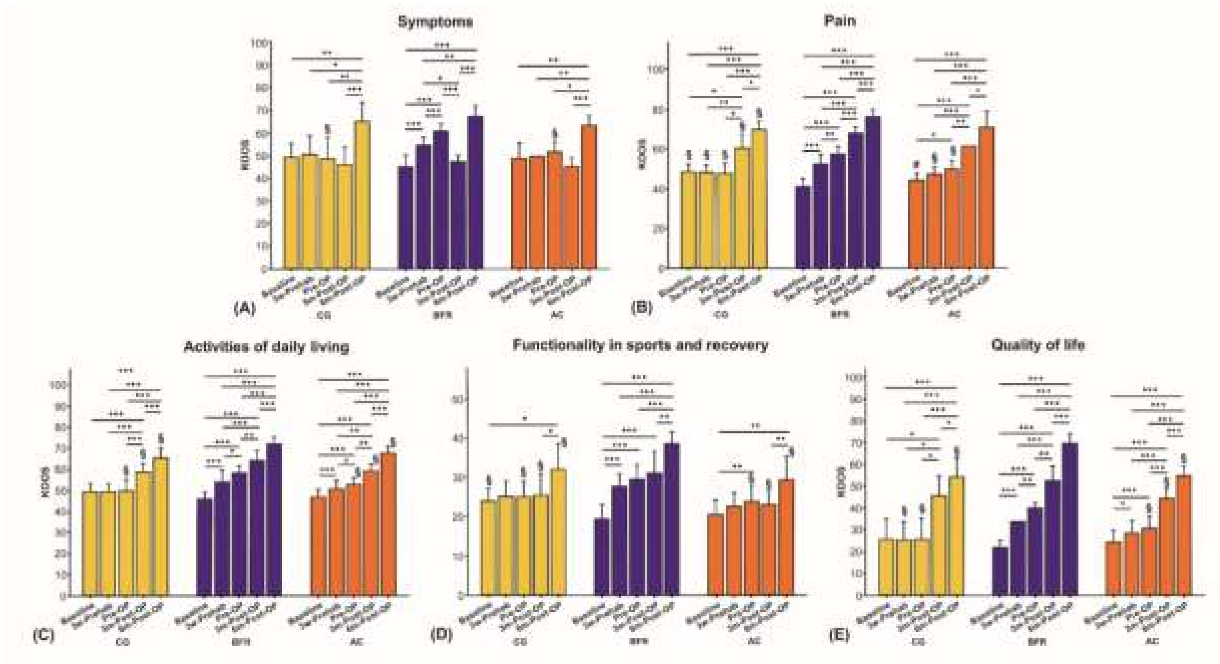


**Abbildung 6** Knee Injury and Osteoarthritis Outcome Score (KOOS) während des prä- und postoperativen Zeitraums. Die Daten werden als Mittelwert (Standardabweichung) angegeben. CON = Kontrollgruppe; BFR = BFR-Trainingsgruppe; AC = aktive Kontrollgruppe. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, signifikanter Unterschied innerhalb der jeweiligen Gruppe. § $p < 0.05$, signifikanter Unterschied zur BFR-Gruppe innerhalb des jeweiligen Zeitpunktes. # $p < 0.05$, signifikanter Unterschied zu CON innerhalb des jeweiligen Zeitpunkts. Quelle: Franz et al. (36)

Insbesondere die Auswirkungen auf das subjektive Schmerzempfinden während und nach den Prähabilitationseinheiten machen das BFR-Training für Patienten mit degenerativen Gelenkerkrankungen interessant. Unsere Ergebnisse zeigen eine signifikante Verringerung der Schmerzen während der sechswöchigen Prähabilitationsphase bei Patienten mit Arthrose des Kniegelenks. Diese Ergebnisse stimmen mit der vorhandenen Literatur überein, die eine signifikante Schmerzreduzierung bei traumatisch und degenerativ ausgelösten Gelenkerkrankungen durch BFR-T zeigt (99, 122). Da Schmerzen eines der Hauptsymptome bei Arthrose des Kniegelenks darstellen (54) und als Prädiktor für die Sterblichkeit in einem Zeitraum von 10 Jahren nach der Operation herangezogen werden kann (28), sind die vorliegenden Ergebnisse zur prä- und postoperativen Schmerzreduktion durch BFR-Prähabilitation von besonderer Bedeutung.

#### 1.5.2.3 Sicherheit des Blood-Flow-Restriction Training im klinischen Setting

Obwohl die wissenschaftlichen Erkenntnisse über die zugrundeliegenden Mechanismen und die Sicherheit von BFR-T in den letzten Jahren zunehmen, ist eine regelmäßige Anwendung von BFR-T in der klinischen Praxis derzeit nicht gegeben (35). Was mögliche unerwünschte Nebenwirkungen betrifft, so sind die häufig diskutierten Risiken einer tiefen Venenthrombose (engl. deep-vein-thrombosis, DVT), einer Rhabdomyolyse oder kardiovaskulärer Ereignisse eher theoretischer als praktischer Natur. In einer nationalen Umfrage von Nakajima et al. (88) lag das Thromboserisiko bei regelmäßigen BFR-Anwendung sämtlicher Altersklassen (n = 14.000) bei etwa 0,06 % und war damit geringer als das DVT-Risiko der Allgemeinbevölkerung Japans ohne jegliche sportliche Betätigung pro Jahr. Selbst bei Risikopatienten, z. B. nach einer orthopädischen Operation, gibt es keine substanziellen Hinweise auf ein erhöhtes Risiko für eine DVT durch eine postoperative BFR-Belastung (13). Systemische Übersichtsarbeiten und Meta-Analysen kamen daher zu dem Schluss, dass BFR-T keinen negativen Einfluss auf die Gerinnungskaskade aufweist (73, 89). In diesem Zusammenhang zeigen Studien keine Veränderungen der D-Dimer-Konzentration nach einer akuten LL-BFR-Belastung (38) oder bei chronischer BFR-Anwendung auf die Parametern Fibrinogen oder der Prothrombinzeit (21). Im Gegenteil, deuten aktuellen Studienergebnisse eher auf eine Erhöhung der Fibrinolyseaktivität hin, z.B. durch eine erhöhte Freisetzung des tissue-Plasminogen activators nach LL-BFR-T (89). Ähnliche Ergebnisse zeigen Studien mit Patienten während der Rehabilitation nach orthopädischen Operationen, die trotz eines erhöhten postoperativen Risikos für eine DVT keinen zusätzlichen Schaden durch LL-BFR-T erleiden (50).

Eine weitere häufig diskutierte theoretische Nebenwirkung des BFR-T ist ein erhöhtes Risiko für eine Rhabdomyolyse, welche durch die höhere Belastung des Muskelgewebes während des BFR-T verursacht werden soll. Eine Rhabdomyolyse ist definiert als eine ausgedehnte Schädigung der Skelettmuskelzellen mit einem signifikanten Anstieg der indirekten Marker für Muskelschädigung im Blutsystem (z.B. > 5000 IU/l Kreatinkinase). Dabei steht nicht die Rhabdomyolyse allein im Vordergrund, sondern das Risiko einer Verlegung des glomerulären Filters der Niere durch Muskelproteine mit nachfolgender Myoglobinurie und erhöhtem Risiko eines akuten Nierenversagens. Einzelne Fallberichte weisen darauf hin, dass BFR-T eine Rhabdomyolyse auslösen kann (zusammengefasst in (128). Obwohl aktuelle Übersichtsarbeiten aufzeigen, dass das Risiko einer Rhabdomyolyse durch BFR-T sehr gering ist und die in den Berichten beschriebenen Fälle hauptsächlich auf eine Kombination aus übermäßigem Stress, gleichzeitig vorliegenden bakteriellen Infektion und/oder Medikation zurückzuführen sind (120), weißt BFR-T nachweislich eine höhere Belastung auf die Muskelarchitektur auf als das Free-Flow-Training (127). Allerdings zeigt eine Querschnittsstudie bei BFR-Anwendern die folgenden häufigsten Nebenwirkungen der Trainingsmethode: verzögert auftretender Muskelkater (39,2%), Taubheitsgefühl (18,5%), Synkope/Schwindel (14,6%) und Blutergüsse (13,1%) (94).

Im Hinblick auf mögliche kardiovaskuläre Ereignisse führt BFR-T aufgrund des zusätzlichen anaeroben Stoffwechselreizes zu einer erhöhten Sympathikusaktivität und dadurch zu gesteigerten Reaktionen der autonomen kardiovaskulären Kontrollmechanismen (114). So werden bei LL-BFR-T im Vergleich zu Free-Flow-Bedingungen signifikant höhere systolische, diastolische und mittlere arterielle Blutdruckwerte sowie Herzfrequenzen beobachtet (111). Diesbezüglich zeigt eine aktuelle Übersichtsarbeit, dass BFR-T zum Teil abnorme kardiovaskuläre Reaktionen hervorrufen kann und dass diese bei Risikopopulationen, z.B. bei Personen mit kardiovaskulären Vorerkrankungen, stärker ausgeprägt sein können (24). Ob BFR-T jedoch negative Auswirkungen auf den Verlauf von kardiovaskulären Erkrankungen aufweist, ist bisher nicht bekannt. Ursächlich hierfür ist die geringe Anzahl der wissenschaftlichen Arbeiten zu dieser Thematik sowie der geringen Menge an diesbezüglich untersuchten Patienten. Obwohl die akute Belastungsreaktion beim LL-BFR-T im Vergleich zum alleinigen LL-RT in kardiovaskulär vorerkrankten Patientenpopulationen eine höhere Muskelbelastung und trainingsassoziierten Schmerzen zeigt, wird BFR-T als eine sichere Trainingsmethode bezüglich Reaktionen der kardiovaskulären Hämodynamik beschrieben (56). Diesbezüglich konnten beispielsweise Nakajima und Kollegen (87) eine signifikante Zunahme der Muskelquerschnittsfläche sowie der maximalen Sauerstoffaufnahme durch LL-BFR-T bei Patienten mit stabiler koronarer Herzkrankheit beschreiben. Um dennoch evidenzbasierte Aussagen über die Sicherheit des Einsatzes von BFR-T in kardiovaskulär-beeinträchtigten Patientenpopulationen treffen zu können, sollten zukünftige Studien darauf abzielen, mögliche unerwünschte Ereignisse als primäre Outcome-Parameter langfristig zu erfassen, um dadurch Rückschlüsse auf den Einfluss von BFR-T auf den Krankheitsverlauf zu ermöglichen.

In Anbetracht der Tatsache, dass diese zum Teil nur in der Theorie beschriebenen Nebenwirkungen eine routinemäßige Anwendung von BFR-T im klinischen Umfeld verhindern, ist es wichtig zu erwähnen, dass die Anwendung von BFR in dieser Studie ohne unerwünschte Nebenwirkungen verlief, kein interventionsbedingter Studienabbruch dokumentiert wurde und gleichzeitig eine steigende Compliance der Patienten zur BFR-Trainingsmethode gezeigt werden konnte. Um die Sicherheit unserer Studie zu erhöhen, wurden Kontraindikationen und mögliche unerwünschte Nebenwirkungen des Prähabilitationstrainings und der BFR-Intervention im Vorfeld mit den Probanden besprochen. Eindeutige Kontraindikationen für das BFR-Training lassen sich bereits anhand der physiologischen Bedingungen der externen Druckanwendung sowie der zugrundeliegenden Veränderungen der metabolischen Homöostase ableiten. Beispielsweise würden die BFR-induzierten hypoxische Bedingungen bei einer zu Grunde liegenden Sicherzellanämie-Erkrankung zu einer Formveränderung der Erythrozyten führen. Infolgedessen sind die Erythrozyten weniger in der Lage, Sauerstoff zu den Zielzellen zu transportieren und können die Niere durch Verlegung des glomerulären Filters schädigen (35). Darüber hinaus ist die anfängliche LOP-Messung sowie die Druckanwendung während des BFR-T problematisch für pathologische und iatrogene Veränderungen der arteriellen Gefäße. Während repetitive externe Druckanwendungen bis zum Gefäßverschluss bei atherosklerotischen Verkalkungen möglicherweise zu einer Plaqueruptur führen können, besteht bei chirurgisch platzierten Stents die Gefahr eines dauerhaften Verschlusses während der LOP-Messung. Ein weiteres Instrument zur Erhöhung der Patientensicherheit in unserer Studie war die Anwendung eines individuellen Belastungsdrucks auf der Grundlage des individuellen LOP.

#### 1.5.2.4 Individueller Ansatz beim Blood-Flow-Restriction Training

Das in dieser prospektiven, klinisch-randomisierten Studie verwendete Belastungsprotokoll des BFR-T beruht auf einem patientenindividuellen Ansatz durch Messung des LOP vor dem Prähabilitationstraining (95). Der LOP beschreibt den Mindestdruck, der erforderlich ist, um den Fluss des arteriellen Blutes in die untersuchte Extremität distal der Manschette zu einem bestimmten Zeitpunkt, mit einer bestimmten Blutdruckmanschette zu stoppen, die an einer bestimmten Extremität eines Patienten an einer bestimmten Position angelegt wurde (78). Die Messung des LOP wird weitestgehend von der Breite der Manschette beeinflusst, die zur Bestimmung des LOP verwendet wird. Im Allgemeinen erfordern breite Manschetten niedrigere Verschlussdrücke, was hauptsächlich auf eine größere Druckfläche zurückzuführen ist (23). Die BFR-Anwendung in der vorliegenden Studie erfolgte mit einem pneumatisch gesteuerten Blutdruckmanschettensystem in chirurgischer Qualität mit einer Manschettenbreite von 11,5 cm. Da Taubheitsgefühle und Blutergüsse häufig zu den Nebenwirkungen nach BFR-T zählen (101), kann ihr Auftreten die Compliance der Patienten gegenüber der Trainingsmethode verringern.

Über den erforderlichen BFR-Belastungsdruck während des Trainings zur Induktion der beschriebenen positiven Effekte auf Muskelmasse und -kraft gibt es eine anhaltende Debatte. Während die Ergebnisse von Ilett und Kollegen (52) zeigen, dass die größte neuromuskuläre Aktivierung während des Trainings bei einer Druckanwendung von ≥ 60% des LOP induziert wird, berichtet Gräfe et al.(22), dass bei regelmäßiger BFR-Anwendung auch Drücke von 40% des LOP zur Induktion von Hypertrophieeffekten ausreicht. In unserer Studie wurde ein BFR-Druck von 40% des LOP angewandt, um eine hohe Compliance der Patienten bei der Prähabilitation zu gewährleisten. Die positiven Ergebnisse dieser Studie lassen den Schluss zu, dass bei einem reduzierten Trainingszustand der Skelettmuskulatur eines Probanden ebenfalls niedrigere BFR-Belastungsdrücke wie 40% des LOP ausreichen, um signifikante Effekte auf Muskelmasse und -kraft zu erzielen. Auf der Grundlage dieses individualisierten BFR-Ansatzes ist es möglich, ein sicheres, patientengerechtes und effizientes Training für Patienten mit Gonarthrose im Endstadium anzubieten.

#### 1.5.2.5 Auswirkungen des Blood-Flow-Restriction Trainings auf die postoperative Rehabilitation von Muskelmasse, Kraft und Lebensqualität nach primärer TKA

Die in dieser Thesis inkludierte prospektive, klinisch-randomisierte Studie konnte initial aufzeigen, dass eine Prähabilitation mit BFR-T zu einer signifikanten Steigerung der Muskelmasse und -kraft mit assoziierten Verbesserung der QoL vor einer geplanten elektiven gelenkchirurgischen Versorgung führt. Da die teilnehmenden Patienten der Prähabilitationsgruppen (AC und BFR) mit erhöhter Muskelmasse und -kraft in die Operation hineingingen, konnte mit der Analyse der postoperativen Regeneration auch die Frage des BiBo-Konzeptes untersucht werden. Dabei hypothetisierten wir, dass die BFR-Prähabilitation einen positiven Einfluss auf die postoperative Regeneration der Muskelmasse und -kraft aufweist, der sich gegenüber den anderen Gruppen statistisch darstellen lässt.

Auch in unseren Daten zeigt sich der zunächst klassische Verlauf der Regeneration der Skelettmuskelmasse und -kraft nach primärer TKA in allen Gruppen, mit einer anfänglichen Abnahme nach der Operation (Tabelle 1 und 2) und einer damit verbundenen inversen Verbesserung des Schmerzempfindens (Abbildung 6) (82). Obwohl ebenfalls die BFR-Gruppe diesem Trend folgt, zeigen unsere Ergebnisse, dass der Rückgang der Muskelmasse und -kraft drei Monate nach der Operation nicht unter die Baseline-Werte vor dem Start in die Prähabilitationsphase fällt. Im Vergleich zur AC-Gruppe, die einen Rückgang der Muskelmasse und -kraft auf den Ausgangswert zeigt, oder zur CON-Gruppe, die teilweise unter die Ausgangswerte fiel, weisen die Patienten der BFR-Gruppe auch drei Monate nach TKA signifikant erhöhte Muskelmasse und -kraft auf als vor Beginn der Prähabilitationsphase. Da diese Ergebnisse mit einer verbesserten Leistung im CRT drei Monate nach der Operation einhergehen, kann daraus geschlussfolgert werden, dass die Prähabilitation mit BFR eine unterstützende Wirkung auf den Muskel- und Funktionserhalt nach TKA aufweist. Diese morphologischen und funktionellen Verbesserungen führen zu einem supportiven Effekt für die frühe Rehabilitationsphase und der postoperativen QoL, was sich durch höhere Punktzahlen im KOOS zeigt (Abbildung 6).

Sechs Monate nach der Operation zeigen alle Gruppen eine signifikante Zunahme der Muskelkraft im Vergleich zum Zeitpunkt drei Monate nach der Operation. Allerdings erzielt ausschließlich die BFR-Gruppe bereits zu diesem Zeitpunkt eine zusätzliche Verbesserung der Muskelmasse und -kraft gegenüber den Werten 3m-Post-OP (Tabelle 1 und 2). Während für die AC-Gruppe keine signifikante Veränderung der Muskelmasse und -kraft gegenüber den Baseline-Werten festgestellt werden konnte, zeigte die CON-Gruppe nach sechs Monaten weiterhin signifikant schlechtere Ergebnisse im Vergleich zum präoperativen Status. Dabei stimmen die Ergebnisse der AC und CG mit der bisherigen Literatur überein, die eine anhaltende Verringerung der Muskelmasse und -kraft nach TKA bei Patienten ohne Prähabilitation zeigen (7). Unsere Ergebnisse deuten darauf hin, dass die Prähabilitation mit BFR-T die Patienten in die Lage versetzt, postoperative muskuläre Defizite schneller zu kompensieren als passive oder aktive Kontrollgruppen ohne BFR-Belastung.

Während der Grundgedanke des BiBo-Konzepts auf retrospektiven Daten basiert die zeigten, dass eine erfolgreiche Rehabilitation von der präoperativen Muskelmasse, -kraft und -funktionalität abhängig ist (14), konnten frühere Prähabilitationsstudien diesen Effekt nicht nachweisen. Die Ergebnisse solcher Prähabilitationsstudien bei TKA oder in der Hüftgelenksendoprothetik zeigten lediglich eine Verbesserung der körperlichen Fitness vor der Operation, jedoch keine signifikanten Auswirkungen auf die postoperative Rehabilitation (84). Dies deutete darauf hin, dass kurzfristige präoperative Verbesserungen der Muskelgesundheit nicht bedeuten, dass die postoperative Rehabilitation im Rahmen eines BiBo-Effektes unterstützt wird. Aus diesem Grund sind die vorliegenden Ergebnisse dieser Studie von besonderer Bedeutung, da sie im Gegensatz zu früheren Erkenntnissen einen signifikanten positiven Einfluss auf die muskuläre und funktionelle Rehabilitation der Muskelmasse und -kraft nach primärer TKA durch BFR-T aufzeigen. Künftige Studien sollten versuchen, die zugrundeliegenden Mechanismen der persistierenden postoperativen Defizite in der Muskelregeneration nach einer TKA-Operation zu untersuchen, um herauszufinden wie eine BFR-Prähabilitation diese Art von katabolen Zuständen beeinflusst haben könnte.

### 1.5.3 Limitierungen

Bei der Interpretation der vorliegenden Ergebnisse sind folgenden Einschränkungen zu beachten. Erstens sollte die in dieser Studie verwendete Methode zur Messung der Muskelmasse anhand des Extremitätenumfangs als Index für die Veränderung der Muskelgröße betrachtet werden. Da diese Art der Messung Weichteil-, Fett-, Binde- und Muskelgewebe umfasst, kann nur eine Schätzung der Muskelmasse und ihrer Veränderung im Verlauf der Studie vorgenommen werden. In künftigen Studien sollten validere Methoden zur Berechnung der Muskelmasse verwendet werden, wie z. B. die Analyse der Körperzusammensetzung durch DXA-Messungen oder MRT-Scans. Zweitens könnte eine mögliche Beeinflussung der Ergebnisse durch ein fehlendes Matching der Gruppen anhand von Ausgangscharakteristika wie das Niveau der körperlichen Aktivität, präoperative muskuläre Defizite oder Beindominanz verursacht werden. Drittens besteht ein mögliches Bias für die präoperativen Ergebnisse in der unterschiedlichen Anzahl an Präsenzterminen zwischen den Gruppen, da die Prähabilitationsgruppen während des wöchentlichen Trainings mehr Besuche bei den Betreuern hatten als die CON-Gruppe. Viertens wurde das Aktivitätsniveau und die Aktivitätsintensität der Patienten nach der Operation nicht erfasst. In künftigen Studien sollte versucht werden, die postoperative Aktivität der Patienten zu überwachen, um valide Daten über die Auswirkungen der Prähabilitation auf die postoperative tägliche Aktivität zu erhalten.

### 1.6 Zusammenfassung und Schlussfolgerung

Die vorliegende Thesis fokussierte die Auswirkungen der Arthrose des Kniegelenks sowie den Einfluss der Therapie mittels TKA auf die Muskelmasse und Muskelkraft betroffener Patienten vom präoperativen bis zum postoperativen Status. Anhand der international publizierten Literatur zeigt sich, dass sich Patienten mit Arthrose des Kniegelenks neben chronischen Schmerzen und Mobilitätseinschränkungen ebenfalls durch eine signifikante muskuläre Atrophie mit assoziierten Kraftverlusten charakterisieren lassen. Postoperative Daten nach elektiver TKA zeigen auf, dass die chirurgische Intervention zwar die chronischen Schmerzen signifikant verbessern kann, die muskulären Defizite jedoch durch den chirurgischen Eingriff und die anschließende Rehabilitationsphase gesteigert werden. Dadurch lassen sich auch mehrere Jahre nach elektiver TKA noch Defizite in der Muskelmasse und Muskelkraft bei Patienten nach TKA im Vergleich zu geschlechts- und altersgematchten Kontrollpopulationen feststellen.

Auf der Basis retrospektiver Daten konnte geschlussfolgert werden, dass präoperative Faktoren wie Muskelmasse, Muskelkraft und das Level der Funktionalität als positiv-prädiktive Vorhersagewerte für eine erfolgreiche Rehabilitation nach chirurgischem Gelenkersatz angesehen werden können. Aus diesem Grund wurde der Forschungsschwerpunkt der Prähabilitation initiiert, um die körperliche und funktionelle Fitness von Patienten vor TKA zu verbessern und damit die Rehabilitation zu unterstützen. Bisherige Literaturergebnisse zeigen jedoch nur einen leichten bis mäßigen Einfluss der Prähabilitation auf die postoperative Regeneration von Muskelmasse, -kraft und Funktionalität auf. Diese Ergebnisse sind überwiegend auf die hohe Diversität an Trainingsübungen, Trainingsintensitäten und Trainingsdauern bestehender Prähabilitationsprotokollen zurückzuführen. Weiterhin zeigt sich das Klientel der Patienten mit Arthrose des Kniegelenks als sehr schmerzgeplagt, auf Basis dessen hohe mechanische Belastung über das degenerativ geschädigte Gelenk kaum zu bewegen sind und somit notwendige Intensität zum Muskelaufbau nicht angewendet werden können.

Das BFR-T liefert in diesem Zusammenhang einen möglichen Zwischenweg zur Induktion signifikanter Muskelhypertrophie trotz der Anwendung nur leichter mechanischer Belastungen. Durch eine extern applizierte spezielle Blutdruckmanschette wird eine arterielle Hypoxämie mit venöser Hyperkapnie in der trainierenden Extremität hervorgerufen und durch Stimulation der anaeroben, laktaziden Energiebereitstellung ein Hypertrophiereiz während eines Trainings mit nur leichten mechanischen Intensitäten herbeigeführt. Auf Basis des an die Patienten angepassten Belastungsnormativ und der bestehenden Literaturdaten hypothetisierte die vorliegende Thesis einen potenziell fördernden Einfluss der BFR-T als Prähabilitationstechnik auf die postoperative Muskelregeneration.

Die in dieser Thesis inkludierte prospektive, klinisch-randomisierte Studie ist die erste, die den unterstützenden Einfluss des BFR-T auf die Skelettmuskelmasse, -kraft, das subjektive Schmerzempfinden und die Lebensqualität sowohl vor als auch nach einer TKA-Operation beschreibt. Die BFR-Prähabilitation zeigt sich dabei als ein sicheres, patientengerechtes, einfach durchzuführendes und wirksames Instrument zur akuten Verbesserung und langfristigen Aufrechterhaltung der prä- und postoperativen Muskelmasse, -kraft und Patientenzufriedenheit in einer Patientenpopulation mit Arthrose des Kniegelenks. Bei einem hochgradig standardisierten klinischen Eingriff wie der TKA ermöglicht die BFR-Prähabilitation eine bestmögliche Vorbereitung der körperlichen Fähigkeiten des Patienten auf die Operation. Darüber hinaus ist die vorliegende Arbeit die erste, die eine Möglichkeit beschreibt, den BiBo-Effekt auf die muskuläre Regeneration nach TKA-Operationen durch eine BFR-Prähabilitation zu induzieren. Aufgrund des bestehenden kausalen Zusammenhangs zwischen einer verzögerten Muskelregeneration und persistierender Muskelschwäche mit subjektiver Unzufriedenheit nach einer TKA-Operation, könnte die BFR-Prähabilitation zu einem neuen erfolgsversprechenden Therapieansatz in der derzeitigen konservativen und operativen Behandlung der Gonarthrose werden.

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# 2. Studie 1: Skeletal Muscle Health in Osteoarthritis and Total Joint Replacement Therapy: Effects of Prehabilitation on Muscular Rehabilitation

**Autoren:** Alexander Franz, BSc [1,2]; Jonas Becker [1]; Michael Behringer, PhD, MD [3]; Constantin Mayer, MD [4]; Bernd Bittersohl, MD [1]; Rüdiger Krauspe, MD [1]; Christoph Zilkens, MD [1,2]

**Affiliation**

1 Department of Orthopedics, University Hospital Duesseldorf, Duesseldorf, Germany

2 ATOS Orthoparc Clinic, Cologne, Germany

3 Institute of Sports Sciences, University of Frankfurt, Frankfurt, Germany

4 Department of Orthopedics, University Hospital Essen, Essen, Germany

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## 2.1 Abstrakt

Die Arthrose des Hüft- und Kniegelenks sind zwei der häufigsten weltweit verbreiteten Erkrankungen des Bewegungsapparates, die mit zunehmender Immobilität und chronischen Schmerzen einhergehen. Die derzeit erfolgreichste Behandlungsmethode bei Arthrose im Endstadium ist die chirurgische Versorgung durch einen totalen Gelenkersatz (eng. Total joint replacement, TJR). Betroffene Patienten leiden zusätzlich unter einer stark eingeschränkten Muskelgesundheit im Vergleich zu gesunden Vergleichskohorten. Diese ist gekennzeichnet durch eine progrediente Muskelatrophie, Kraftverluste und damit verbundenen Defiziten bei der neuromuskulären Aktivierung. Die Bedeutung der Gesundheit der Skelettmuskulatur als Prädiktor für eine erfolgreiche muskuläre und funktionelle Erholung nach TJR in der Indikationsstellung und präoperativen Diagnostik ist klinisch unterrepräsentiert. Daher zielt diese Übersichtsarbeit darauf ab, die prä-, peri- und postoperative Muskelgesundheit der Patienten während des gesamten Prozesses des TJR-Eingriffs zu beschreiben. Darüber hinaus werden die zugrundeliegenden Mechanismen und potenziellen perioperativen Stressfaktoren beschrieben, die für eine beeinträchtigte Muskelphysiologie nach TJR verantwortlich sein können. Als zweites Ziel veranschaulicht diese Übersichtsarbeit die potenziellen Auswirkungen präoperativer Trainingsmaßnahmen, indem sie den Ansatz "better in, better out" in der TJR-Therapie in Frage stellt.

# 3. Studie 2: Blood Flow Restriction Training as a Prehabilitation Concept in Total Knee Arthroplasty: A narrative review about current preoperative interventions and the potential impact of BFR

**Autoren:** Alexander Franz, B.Sc. [1]; Fina Pauline Queitsch [1]; Michael Behringer, PhD, MD [2]; Constantin Mayer, MD [1]; Rüdiger Krauspe, MD, PhD [1]; Christoph Zilkens, MD [1]

**Affiliation**

1 Department of Orthopedics, University Hospital Duesseldorf, Duesseldorf, Germany

2 Institute of Biomechanics and Orthopedics, German Sport University Cologne, Cologne, Germany

**Zitation**

**Franz A**, Queitsch FP, Behringer M, Mayer C, Krauspe R, Zilkens C. Blood flow restriction training as a prehabilitation concept in total knee arthroplasty: A narrative review about current preoperative interventions and the potential impact of BFR. Med Hypotheses. 2018; 110: 53–59. doi:10.1016/j.mehy.2017.10.029.

## 3.1 Abstrakt

Die Arthrose des Kniegelenks ist eine der am häufigsten diagnostizierten Gelenkerkrankungen und verantwortlich für die weltweit steigende Anzahl an Kniegelenks-Totalendoprothesen-Operationen. Während der chirurgische Ansatz in der Lage ist, die chronischen Schmerzen zu lindern, geht die postoperative Rehabilitation häufig mit anhaltenden Dysfunktionen und Atrophien der Skelettmuskulatur einher, die jahrelange funktionelle Defizite verantwortlich sein können. Dabei deuten aktuelle Erkenntnisse darauf hin, dass die präoperative sowie postoperative Immobilität sowie der chirurgische Eingriff, vor allem unter Verwendung pneumatischer Blutsperren, als Ursache langfristiger muskulärer Beeinträchtigungen angesehen werden können. Bei dem Versuch unerwünschte Wirkungen der TKA-Therapie zu reduzieren könnte die präoperative Vorbereitung der Patienten durch spezifische Übungen (als Prähabilitation bezeichnet) die präoperative Gesamtfitness und dadurch die postoperative Rehabilitation verbessern. Aufgrund der eingeschränkten funktionellen Aktivität der Patienten müssen die Prähabilitationstechniken so gestaltet sein, dass sie regelmäßig durchgeführt werden können. Die vorliegende Arbeit basiert auf einer Übersicht über die aktuelle Literatur und stellt eine neue Hypothese auf, nach der Übungen mit Blood-Flow-Restriction Training (BFR) die Compliance der Patienten bei der Prähabilitation verbessern können. Das BFR-Training ist gekennzeichnet durch die Anwendung von Belastungen mit geringem Widerstand und ähnlicher Intensität wie bei Aufgaben des täglichen Lebens in Verbindung mit einer Blockade des venösen Blutflusses in einer Extremität, wodurch signifikante morphologische und neuromuskuläre Anpassungen in der Skelettmuskulatur erreicht werden. Zusätzlich zu den präoperativen Verbesserungen der Muskelgesundheit mit entsprechenden Vorteilen für die allgemeine Fitness könnten die durch die BFR-induzierten molekularen Veränderungen auch in der Lage sein, die durch die TKA induzierten pathologischen Signale zu verringern. Auf der Grundlage der bereits beschriebenen Auswirkungen von BFR-Training auf die Skelettmuskelphysiologie zielt die vorliegende Arbeit daher darauf ab, die potenziell positiven Auswirkungen des BFR-Trainings als Prähabilitationskonzept zu veranschaulichen, die Compliance der Patienten zu den präoperativen Belastungen zu fördern und so eine schnellere Genesung und eine höhere Patientenzufriedenheit zu erreichen.

# 4. Studie 3: Impact of a Six-Week Prehabilitation with Blood-Flow Restriction Training on Pre- and Postoperative Skeletal Muscle Mass and Strength in Patients Receiving Primary Total Knee Arthroplasty

**Autoren:** Alexander Franz, BSc [1,2]; Sanghyeon Ji, M.Sc. [3]; Bernd Bittersohl, MD [4]; Christoph Zilkens, MD [4]; Michael Behringer, PhD, MD [5]

**Affiliation**

1 Department of Orthopedics and Trauma Surgery, University Hospital Bonn, Bonn, Germany

2 Department of Adult Reconstruction, ATOS Orthoparc Clinic Cologne, Cologne, Germany

3 Department of Exercise Physiology, Institute of Exercise Training and Sport Informatics, German Sport University Cologne, Cologne, Germany

4 Department of Orthopedics and Trauma Surgery, University Hospital Duesseldorf, Duesseldorf, Germany

5 Department of Sports Medicine and Exercise Physiology, Goethe University Frankfurt, Frankfurt, Germany

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## 4.1 Abstrakt

***Einleitung*** Die Kniegelenkstotalendoprothese (TKA) ist einer der erfolgreichsten operativen Eingriffe bei Gonarthrose, führt allerdings nachweislich zu Muskelschwund und langfristigen muskulären Defiziten. Um die Rehabilitation nach TKA zu verbessern, wird mit Übungsprogrammen versucht, die Muskelgesundheit vor der Operation zu verbessern, was als Prähabilitation bezeichnet wird. Blood-Flow-Restriction Training (BFR-T) ist eine Trainingsmethode, bei der mit Hilfe von Blutsperren der arterielle und venöse Blutfluss während des Trainings gleichzeitig reduziert wird, um die metabolische Belastung zu erhöhen. Ziel der vorliegenden Studie war es, die Auswirkungen einer sechswöchigen Prähabilitation mit BFR-T auf die prä- und postoperative Muskelmasse, Kraft und Lebensqualität zu untersuchen.

***Methoden*** 30 Patienten mit Gonarthrose im Endstadium nahmen an dieser Studie teil. Die Patienten wurden nach dem Zufallsprinzip in eine von drei Gruppen eingeteilt: 1) Kontrollgruppe (CON): Klinische Standardbehandlung ohne Prähabilitation. 2) Aktiv-Kontroll-Gruppe (AC): Teilnahme an einer Prähabilitation mit Sham-BFR. 3) BFR-Gruppe (BFR): Teilnahme an einer Prähabilitation mit BFR-T. Das Prähabilitationsprotokoll bestand aus einem Fahrradergometertraining, das zweimal pro Woche über sechs Wochen durchgeführt wurde. Während des Trainings wurde BFR-T periodisch dreimal pro Bein mit einem Druck von 40% des individuellen arteriellen verschlussdrucks angewendet. Die Messzeitpunkte waren sechs (Baseline), drei Wochen und fünf Tage vor der Operation (Pre-OP) sowie drei und sechs Monate postoperativ. Messparameter waren die Muskelkraft der Oberschenkelmuskulatur, der Oberschenkelumfang sowie die Lebensqualität und die funktionelle Aktivität, untersucht durch den Sechs-Minuten-Geh- und den Chair-Rising-Test.

***Ergebnisse*** Beide Trainingsgruppen zeigten eine signifikante Verbesserung der Beinmuskelkraft nach der Prähabilitationsphase, wobei die BFR-Gruppe einen besseren Effekt erzielte (BFR: ~170% vs. AC: ~91%, $p < 0.05$). In der CON-Gruppe traten keine signifikanten Veränderungen der Beinkraft auf (~3%, $p = 0.100$). Darüber hinaus wiesen die Patienten in der BFR-Gruppe eine signifikant verbesserte Skelettmuskelmasse auf, die anhand des Oberschenkelumfangs nach der Prähabilitationsphase gemessen wurde (~7 %, $p < 0.05$), während in der CON- (-1,14 %, $p = 0.131$) und AC-Gruppe (~ 3 %,

$p = 0.078$) keine signifikanten Veränderungen auftraten. Nach 3m Post-OP zeigte sich in der CON- und BFR-Gruppe eine signifikante Abnahme des Oberschenkelumfangs im Vergleich zur Prä-OP (CON: ~3%, BFR: ~4%; $p < 0.05$), während die BFR-Gruppe über dem Baselinewert blieb (~3%, $p < 0.05$). In der AC-Gruppe wurde keine signifikante Veränderung des Oberschenkelumfangs festgestellt (~2%, $p = 0.078$). Darüber hinaus führte die Prähabilitation mit BFR-T zu einer deutlichen Verbesserung der Knee Injury and Osteoarthritis Outcome Scores Werte (KOOS), insbesondere bei der Schmerzwahrnehmung, mit einem signifikant höheren Effekt im Vergleich zu den anderen Gruppen (CON: -2%, AC: 13%, BFR: 41%; $p < 0.05$). In der Langzeitrehabilitation nach sechs Monaten zeigten alle Gruppen signifikant verbesserte KOOS-Scores in allen Dimensionen (CON: ~110%, AC: ~132%, BFR: ~225%; $p < 0.01$) und funktionelle Untersuchungen (CON: ~26%, AC: ~16%, BFR: ~53%; $p < 0.01$).

***Schlussfolgerung*** Die vorliegenden Ergebnisse zeigen, dass die Prähabilitation mit BFR-T vor der TKA signifikante Verbesserungen der Muskelfunktion und der Lebensqualität bewirken kann. Darüber hinaus sollte die unterstützende Wirkung der Prähabilitation auf die postoperative Regeneration und Lebensqualität hervorgehoben werden, was die anhaltenden positiven Auswirkungen der BFR auf die muskuläre und funktionelle Leistungsfähigkeit in einer "Better in, better out"-Manier veranschaulicht.

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## 6. Anhang

**Originalpublikationen**

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*Franz A[1,2], Becker J[2], Behringer M[3], Mayer C[4], Bittersohl B[2], Krauspe R[2], Zilkens C[1,2]*

# Skeletal Muscle Health in Osteoarthritis and Total Joint Replacement Therapy: Effects of Prehabilitation on Muscular Rehabilitation

*Skelettmuskelgesundheit bei Arthrose und Totalgelenkersatztherapie: Auswirkungen der Prähabilitation auf die Muskelrehabilitation*

**REVIEW**

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1. ATOS ORTHOPARC CLINIC COLOGNE, *Department of Adult Reconstruction, Cologne, Germany*
2. UNIVERSITY HOSPITAL DUESSELDORF, *Department of Orthopedics, Duesseldorf, Germany*
3. UNIVERSITY OF FRANKFURT, *Institute of Sports Sciences, Frankfurt, Germany*
4. UNIVERSITY HOSPITAL ESSEN, *Department of Orthopedics, Essen, Germany*

## Summary

› **Osteoarthritis (OA)** of the hip and knee joint is a common disease worldwide and is associated with chronic disability and progressive pain. Currently, the most suitable treatment method in end-stage OA is surgical restoration by total joint replacement (TJR).

› **In this regard,** patients' suffering from end-stage OA and waiting for TJR intervention are also affected by extensively impaired skeletal muscle health. This is characterized by progressive muscle atrophy, strength decline and associated deficits in neuromuscular activation. Unfortunately the importance of skeletal muscle health, as a predictor for a successful muscular and functional recovery, is clinically underrepresented in medical indication and preoperative diagnostics.

› **Therefore,** this review aims to describe patients' pre, peri and postoperative muscle health during the whole process of a TJR intervention. Additionally, underlying mechanisms and potential perioperative stressors, which may be responsible for impaired muscular physiology after TJR, will be described.

› **As a second purpose,** this review illustrates the potential impact of preoperative exercise interventions by challenging the "better in, better out" approach in TJR therapy.

## Zusammenfassung

› **Degenerativen Erkrankungen** des Knie- (Gonarthrose) und Hüftgelenkes (Coxarthrose) beschreiben zwei der häufigsten Ursachen von chronischen Gelenkschmerzen und progressiven Funktionseinschränkungen. Die zurzeit erfolgreichste Therapie der endständigen Arthrose ist deren Versorgung mittels einer Endoprothese.

› **Neben der Gelenk-bezogenen Symptomatik**, weisen Arthrose-Patienten eine ebenfalls stark beeinträchtige Muskelgesundheit auf. Diese ist charakterisiert durch eine atrophierte Skelettmuskulatur und signifikante Verluste in der neuromuskulären Ansteuerung und Kraftgenerierung. Trotz des weitreichenden Einflusses einer gesunden Skelettmuskulatur, als positiver Prädiktor für eine erfolgreiche funktionelle Rehabilitation, ist deren Diagnostik in der klinischen Versorgung ein unterrepräsentiertes Feld.

› **Aus diesem Grund** thematisiert diese Übersichtsarbeit die Beschreibung der Muskelgesundheit von Arthrose-Patienten im zeitlichen Verlauf einer Gelenkersatztherapie. Weiterhin werden perioperative Stressoren und zu Grunde liegende Mechanismen der langfristig gestörten Skelettmuskelphysiologie nach einer endoprothetischen Versorgung beschrieben.

› **Auf dieser Basis** richtet sich der sekundäre Schwerpunkt dieses Artikels auf die Beschreibung präoperativer sporttherapeutischer Interventionen (Prähabilitation) und der kritischen Auseinandersetzung mit der geringen statistischen Evidenz eines "better in, better out" Konzeptes.

**KEY WORDS:**
Muscle Atrophy, Total Knee Arthroplasty, Total Hip Arthroplasty, Preoperative Intervention, Arthrogenic Muscle Inhibition

**SCHLÜSSELWÖRTER:**
Muskelatrophie, Knie-Totalendoprothese, Hüft-Totalendoprothese, Präoperative Intervention, Arthrogene Muskelinhibition

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**CORRESPONDING ADDRESS:**
Alexander Franz
Department of Adult Reconstruction,
ATOS Orthoparc Clinic Cologne
Aachener Strasse 1021B
50858 Cologne, Germany
: alexander.franz@atos.de

## Introduction

Osteoarthritis (OA) of the hip and knee joints are associated with chronic disability and progressive pain in affected patients and characterized two of the most commonly diagnosed joint ailments worldwide. Within the context of a progressively ageing population and concurrent higher mobility expectations, research on efficient treatment methods and prevention strategies becomes increasingly important.

The currently most suitable treatment method in end-stage OA of the hip and knee joint is a surgical restoration by total joint replacement (TJR), with increasing implementation rates all over the world (42). However, despite advantages in prosthesis designs, standardization in surgical techniques and application of rapid recovery programs (RR), patients often note functional limitations after TJR compared › with their age- and gender-matched controls (4). Especially patients after total knee arthroplasty (TKA) show less satisfaction with their primary TKA (12), reporting progressive postoperative muscle atrophy and associated strength loss of the lower extremities (56, 68). Within this regard, Farquhar and colleagues (23) reported that overall functional performance as well as muscular strength of the operated and non-operated leg declined significantly during the first three years post-surgery in comparison to control groups. Since prolonged reduced functionality after TJR can be linked to long-term documented muscular impairments (e.g. muscle atrophy, strength and flexibility declines), the importance of patients' skeletal muscle health pre- and postoperatively is underrepresented in clinical routine diagnostics. Therefore, this review aims to describe patients skeletal muscle health in process of a TJR intervention. Additionally, underlying mechanisms and potential perioperative stressors, which may be responsible for an impaired muscular physiology after TJR, will be described. As a second purpose, the potential impact of preoperative exercise interventions will be discussed by challenging the "better in, better out" approach in TJR therapy.

## Skeletal Muscle Health in Osteoarthritis and TJR Therapy

In consideration of clinical indications for TJR interventions like chronic disability and progressive pain, OA patients are also characterized by an extensively affected muscle health. Especially due to prolonged immobility, the skeletal muscle tissue is affected by long-term muscle atrophy signaling and associated loss of muscle strength (20, 37). Skeletal muscle atrophy is characterized by the active degradation and removal of contractile proteins with a concurrent reduction in muscle fiber size (11). Studies investigating muscle atrophy induction revealed that a common transcriptional program is induced by immobilization. Subsequently, gene expression regarding energy production and carbohydrate metabolism are down- whereas genes involved in protein degradation and metabolism are concurrently upregulated (45). OA models in rodents showed indirectly that one of the key regulators in protein metabolism, proteinkinase B (Akt), is downregulated by reporting increased expression of downstreaming products of Forkhead box O3 (FoxO3a), which are involved in proteasomal protein degradation (e.g. muscle RING finger 1 (MuRF1), muscle atrophy F-Box (MAFbx)) (3). In addition to the upregulation of atrophy-related genes, muscles of OA patients are also characterized by an increase inflammatory cytokine expression which in fact can be seen as an accessory inductor for muscle atrophy signaling (48).

Whereas the preoperative immobility is causing significant declines in muscle mass and strength, especially the postoperative hospitalization, immobility and protective posture become often linked as the reasons for long-term muscular impairments after surgery. Confirmatory, one week of postoperative hospitalization, which is an average time in several countries (e.g. Germany, Denmark) (36), is able to induce significant muscle atrophy in TJR patients, especially in older patient populations (41). In detail, Ratchford and colleagues (69) documented a significant decline of quadriceps muscle mass during the first two weeks post TKA surgery of 12% in the operated and 6% in the non-operated leg. Additionally, both-sided declines in muscle strength and irritations in muscle activation complete the impaired muscle health of TJR patients after surgery (56, 83).

Particularly disturbances in neuromuscular activity are well known complications after surgical interventions in clinical orthopedics (30, 49, 53). This so called "arthrogenic muscle inhibition" (AMI) describes a deficit in neuronal muscle activation and muscle fiber recruitment without indicating associated structural damages of the muscle or innervating nerve (35). Presumably caused by a disordered afferent sensory, studies were able to show that OA- or surgical-induced changes in tissue homeostasis (71), inflammation (72), tissue damage (34) and particular pain have an adverse effect on neuromuscular activation and could contribute the onset of AMI (40). Therefore, pathological changes in muscle function before as well as after TJR intervention seems to be highly affected by AMI, subsequently leading to an impaired early postoperative recovery. Unfortunately, even after two years post-TJR, patients muscle health can be described as still reduced by showing fatty muscle atrophy (64), prolonged declines in muscle strength and activation with associated impaired functionality (32, 68). In this regard, review articles by Arnold (2) and Harding (29) concluded that physical activity of OA patients did not significantly differ between pre- and postoperative measurements over a two-year period (Figure 1).

Within the background of reduced rehabilitation ability, RR programs were integrated into clinical practice to attain a faster rehabilitation for TJR patients. These programs were mostly distinguished by perioperative pain management, early postoperative mobilization and accelerated transition into a specific rehabilitation program (18, 70). Supporting evidence for early postoperative mobilization is emerged by studies focusing physiological changes in functional unloading, showing that the atrophic process in skeletal muscle is enhanced by the reduced impact of load-bearing muscle contractions (54) and that stimulated contractions may have counteracting effects (26). Although, clinical outcomes like length of hospital stay (LOS) and clinical readmissions could be significantly reduced by RR interventions (10, 79), a faster discharge and begin of intensive physiotherapeutic intervention can only be correlated with short-term benefits, without indicating long-term improvements in functional and muscular recovery (52, 87). These findings are supported by investigations showing that muscle regeneration in elderly patients is diminished due to decreased satellite cell proliferation in association with an impaired regulation of myostatin (81). Therefore, postoperative interventions seem to have only a minor impact on muscular rehabilitation after TJR, which could be caused by a secondary induction of muscle atrophy signaling during the elective surgical approach (60, 88).

## Potential Perioperative Causes for Skeletal Muscle Atrophy in TJR

Although, current surgical approaches try to prevent direct muscle damage routinely, research outcomes document an indirect impact on muscle physiology by showing alterations in muscle protein synthesis and degradation balance. Molecular analyses of muscle samples from M. vastus lateralis during tourniquet associated TKA surgery revealed that protein synthesis is down- and concurrently expression of key atrophy genes is upregulated (5, 69). In detail, the ischemic disposition and following reperfusion is not only a serious risk for skeletal muscle damage (46), it also caused the dephosphorylation of Akt which implies an inhibition of the Akt-mTORC pathway. Consequently, protein synthesis is blocked by less building of the translation initiation complexes with concurrent upregulation of FoxO3a products (MuRF1, MAFbx), enhancing muscular protein breakdown during and after surgery. Furthermore, tourniquet- or even surgical trauma-induced formation of reactive oxygen

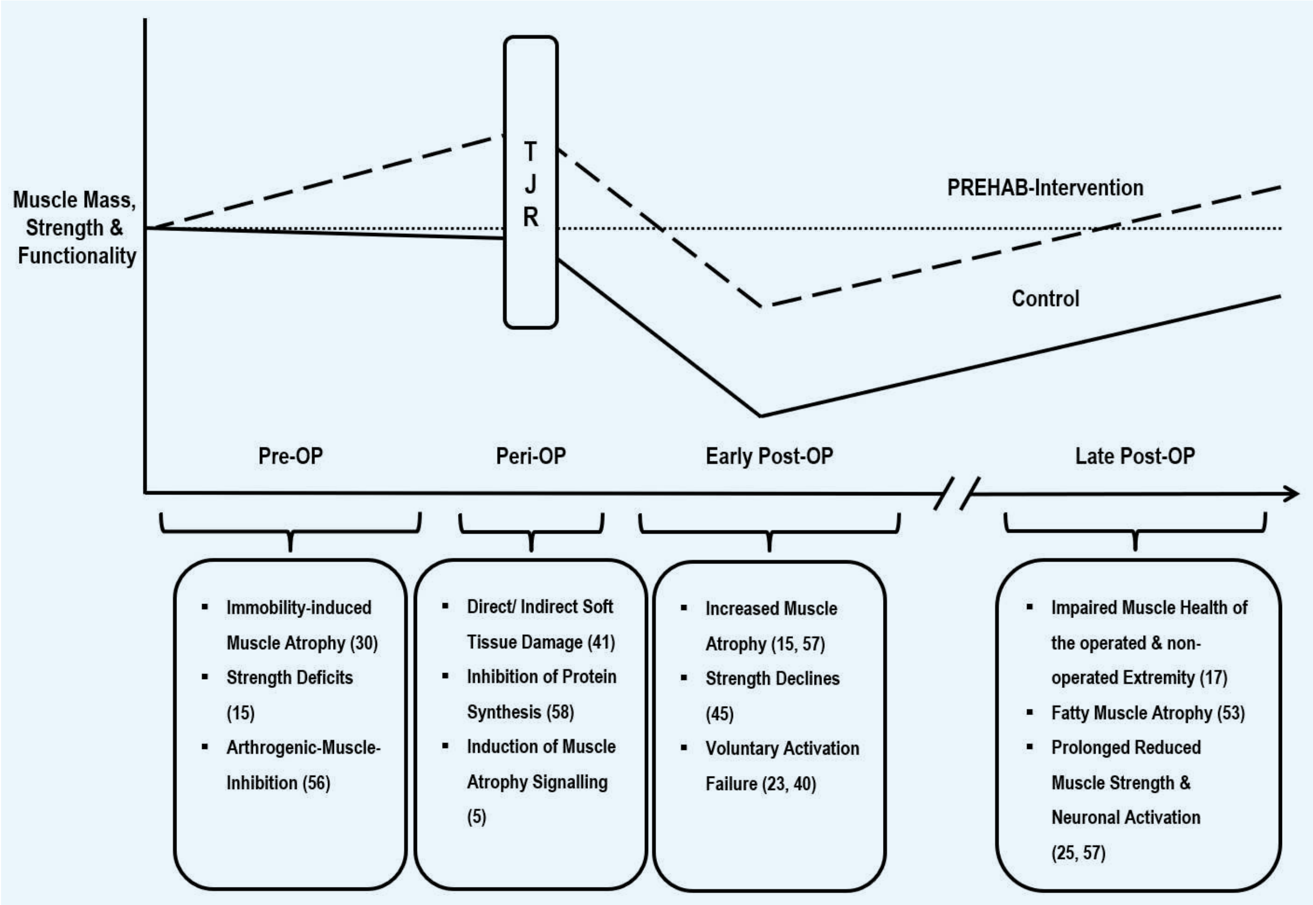


Figure 1

Muscle Health of OA patients with the indication for elective total joint replacement surgery (TJR) to different time points during the therapy process. The continous line describes the process of muscle mass, strength and functionality of a patient during the process of elective TJR therapy. In contrast, the discontinous line illustrates the theoretical model for a prehabilitation approach in TJR (based on Topp and colleagues, 70). In addition, basic characterstics of impaired muscle health to different time points in TJR therapy are listed below the graphic with corresponding references.

species is able to initiate a subsequent acute immune response triggering prolonged tissue stress by enhancing protein breakdown as well (7, 47).

Although, underlying mechanisms of surgical induced alterations in skeletal muscle physiology are well described, the extensive discussion regarding tourniquet use during TKA is mostly guided by regularly documented parameters (pro: less bleeding, less surgery time; contra: deep vein thrombosis risk, delayed recovery) (1, 33, 50, 86). Focusing skeletal muscle physiology and perioperative tourniquet use, Jawhar and colleagues reported less proteasome-dependent peptidase activities in M. vastus medialis muscle cells during tourniquet free approaches (38). Unfortunately, clinical outcomes revealed no statistical superiority of tourniquet free surgeries regarding short-term postoperative pain, swelling or muscular recovery (22). Additionally, in terms of long-term follow up, Dennis et al. (19) revealed only small differences in muscle activation and strength rehabilitation in favor of tourniquet-free TKA approaches, however by still documented muscle atrophy.

Similarly to TKA, also total hip arthroplasty (THA) patients complain about prolonged muscle atrophy and strength decreases postoperatively (68). Since THA surgeries do not use perioperative tourniquets, underlying mechanisms for postoperative muscle impairments could be equally generated as reported after tourniquet-less TKA surgery. Müller et al. (59) were able to show, that minimal invasive approaches in THA (antero-lateral approach vs. direct lateral approach) are able to reduce MRI measured muscle atrophy in gluteus medius muscle in comparison, without showing impact on functional rehabilitation. Regarding the underlying mechanism, it is still hypothetical why also tourniquet free or even minimal invasive surgical approaches induce muscle atrophy signaling.

Since TJRs are still connected with an increase damage of the soft-tissue and blood vessels, the mechanical trauma may be able to reduce the sympathetic impact on the muscle tissue, leading to prolonged muscle catabolism. In fact, pharmacological studies were able to illustrate the impact of the adrenergic system on skeletal muscle homeostasis by reporting anti-cachectic properties of β2-agonists through down-regulation of muscle specific proteolytic systems (e.g. myostatin) with concurrent stimulation of the Akt-mTORC pathway (21, 28, 39). Within this regard, research projects using various kinds of animal-based atrophy models were able to show that administration of β2-agonists can reduce skeletal muscle breakdown significantly (9, 74, 78). Supposing that the surgical trauma may irritates or even destroys vessel-guided vegetative nerve bundles, the decline in sympathetic input could be able to cause a prolonged muscle protein breakdown by simultaneously decreasing protein anabolism capabilities in several affected muscles. However, whereas this approach would be able to explain the reduced local muscle atrophy in minimal invasive approaches, the reasons for postoperative muscle impairments in remote lying muscles, which are partially not even acting against the gravity (e.g. knee flexors), are still unknown (20).

Therefore, a kind of systematic induction of muscle atrophy perioperatively seems to be more etiological for mentioned postoperative disturbances in muscle physiology then the postoperative immobility alone.

In summary, research outcomes revealed that despite advantages in surgical procedure, the TJR intervention can be considered as a supporter and inductor for prolonged skeletal muscle atrophy with significant impact on functional rehabilitation. These data highlight a fundamental clash between practical surgical considerations and basic research on underlying molecular/cellular mechanisms of surgical induced muscle impairments. Where on the one hand the gold-standard in end-stage OA can reduce successfully pain by associated improvements in joint mobility, reviewed data show contrariwise that the TJR intervention negatively affects the muscle physiology for several years, leading to substantial deficits in functionality. However, more research is needed for the clear cause identification of muscle atrophy induction and the development of new candidate interventions to interfere with mentioned pathological signaling cascades.

Interestingly, epidemiological data reported by Mizner et al. (55) were able to show that several physical factors, e.g. higher preoperatively muscle mass, muscle strength, range-of-motion (ROM) and the abilities to complete functional tasks can be seen as positive predicted values for a successful and faster recovery after TJR. Nevertheless, a specific diagnostic battery for the evaluation of the actual condition of patients' muscle health is not integrated into clinical preoperative routine. Instead, without consideration of potential preconditioning interventions, the elective surgery will be performed, although patients muscle condition is supposedly on the lowest level of health in his/her life, without the perspective of advancements. Therefore, preoperative training of patients' fitness and muscle health could be a promising tool to improve postoperative muscle health in a "better in, better out" approach.

## "Better In, Better Out" by Prehabilitation

The concept by using specific exercise interventions or intense physical therapy preoperatively to improve patients muscle health is called "prehabilitation" and aims to maintain a normal level of functionality during and after surgery (14). Since mentioned surgical atrophy pathways are not diminished by prehabilitation in the first place, gains in muscle mass, strength and concurrent improvements in functionality could be seen as a compensatory "buffer" to enable better long-term clinical outcomes and increased subjective satisfaction (82).

In TKA, several studies were able to report significant improvements in preoperative leg strength, ROM and subjective pain perception through prehabilitation (51, 77), without showing beneficial effects on postoperative muscular and functional rehabilitation (8). In fact, clinical postoperative parameters, like LOS, ROM and Sit-to-Stand-time, were improved by prehabilitation, without showing impact on long-term muscle strength, pain and functional assessments (e.g. 6-minutes-walking) (16). Based on several inconsistent types of applied training protocols (e.g. home-based vs. attended sessions), exercise intensities (e.g. 10 reps by 80% 1RM vs. bodyweight-exercises) or even durations (e.g. 4 weeks vs. 8 weeks), a scientifically valid evaluation of the usefulness of prehabilitation for clinical practice is not possible. In comparison, only two studies in THA patients were using a prehabilitation concept, consisting of either strength training in water and later with machines (73) or home-based exercises (24). Comparable to results in TKA patients, prehabilitation in THA showed significant improvements in several preoperative subjective (Pain, WOMAC-, SF-36 Score) and functional assessments (muscle strength, timed up and go test) as well, by documenting no statistical impact on postoperative muscular and functional recovery.

In reference to mentioned epidemiological data, current applied prehabilitation concepts failed to support the conclusion that preoperative fitness predicts a successful postoperative recovery. Although, the reported prehabilitation concepts were able to show significant improvements in preoperative patients' muscle health, there is no statistical impact on postoperative rehabilitation. Since shorter LOS or less time needed to reach 90 degrees in TKA can be seen as important factors in hospital reimbursement, functional and muscular recovery seems not to be supported by current applied prehabilitation strategies (16). Therefore, a meta-analysis by Moyer and colleagues revealed that overall effect sizes for prehabilitation in a "better in, better out" approach in TJR therapy can only be seen as small to moderate (58).

## Conclusion: Prehabilitation in TJR Surgery?

Although, these results challenge the fundamental concept of prehabilitation, it is questionable if the current applied exercise regimes were the most suitable to enable enhancements in muscular recovery. Based on the described characteristics of affected skeletal muscle health in OA patients, training concepts in clinical prehabilitation settings should try to reduce AMI by concurrent enhancements in muscle size and strength to ensure long-term improvements in patients' recovery. Regarding volitional muscle activation, transcutaneous electrical nerve or direct muscle stimulation (TENS, NMES) is an intensive investigated research field in OA patients, reporting beneficial outcomes in OA- and TJR-induced AMI (65, 67, 80). However, previous approaches failed to report significant improvements by NMES on muscle mass and strength in OA (27, 62) even if it is combined with regular exercise therapy (22, 44) or applied as preoperative training therapy (57, 61). Therefore, it seems still necessary to identify suitable exercise concepts for OA patients to assess additional improvements in muscle mass and strength.

Within this regard, enhancements in muscle mass, strength and functionality in older subjects are primary attainable by using high mechanical loads or specifically triggering eccentric exercise contractions (31, 75). However, despite beneficial outcomes in rehabilitation settings (43), the application of high-mechanical loads in regular OA therapy and present prehabilitation protocols is still limited due the induction of pain and concurrent reduction in patients' compliance to the training mode (63). For this reason, a new training concept has emerged more attention in clinical conservative therapy during the last decade by reporting significant improvements in muscle health without using high mechanical loads (84). Blood-Flow-Restriction Training (BFR) describes a training concept which is using low mechanical loads (30% 1RM) in combination with an external venous occlusion to induce a shift from a primary mechanically to a more metabolically demanding exercise stimulus (66). Bryk et al. (13) were able to show that a six-week training protocol of BFR in combination with low-mechanical loads were able to show similar improvements in muscle strength, functionality and pain perception in OA patients as resistance exercises with high-mechanical loads, by simultaneously inducing less joint pain during the exercises. Within the context of safety application, several studies were document the beneficial impact of BFR training on endothelial function and peripheral tissue perfusion without indicating acute adverse effects in healthy older subjects (76) as well as in vulnerable clinical populations (e.g. cardiovascular patients) (6, 15). Although, the underlying mechanisms of BFR-induced muscle adaptations are still under investigation, studies revealed that the venous occlusion is resulting in an increase metabolic stress by associated enhance neuromuscular activation (89). In addition to beneficial effects on preoperative muscle health, BFR applied as prehabilitation strategy may have the ability to improve skeletal muscles resistance against perioperative induced pathological cascades, by interfering muscle atrophy induction through long-term upregulation of the Akt-mTORC pathway and preoperative Nrf2 stimulation (17, 25, 85).

In summary, despite several varying types and intensities of applied exercise protocols, all prehabilitation trials were able to induce beneficial improvements in preoperative muscle health and patient satisfaction. Unfortunately, meta-analyses revealed that current approaches failed to improve muscular and functional recovery after TJR, indicating that a simple mechanistic approach as postulated by the term "better in, better out" is not supportable. Therefore, future prehabilitation concepts should try to focus on exercise interventions which are able to induce anabolic and perioperative useful adaptations by concurrent feasibility for OA patients.

**Conflict of Interest**
*The authors have no conflict of interest.*

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# Blood flow restriction training as a prehabilitation concept in total knee arthroplasty: A narrative review about current preoperative interventions and the potential impact of BFR

Alexander Franz[a,*], Fina Pauline Queitsch[a,*], Michael Behringer[b], Constantin Mayer[a], Rüdiger Krauspe[a], Christoph Zilkens[a]

[a] Department of Orthopedics, University Hospital Duesseldorf, Duesseldorf, Germany
[b] Faculty of Sport Sciences, Goethe University Frankfurt, Frankfurt, Germany

ABSTRACT

Osteoarthritis of the knee is one of the most commonly diagnosed joint ailments and responsible for increased rates of total knee arthroplasty surgeries worldwide. Whereas the surgical approach is able to diminish the perceived knee pain of concerned patients', the postoperative recovery is often accompanied by persistent skeletal muscle dysfunctions and atrophy, which is responsible for functional deficits for up to several years. Recent findings indicate that surgery induced adverse effects on skeletal muscles are largely associated with the use of pneumatic tourniquets, wherefore several studies try to reduce tourniquet use in orthopedic surgery. However, due to comparable incidence of muscle impairment and increased surgical challenge, the most frequently applied surgical technique in TKA is still associated with the use of tourniquets. When attenuating TKA induced adverse effects, the preoperative preparation of patients by specific exercises (called prehabilitation) was able to enhance preoperative overall fitness through associated accelerated recovery. Based on patients' limited functional activity, prehabilitation techniques have to be particularly designed to allow regular adherence. The present paper is based on a narrative review of current literature, and provides a novel hypothesis by which blood flow restriction exercises (BFR) are able to improve patients' compliance to prehabilitation. BFR training is characterized by the application of low-resistance exercise with similar intensities as daily living tasks in association with a suppression of venous blood flow in an extremity, achieving significant morphological and neuromuscular adaptations in skeletal muscles. In addition, preoperative enhancements in muscle health with corresponding benefits in overall fitness, BFR induced molecular alterations could also be able to interfere with TKA induced pathological signaling. Therefore, based on the known major impact of BFR on skeletal muscle physiology, the present paper aims to illustrate the potential beneficial impact of BFR training as a prehabilitation concept to promote patients regular adherence to preoperative exercises and thus achieve an accelerated recovery and increases in patients' satisfaction.

## Introduction

Osteoarthritis (OA) of the knee is associated with chronic disability and progressive knee pain in concerned patients and characterized as one of the most commonly diagnosed joint ailments worldwide [1]. Within the context of a progressively ageing population, research on efficient treatment methods and prevention strategies becomes increasingly important. The currently most suitable treatment method in OA of the knee is a surgical restoration by total knee arthroplasty (TKA), with increasing implementation rates over the past decade all over the world [2]. Whereas in 2008, more than 650.000 TKAs were performed in the U.S. with a total cost of $9 billion, the expected rate in 2030 is projected to be around 3.5 million TKAs with associated increases in costs [3]. However, despite improvements in surgical care, prosthesis design and standardized pre- as well as post-surgical procedures, only around 80% of patients are satisfied with their primary TKA [4]. This is often related to an incomplete restoration of physical function. Therefore, an important challenge for medical research is to improve patient care while maintaining or decreasing medical expenses.

Within this background, "fast recovery" programs are created, aiming to reduce the length of hospital stay (LOS), thereby reducing

* Corresponding authors at: Department of Orthopedics, University Hospital Duesseldorf, Moorenstrasse 5, 40225 Duesseldorf, Germany.
E-mail addresses: alexander.franz@hhu.de (A. Franz), fina.queitsch@hhu.de (F.P. Queitsch).

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costs and supporting an accelerated transition into a specific rehabilitation program [5]. Fast recovery programs mostly focus on perioperative pain management [6] or early mobilization post-surgery, latter being associated with a short-term increase in analgesic intake [7]. Thus, TKA surgery in collaboration with reported programs seems to be a beneficial concept for physicians and patients, able to successfully resolve chronic knee pain and reduce expenditures. However, postoperative recovery is often accompanied by persistent muscle atrophy, which is responsible for functional deficits for up to approximately 3 years post-surgery [8]. Furthermore, several case reports documented the formation of extensive rhabdomyolysis in TKA or other orthopedic surgical procedures, indicating its significant impact on skeletal muscle physiology [9,10]. Although skeletal muscle atrophy is a physiological response to common changes in gene expression [11] and local muscle damage in TKA presupposes alterations in ionic handling, metabolic demands and pro-inflammatory responses [12], both scenarios are potentially caused by the use of pneumatic tourniquets during TKA [9,11]. The present paper discusses the potential impact on preoperative exercise routines on reported adverse effects in TKA surgery, especially focusing on a novel technique of prehabilitation by blood flow restriction training (BFR).

## Tourniquet use in TKA: benefits and adverse effects

Independent of the surgical approach or implant type, tourniquets are commonly applied in TKA to reduce blood loss and obtain a clear visualization of the operative field for the surgeon [13]. In consideration of reported clinical outcomes, several different application strategies were constructed to prevent adverse effects of tourniquet use, e.g. surgery without tourniquets [14] or application during the cementing process only [15]. Non-tourniquet TKA surgeries are reported to be beneficial in preventing adverse effects e.g. deep vein thrombosis or pulmonary embolism [16] and support an early recovery of patients [17], supposedly by maintaining muscle strength and health [18]. Certainly, the influence of non-tourniquet surgery on muscle damage and atrophy pathways is not investigated yet. However, possibly due to its increased effort and difficulty [19] the use of tourniquets is still the most applied technique in orthopedic surgery with valuable impacts in the prevention of intraoperative bleeding and the cementation process [20]. Since the cementation process is essential in context of long-term results [21], several studies discuss the use of a tourniquet during cementation only. In comparison to full-length application, this technique provides advantages in postoperative muscle damage and inflammation markers [15], without affecting early rehabilitation [22]. These results are supported by studies already performed in 1993, documenting that skeletal muscle is already severely affected during relatively short periods of tourniquet induced ischemia ($\geq 15$ min), supporting the formation of severe muscle atrophy after orthopedic surgery [23]. Therefore, surgeons need to discuss and choose between the reported techniques in context of practicability and utility within the background of every individual patient before TKA.

## TKA Surgery: tourniquet induced muscle atrophy and damage

Magnetic resonance imaging (MRI) was able to document a decrease of 12–14% in quadriceps volume through tourniquet application during TKA on the operated leg with an associated 6% decrease in mass on the contralateral leg within the first two weeks after surgery [24]. Based on measurements six weeks after surgery that showed a decline of about 18%, it is indicated that approximately 80% of the post-surgical muscle atrophy occurs within the first two weeks [25].

Comprehensive research on skeletal muscle physiology and atrophy formation during TKA surgery indicates that a decline in protein synthesis [24] as well as increased activation of protein degradation pathways [11] may be responsible for related adverse effects. Analyses of muscle biopsies suggest that the phosphorylation status of key proteins in the mammalian target of rapamycin complex 1 (mTORC1) signaling cascade are affected through tourniquet induced ischemia, subsequently leading to alterations in protein synthesis and anabolic/catabolic homeostasis.

Protein synthesis is dependent on the formation of the ternary initiation complex (eIF4F) to enable protein translation, which is regulated through the phosphorylation status of the IF4E-binding protein 1 (4E-BP1). Phosphorylation of 4E-BP1 by mTORC1 leads to its dissociation from eukaryotic initiation factor 4E (eIF4E) and promotes the formation of the eIF4F. When using a tourniquet during TKA surgery, 4E-BP1 becomes dephosphorylated and subsequently impairs the formation of eIF4F by binding eIF4E [24]. This outcomes indicates a downregulation of anabolic signaling during and long-termed after TKA [26], supposedly for ATP conservation. Furthermore, in addition to a decreased ability for protein synthesis, direct alterations in muscle cell homeostasis through imbalances between muscles catabolic and anabolic pathways may also play an important role in TKA-induced muscle atrophy. Bailey and colleagues [11] reported an increased activity of Forkhead box O (Foxo) transcription factors during TKA with associated elevated cytoplasmatic protein levels of two muscle-specific E3 ubiquitin ligases, muscle RING finger 1 (MuRF1) and muscle atrophy F-Box (MAFbx), indicating increased catabolic conditions by downregulation of Akt signaling. Whereas MuRF1 and MAFbx proteins are typical components of the 26S proteasomal pathway which may catabolize soluble and myofibrillar proteins (e.g. actin, myosin, titin) [27], outcomes suggest that also autophagic/lysosomal pathways become increased through TKA [11]. Enhancements in FoxO3a signaling is documented to induce the expression of the Bcl2/adenovirus EIB 19-kDa-interacting protein 3 (Bnip3) in ischemia/reperfusion-injury (I/R-injury), which as a proapoptotic member of the Bcl-2 family regulates protein degradation by autophagic/lysosomal pathways [28].

Whereas reported alterations in skeletal muscle physiology may be responsible for catabolic signaling during TKA, additional tourniquet induced disturbances seems to be responsible for extensive muscle damage or even necrosis (rhabdomyolysis) after TKA. This has been documented by several case reports [9,10]. Initially, during ischemia, soft tissue energy supply temporarily changes from an aerobic to an anaerobic metabolism to sustain ATP-levels, leading to an accumulation of lactate, thereby inducing a metabolic acidosis [29]. When sustained over a prolonged period of time, the anaerobic metabolism leads to a depletion of stored substrates, which subsequently causes impairments in ATP-depending systems [30]. Additionally, disturbed ionic handling is responsible for an enhanced activity of the $Na^+/Ca^{2+}$-exchanger [31], subsequently leading to an accumulation of intracellular $Ca^{2+}$-ions [32]. Whereas on the one hand, increased $Ca^{2+}$ is able to induce protein degradation by calpain mediated proteolysis and thus supporting atrophy formation [33], the disturbed ionic handling also increases the formation of reactive oxygen species (ROS) by increased activity of xanthine oxidase [34] and disturbances in mitochondrial function [35]. Since ROS-related metabolic stress has also shown to provoke upregulations of the FoxO3a signaling by the SAPK/JNK/MAPK pathway, tourniquet induced ischemia is able to affect muscle atrophy formation through various cascades [11,36].

Tourniquet release and the subsequent reperfusion of the former ligated limb are also associated with serious stressful physiological alterations in skeletal muscles, which can lead to the formation of severe muscle damage (I/R-injury). The extensive formation of ROS during ischemia is responsible for increased pro-inflammatory signaling in skeletal muscle which induces the expression of neo-antigens, adhesive proteins and pro-inflammatory cytokines [37]. The subsequent reperfusion enables the interaction of immune cells and the complement system with the stressed muscle tissue [38], leading to severe muscle damage through enhanced metabolic stress caused by migrated immune cells [39]. I/R-injury in skeletal muscles is also associated with a systemic tumor necrosis factor-alpha (TNF-α) response [40], illustrating the impact of the activated immune response and declaring the influence of I/R-stress on muscle atrophy formation, since TNF-α is a documented inductor of muscle atrophy signaling [41].

In summary, the application of tourniquets in TKA is associated with increased physiological alterations in skeletal muscle homeostasis during both ischemia and reperfusion. Reported physiological modifications in metabolic supply, ionic handling and interaction with immune cells are crucial triggers of postoperative muscle atrophy formation and are responsible for the development of rhabdomyolysis in TKA.

## TKA induced muscle atrophy and damage: intervention concepts

Several intervention concepts try to minimize tourniquet induced adverse effects in TKA through modifications in surgical (e.g. minimal invasive arthroplasty) [42] or even postoperative patient care (e.g. fast-track protocols) [43]. Additionally, also non-surgical intervention strategies were shown to be effective in counteracting TKA induced postoperative pain and enhancing patient's early recovery. In this regard, preoperative patient education [44], postoperative cryotherapy [45] and perioperative analgesia strategies [46] were reported being effective in reducing LOS, latter even in reducing patient's postoperative pain levels. Due to decreases in skeletal muscle mass and strength post-surgery [47], recent studies have tried to focus on modifications in skeletal muscle metabolism and its impact on early recovery in TKA. Dreyer and colleagues [25] were able to report less muscle atrophy after TKA through the intake of essential amino acids already pre- as well as postoperatively. Especially the post-operative intake of amino acids combined with physical therapy increases functional mobility post-TKA, suggesting that modifications in anabolic and catabolic signaling may have crucial impacts on maintaining muscle mass and early recovery.

Based on these findings, it seems reasonable to identify intervention strategies focusing the modification of skeletal muscle homeostasis to counteract or at least lower TKA induced muscle atrophy. Whereas modifications in nutrition are reported to reduce sarcopenia related muscle atrophy in older populations [48], physical exercises are additionally able to induce significant gains in muscle mass and functional ability [49]. Adapted to these findings, previous studies were able to report beneficial effects of specific physical therapies postoperatively on maintaining muscle mass and enhancements in early recovery [50]. Whereas these interventions focus the decrease of surgery induced alterations in skeletal muscle homeostasis postoperatively, another possibility is represented through exercises before the atrophy triggering surgery, to interfere directly with the corresponding signaling pathways. Supportive evidence for this concept is emerged by investigations in animal models, which were able to document that physical exercises before a chronic hind limb unloading experiment were able to decrease muscle atrophy [51,52]. Translating this theoretical construct of preparing the body through physical exercise in terms of surgical care is called "prehabilitation" [53]. To the best of the author's knowledge, only few studies have investigated the impact of prehabilitation specifically on postsurgical atrophy, reporting beneficial influence in maintaining muscle mass [54,55].

## Prehabilitation in medical care

Preconditioning of muscles, tendons and the surrounding soft tissue by specific exercises as a tool to prevent the onset of injuries is a well investigated field in sports medicine. Caraffe et al. [56] were able to show that a specific proprioceptive training prior to physical exercise reduces the amount of anterior cruciate ligament injuries in soccer players from 1.15 injuries per team to only 0.15 injuries per team per season. These results showed that a specific training prior to musculoskeletal stress can lead to adaptations in soft tissue, or in other words prepare the body for stressful events. Translated to internal surgical care, a prehabilitation program consisting of aerobic cycling and a strengthening protocol of bodyweight exercises a duration of four weeks was able to show functional improvements in patients undergoing scheduled colorectal surgery [57]. The patients showed improved subjective feeling and faster well-being after surgery which leads the responsible scientist to suggest prehabilitation as a meaningful preoperative program [58]. Furthermore, studies in animal models suggest that regular exercise is able to reduce the amount of I/R-injury and subsequent inflammatory response in infarct experiments [59] as well as myotoxic adverse effects of medications in oncology research by reducing the amount of metabolic stress and proteases activity [60]. Therefore, the magnitude of protective impacts induced through exercise seems to be extensive and multidirectional, indicating beneficial effects in various medical disciplines.

In context of orthopedic care and TKA, osteoarthritis regularly leads to a reduced mobility and disuse of the joint, which is often associated with skeletal muscle weakness [61] or even serve atrophy [62]. Former studies suggest that the most important predictive parameters concerning rehabilitation after surgery are preoperative strength, range of motion (ROM), flexibility, subjective pain and the ability to complete functional tasks, which are highly affected by preoperative immobility [53,63]. Therefore, exercise induced improvements in cardiovascular fitness, muscle, tendon and ligament strength as well as flexibility are likely to improve postoperative recovery.

Intervention studies in TKA patients revealed that subjects undergoing prehabilitation not only show better functional outcomes post-surgery, but also improved functional abilities and less pain prior to surgery [63,64]. These post-surgical outcomes even apply to patients admissioned to intensive care units as shown by Topp and colleagues [65]. A case report by Brown et al. [66] compared outcomes in a single patient undergoing TKA in both legs without prehabilitation measures on the right and with a four week prehabilitation by training prior to surgery on the left side. Each prehabilitation session consisted of resistance exercises with Thera-Bands and short-timed step training, followed by light static stretching. The patient showed much better postoperative results (e.g. lower pain, faster recovery, higher post-operative strength) on the left side than compared to the right side treated through clinical routine. The preoperative prehabilitation leads to greater strength in both legs and an enhanced recovery of the patient. It is noteworthy that exercising protocols in prehabilitation have to be adapted to the patient's individual functional capacity, caused by a reduced compliance in patients experiencing immobility and pain. Therefore, prehabilitation programs often combine a variation of step-training, (low) resistance training and flexibility exercises. For resistance training, studies have often used Thera-Bands [53,63,66] which can be considered as a relatively imprecise stress inductor in context of training strategy, periodization and scientific observation compared to usual exercise routines healthy subjects undergo to improve personal fitness. This leads to an uncertainty whether patients have used their full potential preoperatively or whether maybe intensities could have been raised during training. However, even these moderate exercises were able to improve patient's postoperative well-being and recovery.

Basically, the benefit of prehabilitation seems to depend on the preoperative duration and presumably the intensity of the training protocols as well [66]. Studies showed that prehabilitation periods of four to eight weeks before surgery are able to effectively increase strength and functional abilities in patients suffering from OA [67]. Due to decreased functional ability and increased pain, studies don't extend the duration of prehabilitation periods or use more intense training methods, even though research suggest that prehabilitation measures should be taken as long as possible beforehand and that with increased exercise levels, recovery processes would be faster to achieve [66].

Whereas most prehabilitation strategies so far focused on mechanically-based strength training, evidences suggest that metabolic stimuli are also able to counteract skeletal muscle atrophy. Kubota and colleagues [68] were able to report that the application of short, intermittent tourniquet-induced ischemic periods twice a day were able to reduce muscle atrophy in an immobilization induced atrophy model. Similar findings were reported in patients after anterior cruciate ligament reconstruction, where vascular occlusion periods were able to significantly reduce muscle atrophy [69]. Therefore, based on the interference effect of metabolic stress in muscle atrophy signaling and in context of patient's preoperatively functional abilities, a shift in prehabilitation exercise type from a primary mechanical resistance to a rather metabolically challenging exercise or even the combination of both seems promising.

## Blood flow restriction training: mechanical load with a metabolic component

Several studies in the field of sport science investigated the effects of training under blood-flow-restriction (BFR-training) [70,71]. BFR describes a concept introduced by Dr. Yoshiaki Sato that achieves muscular hypertrophy through low-resistance training (LI) combined with a suppression of venous blood flow in an extremity [72]. According to annual guidelines of the *American College of Sports Medicine* (ACSM) muscular hypertrophy can only be achieved when using a minimum of at least 70–80% of the individuals one repetition maximum (1RM) (ACSM 2009). However, training with BFR has shown to induce a comparable muscle hypertrophy at around 20–30% 1RM which corresponds to the intensity of so called 'daily living tasks' [73].

The pressure needed to block venous blood flow in the extremities is applied via a conventional tourniquet commonly used during TKA and is sonographically determined in relation to the occlusion pressure (e.g. 60% of the occlusion pressure) [74]. Numerous scientific papers have focused on the underlying mechanisms behind named muscle adaptions following reduced blood flow in the past [73]. Previous studies were able to show an increased release of growth hormone (GH) [75] and insulin-like-growth-factor 1 (IGF1) [76] after BFR-training. Furthermore, GH serum concentrations were significantly greater in subjects undergoing a low resistance training with BFR in comparison to subjects undergoing a high resistance training (~80% 1RM) without BFR [75]. Therefore, in context of prehabilitation, BFR may allow patients unable to go through high-resistance exercise because of massive pain caused by advanced joint degeneration to switch from a mechanically to a metabolically stress [77] and thereby inducing favorable muscle adaptations preoperatively.

## The hypothesis: BFR induced interference effects in TKA induced muscle atrophy

Clinical studies revealed that susceptible factors like muscle volume, muscle strength, flexibility and functional ability are crucial preoperative predictors for a successful early recovery in TKA patients. Due to the reduced mobility and increased subjective knee pain, patients would experiences advantage using BFR in association with LI exercises to prepare themselves prior to surgery. Abe and colleagues [78] were able to report that BFR in association with aerobic walking was able to enhance muscle size, strength and functional ability in elderly men and women. Similar results were obtained in patients with chronic quadriceps and hamstring weakness through BFR with LI exercises [79]. In context of applicability of BFR in elderly populations, Yasuda et al. [71] were able to document that next to enhancements in muscle size and strength, BFR training did not negatively affect arterial stiffness in older adults. In contrast, studies suggest that BFR training improved vascular endothelial function and peripheral blood circulation in older populations [80]. Additionally, a study by Pinto et al. [81] investigated the effects of BFR training in elderly hypertensive women and reported similar hemodynamic and cardiovascular responses as observed during traditional high-intensity resistance training. They also concluded that based on these similar results between groups, BFR training could be a more practicable training method in this particular patient population. Based on these findings, prehabilitation with BFR trainings seems to be a safe training strategy for elderly patients, offering significant adaptation potential in muscle strength and increases in functional ability by simultaneous improved feasibility through application of less mechanical impact.

Whereas these outcomes indicate potential benefits through BFR prehabilitation on postoperative rehabilitation in TKA patients, BFR may additionally have the ability to interfere directly with subsequent tourniquet induced atrophy signaling. The documented elevated levels of GH and IGF-1 through BFR [75,76] suggest an increased activation of Akt by subsequently increased mTORC1 signaling, providing muscle hypertrophy through increased protein synthesis [70,82]. Besides the supportive effect on muscle hypertrophy in patients preoperatively, the long-term enhancements in GH and IGF-1 concentrations [83] and the associated long-lasting upregulation in Akt activity could be able to interfere with the reviewed muscle atrophy cascade perioperatively. The increased induction of IGF1/PI3K/Akt signaling may be able to counteract the tourniquet induced atrophy pathway by suppression of FOXO transcription factors [84]. Additionally, studies were also able to show a significant supportive influence of increased IGF1 levels on the regeneration of skeletal muscle tissue after muscle stress or damage [85], suggesting that postoperative rehabilitation could be benefited as well (Fig. 1).

Furthermore, supposedly by the formation of greater metabolic perturbation (e.g. increased lactate and adenosine metabolites concentrations), BFR training is characterized by increased activation of AMP-activated protein kinase (AMPK) and subsequently increased expression of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) [86,87], which as transcriptional coactivator acts as a regulator of mitochondrial biogenesis [88]. Increased PGC-1α activity is usually reported after endurance exercises and causes elevations in mitochondrial enzyme content with the additional ability to support a fiber type switch to aerobic slow-twitch fibers in muscle tissue [89]. Patients undergoing BFR prehabilitation could benefit twice through these physiological adaptations. First, it is reported that muscle damage during I/R-events mostly affects glycolytic fast-twitch muscle fibers, supposedly due to the lower mitochondrial content in comparison to oxidative slow twitch fibers [90]. A shift in fiber type towards increased oxidative capacity may act supportive in fibers experiencing I/R-stress by reducing the impact of impaired ionic handling, leading to less muscle damage in TKA. Furthermore, it is also assumable that regular adherence to BFR sessions and exposure to its associated metabolic stress, may induce significant modifications in antioxidative capacity [91] and peripheral immune response [92]. This would enable an improved counteraction against tourniquet induced metabolic stress. Supporting evidence for this hypothesis is emerged by findings reporting that metabolic stress is associated with an increased long-term expression rate of target genes of the transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) (e.g. glutathione, MnSOD, catalase) [86]. Whereas this adaptation would support the antioxidative defense system against tourniquet induced metabolic stress in TKA patients, Nrf2 seems to have the additional ability to interfere with pro-inflammatory signaling (e.g. NF-κB) [93], indicating its influence on peripheral immune response in I/R-induced skeletal muscle damage [94] and possibly after TKA as well [95]. Secondly, PGC-1α overexpression in transgenic mice was shown to decrease muscle atrophy by associated reduced induction of FoxO3 target genes [96]. Therefore, several physiological adaptations could be induced by BFR prehabilitation, providing improved handling of surgery induced physiological alterations as well as interference effects concerning subsequently induced muscle atrophy.

## Conclusion

Several studies indicate that the use of pneumatic tourniquets in TKA is related to different side effects, such as muscle atrophy or

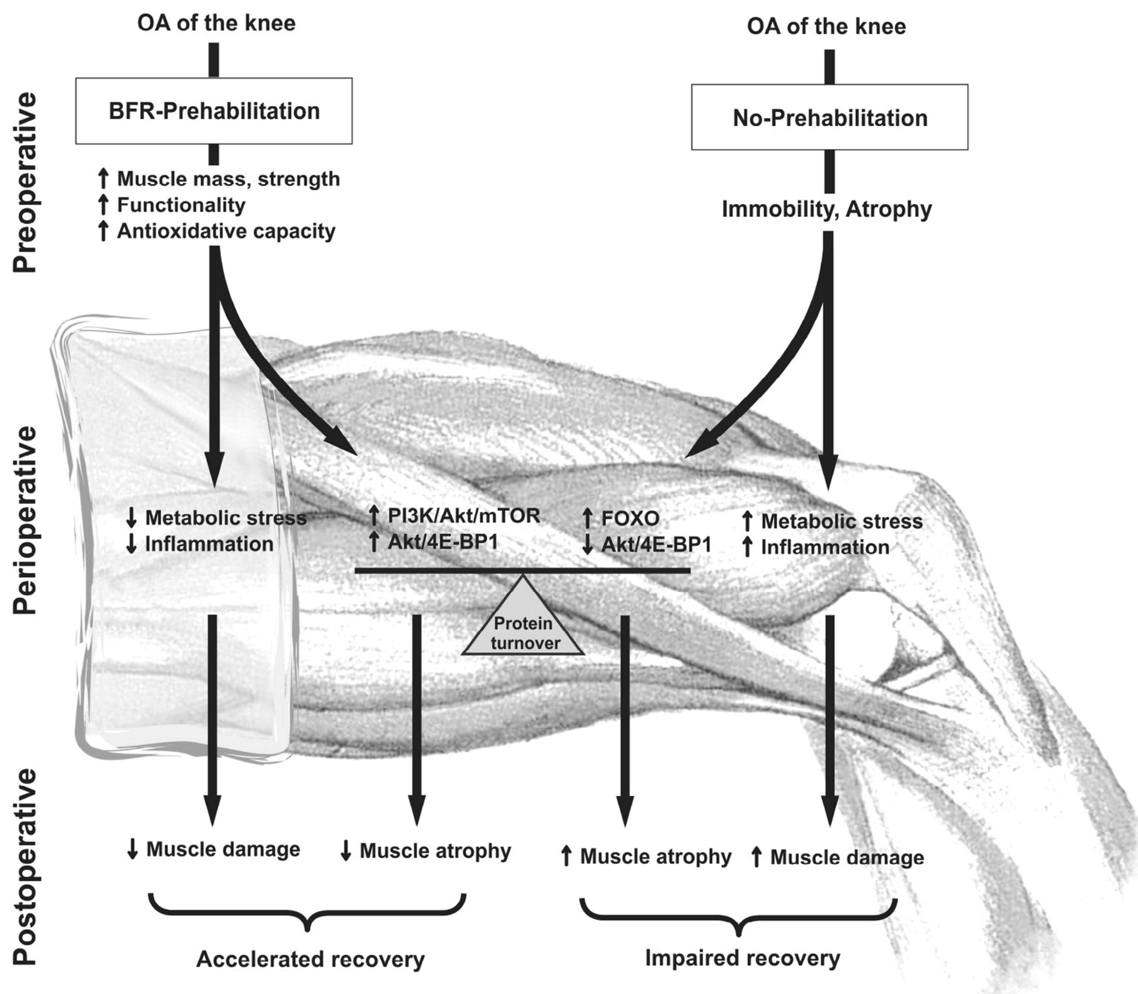


**Fig. 1.** Potential impact of BFR training as prehabilitation concept in comparison with TKA outcomes without prehabilitation intervention.

rhabdomyolysis. These potential adverse effects influence the postoperative recovery and are additionally responsible for increased medical costs. Based on the predicted rising amount of TKA surgeries, it is necessary to identify intervention strategies to reduce named postoperative adverse effects. Whereas the supportive impact of exercise prehabilitation has been shown, strength training techniques are not always practical due to high mechanical loads. Through the shift from a mechanically to a more metabolically challenging exercise regime, BFR training appears to be a promising prehabilitation strategy. Due to potential gains in muscle mass and strength preoperatively in association with reviewed molecular adaptations, BFR has the potential to counteract TKA side effects and thereby reducing LOS and altering patients' postoperative subjective feeling. Future studies should focus the application of BFR or comparable training strategies to enable patients' individual exercise training concepts in order to prepare the body for different medical interventions.

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# Impact of a Six-Week Prehabilitation With Blood-Flow Restriction Training on Pre- and Postoperative Skeletal Muscle Mass and Strength in Patients Receiving Primary Total Knee Arthroplasty

*Alexander Franz*[1,2]*, *Sanghyeon Ji*[3], *Bernd Bittersohl*[4], *Christoph Zilkens*[4] and *Michael Behringer*[5]

[1]*Department of Orthopedics and Trauma Surgery, University Hospital Bonn, Bonn, Germany,* [2]*Department of Adult Reconstruction, ATOS Orthoparc Clinic Cologne, Cologne, Germany,* [3]*Department of Exercise Physiology, Institute of Exercise Training and Sport Informatics, German Sport University Cologne, Cologne, Germany,* [4]*Department of Orthopedics and Trauma Surgery, University Hospital Duesseldorf, Duesseldorf, Germany,* [5]*Department of Sports Medicine and Exercise Physiology, Goethe University Frankfurt, Frankfurt, Germany*

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*Gregory C. Bogdanis, National and Kapodistrian University of Athens, Greece*

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***Correspondence:**
*Alexander Franz*
*alexander.franz@ukbonn.de*

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**Introduction:** Total Knee Arthroplasty (TKA) is one of the most successful interventions in gonarthrosis, however the operation is leading to muscle atrophy and long-term muscular deficits. To enhance rehabilitation after TKA, exercise programs try to improve muscle function preoperatively, called prehabilitation. Blood-Flow-Restriction Exercises (BFRE) is a training method which is characterized by using tourniquets to reduce arterial and occlude venous blood flow simultaneously during the exercise to increase metabolic stress. The present study aimed to evaluate the effects of a 6-week prehabilitation with BFR on pre- and postoperative muscle mass, strength, and quality of life (QoL).

**Methods:** 30 patients with end-stage gonarthrosis participated in this study. Patients were randomized into one of three groups: 1) Control-Group (CON): Standard clinical approach without prehabilitation. 2) Active-Control-Group (AC): Participation in a prehabilitation with sham-BFR. 3) BFR-Group (BFR): Participation in a prehabilitation with BFR. The prehabilitation protocol consist of a cycling-ergometer-based training performed twice per week over 6 weeks. During exercise, BFR was applied periodically three times per leg with a pressure of 40% of the individual-limb-occlusion-pressure. Measurement time points were six- (baseline), 3-weeks and 5-days before the surgery (Pre-OP), as well as three- and 6-months postoperatively. Outcome measures were muscular strength of the thigh muscles, thigh circumference as well as QoL and functional activity, examined by 6-min walking- and chair rising test.

**Results:** Both training groups indicated significantly improved leg muscle strength following the prehabilitation period with a superior effect for the BFR-group (BFR: ~170% vs. AC: ~91%, $p < 0.05$). No significant changes in leg strength occurred in the CON (~3%, $p = 0.100$). Further, patients in BFR-group indicated significantly improved skeletal muscle mass assessed by femoral circumference following prehabilitation period (~7%, $p < 0.05$), while no significant changes occurred in the CON (−1.14%, $p = 0.131$) and AC-group (~3%, $p = 0.078$). At 3-months Post-OP, the CON and BFR-group revealed a significant decrease in femoral circumference compared to the Pre-OP (CON: ~3%, BFR: ~4%; $p < 0.05$), but BFR-group remained above the baseline level (~3%, $p < 0.05$). No significant change in femoral circumference was found for AC-group (~2%, $p = 0.078$). In addition, the prehabilitation with BFR provided notably improved Knee Injury and Osteoarthritis Outcome Scores (KOOS) especially in pain perception with significant higher effect compared to other groups (CON: −2%, AC: 13%, BFR: 41%; $p < 0.05$). In long-term rehabilitation after 6-months, all groups showed significantly improved KOOS scores in all dimensions (CON: ~110%, AC: ~132%, BFR: ~225%; $p < 0.01$), and functional examinations (CON: ~26%, AC: ~16%, BFR: ~53%; $p < 0.01$).

**Conclusion:** The present findings show that BFR-prehabilitation induce significant improvements in muscle function and QoL before TKA surgery. In addition, the supporting effect of prehabilitation on postoperative regeneration and QoL should be highlighted, illustrating prolonged beneficial effects of BFR on muscular and functional performance in a “better in, better out”-manner.

**Keywords: venous occlusion, kaatsu training, muscle atrophy, rehabilitation, exercise therapy**

## INTRODUCTION

Total Knee Arthroplasty (TKA) is one of the most popular and successful interventions in gonarthrosis leading to significant improvements in subjective pain and quality of life (QoL) (Vos et al., 2012). However, knee osteoarthritis (OA) as well as surgical therapy have adverse effects on skeletal muscle mass and strength (Franz et al., 2019). Predominantly due to pain-related reductions in mobility and exercise, patients receiving TKA are characterized by reduced muscular function preoperatively (Dreyer et al., 2013). Although postoperative rehabilitation shows a significant impact on patient mobility and QoL, recent meta-analyses show that TKA patients are affected by persistent muscle weakness and atrophy for several years (LaStayo et al., 2009; Thomas and Stevens-Lapsley, 2012).

Since physical patient characteristics like muscle mass, strength and functionality can be seen as positive predicate outcomes parameters for a successful rehabilitation (Mizner RL. et al., 2005; Devasenapathy et al., 2019), several studies try to support rehabilitation after TKA by improving muscle function already preoperatively through exercise, called prehabilitation. Unfortunately, common training techniques cannot provide an adequate stimulus for muscular adaptations without provoking increased pain (Juhl et al., 2014). Consequently, the current impact of available prehabilitation concepts is rated as only slight to moderate (Wang et al., 2016; Moyer et al., 2017).

Blood-Flow-Restriction Exercises (BFRE) are a new training method that is characterized by the use of specialized tourniquets to restrict venous and reduce arterial blood flow during the exercise in the working limb to increase metabolic stress. Since BFRE can gain significant effects on muscle mass and strength by using only low mechanical loads (Ferraz et al., 2018; Franz et al., 2020) its application in patients with degenerative joint diseases could be able to improve the applicability and effectiveness of prehabilitation concepts (Franz et al., 2018; Žargi et al., 2018; Kacin et al., 2021).

Therefore, the present study aimed to assess the impact of a 6-week prehabilitation protocol with BFRE on pre- and postoperative muscle mass, strength, functionality and subjective pain perception in patients receiving an elective primary TKA.

## METHODS

### Subjects

30 patients suffering from end-stage gonarthrosis (male = 18, female = 12, age = 63.5 ± 8.1 y, height = 176.4 ± 7.2 cm, weight = 86.9 ± 16.1 kg) participated in this study. Patients were randomly assigned into one of three groups: 1) Control-Group (CON): This group followed the standard clinical treatment without a specialized prehabilitation protocol. 2) Active-Control-Group (AC): The second group followed the standard clinical treatment and participated in a 6-week prehabilitation protocol with a sham-BFR application. 3) BFR-Group (BFR): The third group followed the standard clinical treatment and participated in a 6-week prehabilitation protocol with additional BFR application. The standard clinical treatment consists of the surgery and 7 days of hospitalization with daily physical therapy, which was followed by 3 weeks of inpatient rehabilitation.

### Study Design

The study design consists of a prospective, single blinded, parallel study design to determine the influence of

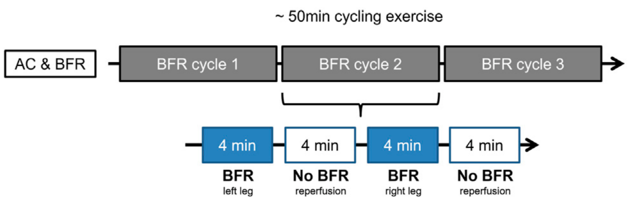


**FIGURE 1 |** Example of prehabilitation week four for AC- and BFR-group. The 50-min ergometer exercise is divided into three cycles. Each cycle consists of the application of the BFR stimulus to both legs in alternation, followed by a rest. As shown here, the left leg is loaded with BFR first (for 4 minutes in week four), followed by a rest of 4 min. This is followed by BFR application to the right leg with a subsequent break. This cycle is repeated a total of three times.

prehabilitation on pre- and postoperative skeletal muscle mass and strength. While the CON underwent routine clinical practice without prehabilitation, the other groups completed an identical 6-week prehabilitation protocol, one with additional BFRE (BFR-Group) and one with a sham-BFR application (AC-Group) before TKA, to reduce a potential bias in expectations of the intervention effect between groups. Preliminary visits were conducted before the start of the study to familiarize the patients with the cycling ergometer, testing protocols and tourniquet pressures.

Measurement time points were 6 weeks- (baseline), 3 weeks- (3w-Prehab) and 5 days before surgery (Pre-OP), as well as 3- (3m-Post-OP) and 6-months (6m-Post-OP) postoperatively.

### Prehabilitation

The prehabilitation protocol consist of a cycling ergometer-based training protocol performed twice per week for about 50 min with an individualized intensity. Ergometer intensity was determined based on a calculated exercise heart rate (EHR) (Mangione et al., 1999).

For determination of EHR, maximal heart rate [HR (max) = 220—Age) and heart rate reserve (HRR = HR (max)—HR (rest)] of each participant was calculated. Subsequently, the EHR was determined by the following calculation model:

$$EHR = HR(rest) + (HRR\,x\,0.5)$$

The load in watts matching the calculated EHR was determined during an incremental step test on the cycling ergometer. The test person starts at an intensity of 20 W (W) on the cycling ergometer, which was increased by 20 W every 3 minutes. Vital signs such as blood pressure (RR) and HR are determined at the beginning and end of each stage. As soon as the test person has reached the calculated EHR, the test was finished.

The additional BFRE protocol was applied during the cycling exercise on both lower limbs periodically three times per leg for a duration of 1 min (first week) to 6 min (sixth week). While the AC group performed a sham-BFR exercise with a fixed value of 20 mmHg, the BFR-group was loaded with 40% of the individual limb occlusion pressure (LOP; right = 88.27 ± 8.46 mmHg, left = 87.32 ± 7.39 mmHg) (**Figure 1**).

To determine the LOP, the inflatable tourniquets of 11.5 cm width were placed proximal at the exercising legs before the training session (PBFR, Delfi medical Inc., Vancouver, Canada). After a 10-min rest period, LOP was determined sonographically in a lying position by displaying the femoral artery with an ultrasound device and using a Doppler to assess the blood flow within the vessel. Subsequently, the cuff was infiated until no further blood flow was detectable. This pressure was defined as the individual LOP.

### Outcomes Measures

The examination battery consisted of general vital and anthropometric data, muscular function parameters, functional examinations, and questionnaire-based data collection.

## Vital- and Anthropometric Data

At each time point, vital parameters like blood pressure (RR) and heart rate (HR) were recorded. Anthropometric data consist of recording body weight (BW), body height (BH) as well as the circumference of both thighs and calves for estimation of skeletal muscle mass of the lower extremities. To visualize the femoral circumference an anatomic reference line was drawn between the spina iliaca anterior superior and the margo superior patella. At 50% (FC-50) length of this reference line, the femoral circumference of both legs was determined. The calf circumference was determined after multiple measurements at the largest diameter. The measurement was performed three times at all points and the mean value was determined. Furthermore, the circumference of both knees was recorded to illustrate swelling pre- and postoperative. Measurement points were above the margo superior patellae, in the middle of the patella as well as above the apex patellae.

## Muscular Strength

Muscular function in this study was analyzed by a unilateral six-repetition maximum test (6RM) of the leg-extension and leg-curl machine (Paoli et al., 2013). Following a warmup, a maximum of five trials separated by 5 min of recovery was allowed to obtain a true 6RM. With an accuracy of 1.00 kg, the highest load that the subject was able to lift six times to a knee extension of approximately zero degrees was accepted as 6RM.

## Assessment of Function

The functionality of the participating patients was determined by active knee joint mobility (range of motion, ROM) as well as the chair-rising- (CRT) and 6-min walking test (6MWT). The ROM of the knee joint was determined in the supine position. A goniometer was used to measure the active extension and flexion of the knee joint (Bade et al., 2014). In CRT, the subject sits on an ordinary chair without armrests. With arms crossed on the chest, the test person performs as many stand-up and sit-down movements as he or she can manage within 30 s (Gill and McBurney, 2008). A complete repetition was then scored after the test person was in full extension while standing, as well as with a leaning back in a sitting position. The 6MWT is used to estimate and monitor cardiovascular and

**TABLE 1 |** Patient characteristics and surgical data for each group.

| | CON (*N* = 10) | BFR (*N* = 10) | AC (*N* = 10) | One-way ANOVA ($p/\eta_p^2$) |
|---|---|---|---|---|
| Operated limb | Left: 4/Right: 6 | Left: 9/Right: 1 | Left: 4/Right: 6 | - |
| Sex | Male: 6/Female: 4 | Male: 7/Female: 3 | Male: 7/Female: 3 | - |
| Age (yr) | 66.3 (7.1) | 61.5 (8.8) | 64.2 (7.7) | 0.410/0.064 |
| Height (cm) | 175.4 (8.8) | 178.4 (7.2) | 175.3 (5.5) | 0.565/0.041 |
| Body weight (kg) | 90.3 (17.5) | 85.3 (15.3) | 85.1 (16.5) | 0.713/0.025 |
| Blood pressure (mmHg) | | | | |
| Systolic | 129.9 (10.1) | 127.5 (5.9) | 124.7 (7.9) | 0.629/0.034 |
| Diastolic | 81.7 (6.9) | 81.5 (7.1) | 80.8 (4.4) | 0.448/0.058 |
| Rest heart rate (bpm) | 73.7 (7.2) | 66.7 (6.9) | 69.8 (7.6) | 0.114/0.148 |
| Duration of surgery (min) | 111.7 (14.4) | 112.3 (14.4) | 109.6 (16.4) | 0.916/0.006 |
| Blood loss during surgery (mL) | 174.0 (63.5) | 185.0 (65.4) | 168.0 (55.7) | 0.824/0.014 |

*Data are provided as mean (standard deviation). CON, control group; BFR, BFR-training group; AC, active control group.*

pulmonary performance below the anaerobic threshold. Participating patients walk for 6 minutes along a 20 m walkway. The goal for the patient is to complete as much distance as possible in the given time window. Individual pace changes and pauses are allowed. After 6 minutes, the time is stopped, and the walking distance is written down in meters.

## Patient Self-Assessment Tools

To assess the subjectively experienced functional status, pain perception and quality of life of the patients, the Knee Injury and Osteoarthritis Outcome Score (KOOS) was used. KOOS contents of 42 questions in five different dimensions: Symptoms (seven questions), pain (nine questions), activities of daily living (17 questions), functionality in sports and recovery (five questions) and quality of life-related to the affected knee (four questions).

## Statistics

Statistical analyses were performed using SPSS (SPSS, v.27, Chicago, IL, United States). Normal distribution and homogeneity of variance were verified using Shapiro-Wilk and Levene's Test, respectively. Potential group differences in baseline and surgical data (i.e., age, height, body weight, duration of surgery, etc.) were assessed using one-way ANOVAs. To compare the changes in measures over time among groups, two-way repeated-measures ANOVAs (rANOVAs; time x group) were performed. In case of significant time × group interactions, separate one-way repeated measures ANOVAs were used to analyze the simple main effects for time within each group. The mean differences between groups (i.e., simple main effects for group) within each time point were assessed using separate one-way ANOVAs. If the main effects for time or group were detectable, *post hoc*-tests with Bonferroni correction were performed to check which factor levels differ significantly from one another. For the interaction and main effects, the partial eta squared $\eta_p^2$ was calculated as effect strength measure and interpreted as follows (Cohen, 1988): a $\eta_p^2 \geq 0.01$: small effect, ≥ 0.06: medium effect, and ≥0.14: large effect. For all results, an alpha level of 0.05 was interpreted as statistically significant. To reduce investigator bias, data analysis was blinded to the evaluating researchers.

# RESULTS

**Table 1** presents the baseline and surgical data for each group. At baseline, there were no significant differences regarding their demographic data. In addition, the mean duration of surgery and blood loss during surgery did not differ among all groups.

## Exercise Intensity and Physiological Responses During Prehabilitation

**Table 2** summarizes the training data during phase 1 (session 1–6) and 2 (session 7–12) of the prehabilitation including exercise intensity, mean HR and RR during training and individual LOP measured before training. All patients in the training groups completed all planned training sessions during the 6-weeks prehabilitation period. The current study documented a dropout rate of 0% and no exercise or BFR-related adverse events. For exercise intensity, there were a significant time × group interaction ($p < 0.001$, $\eta_p^2 = 0.599$) and time effect (BFR-group: $p < 0.001$, $\eta_p^2 = 0.902$; AC-group: $p < 0.001$, $\eta_p^2 = 0.900$). *Post hoc*-tests revealed that the training intensity in both training groups significantly increased during the 2. phase of prehabilitation. No statistically noticeable changes in physiological measures during the training period were detected in any group (**Table 2**).

## Estimation for Skeletal Muscle Mass of the Lower Extremities

**Table 3** summarizes the femoral- and calf-circumference of both operated- (OP) and non-operated (NonOP) legs and their percent difference during the prehabilitation- and post-operative-period. Significant time × group interaction effects were indicated for all measured femoral circumference values ($p < 0.001$, $0.350 < \eta p2 < 0.494$). Further analyses revealed significant time effects in the BFR-group ($p < 0.001$, $0.674 < \eta_p^2 < 0.754$) and CON ($p \leq 0.001$, $0.627 < \eta_p^2 < 0.728$). The AC-group did not indicate any time effects ($p \geq 0.078$, $0.178 < \eta_p^2 < 0.262$). For the calf circumference, no changes were detected in any group despite of the significant interaction effect ($p = 0.018$, $\eta_p^2 = 0.205$) and main time effect in CON for the NonOP leg ($p = 0.013$, $\eta_p^2 = 0.426$). Post hoc-tests revealed

**TABLE 2 |** Measures related to training during the 6-weeks prehabilitation period of both training groups.

| | BFR ($N$ = 10) | AC ($N$ = 10) | One-way ANOVA/rANOVA ($p/\eta_p^2$) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Time | | Group | | Time x group |
| | | | BFR | AC | Phase 1 | Phase 2 | |
| Exercise intensity (W) | | | | | | | |
| Phase 1 (session 1–6) | 62.5 (17.5) | 69.0 (17.5) | <0.001/0.902 | <0.001/0.900 | 0.417/0.037 | 0.474/0.029 | <0.001/0.599 |
| Phase 2 (session 7–12) | 81.8 (15.2)* | 76.5 (15.2)* | | | | | |
| Mean heart rate during training (bpm) | | | | | | | |
| Phase 1 (session 1–6) | 106 (10) | 103 (10) | 0.542/0.021 | | 0.350/0.049 | | 0.452/0.032 |
| Phase 2 (session 7–12) | 108 (11) | 103 (11) | | | | | |
| Mean blood pressure during training (mmHg) | | | | | | | |
| Systolic | | | | | | | |
| Phase 1 (session 1–6) | 143.0 (9.7) | 135.9 (9.7) | 0.015/0.288 | | 0.053/0.192 | | 0.209/0.086 |
| Phase 2 (session 7–12) | 147.2 (9.7) | 137.4 (9.7) | | | | | |
| Diastolic | | | | | | | |
| Phase 1 (session 1–6) | 82.5 (7.8) | 81.4 (7.8) | 0.040/0.214 | | 0.723/0.007 | | 0.890/0.001 |
| Phase 2 (session 7–12) | 84.3 (7.9) | 83.1 (7.9) | | | | | |
| LOP-Left (mmHg) | | | | | | | |
| Phase 1 (session 1–6) | 226 (14) | 228 (14) | 0.072/0.169 | | 0.246/0.074 | | 0.100/0.143 |
| Phase 2 (session 7–12) | 217 (11) | 228 (11) | | | | | |
| LOP-Right (mmHg) | | | | | | | |
| Phase 1 (session 1–6) | 228 (13) | 229 (13) | 0.024/0.254 | | 0.389/0.042 | | 0.075/0.166 |
| Phase 2 (session 7–12) | 220 (14) | 228 (14) | | | | | |

*Data are provided as mean (standard deviation). BFR, BFR-training group; AC, active control group; LOP, individual limb occlusion pressure; rANOVA, repeated-measures analysis of variance. *p < 0.05, significantly different to phase 1*

that the femoral circumference of both legs significantly increased in the BFR-group already at 3w-Prehab ($p$ = 0.002). In addition, the BFR-group showed a further improvement in the femoral circumference of the OP leg after the prehabilitation period ($p$ = 0.006). The CON did not indicate any changes in the femoral circumference during and after the prehabilitation period ($p$ = 0.131). At 3m-Post-OP, both CON and BFR-group showed significantly decreased femoral circumference of both legs compared to the Pre-OP-level ($p \leq 0.017$), but the BFR-group still remained above the baseline level ($p$ = 0.023). At 6m-Post-OP, all femoral circumference in the BFR-group increased again ($p \leq 0.030$) with significantly higher values compared to the baseline level ($p < 0.001$). In contrast, the CON demonstrated significantly reduced femoral circumference of both legs at 6m-Post-OP with significantly lower values compared to the pre-operative level ($p \leq 0.05$).

Regarding the percent difference between the OP and NonOP leg, significant time × group interaction effects were observed for the femoral circumference ($p$ = 0.014, $\eta_p^2$ = 0.186), while for the calf circumference, there were no significant main or interaction effects (**Table 3**). Further analyses on percent difference in the femoral circumference revealed a significant time effect only for the CON ($p$ = 0.002, $\eta_p^2$ = 0.469) and a significant group effect at the baseline ($p$ = 0.037, $\eta_p^2$ = 0.217). Despite the absence of the significant time effects, both training groups indicated a decreased percent difference in the femoral circumference between both legs following the prehabilitation, which increased again during the post-operative period but not beyond the baseline level (**Table 3**). In contrast, the percent difference in the femoral circumference between both legs in the CON continually increased during the postoperative study period. It was higher at 6m-Post-OP than the baseline level ($p$ = 0.013).

## Knee Swelling Measurements

The knee circumference measured at three different places of both OP and NonOP legs during the prehabilitation- and postoperative-period are presented in **Table 4**. Regarding the knee circumference, we found no time × group interaction effects ($p$ > 0.059, 0.060 < $\eta_p^2$ < 0.164) except for the upper knee circumference of the Non-OP leg ($p$ = 0.010, $\eta_p^2$ = 0.213), which indicated no further time or group effects (**Table 4**).

Further analyses revealed a significant time effect only for the lower knee circumference of the OP leg ($p$ = 0.017, $\eta_p^2$ = 0.072), indicating that knee circumference increased at 3m-Post-OP and returned to baseline level at 6m-Post-OP.

Regarding the knee swelling accessed by the percent difference between OP and NonOP knee, a significant time × group interaction effect was found only for upper knee ($p$ = 0.049, $\eta_p^2$ = 0.172). For the swelling measured at middle knee, we found a significant group effect ($p$ = 0.046, $\eta_p^2$ = 0.211) indicating lower values in the BFR-group compared to other groups. For lower knee, found a significant time effect ($p$ < 0.001, $\eta_p^2$ = 0.373) with a continually decreased swelling during the prehabilitation period, which increased at 3m-Post-OP and returned to baseline level at 6m-Post-OP.

Further analyses for the swelling measured at upper knee detected significant time effect only in the CON ($p$ = 0.017, $\eta_p^2$ = 0.445). In addition, there were significant group effects at baseline ($p$ < 0.012, $\eta_p^2$ = 0.280) and 3m-Post-OP ($p$ < 0.049, $\eta_p^2$ = 0.200). At baseline, the upper knee swelling was significantly higher in the AC-group that the CON ($p$ = 0.043), while the BFR-group did not differ to other groups ($p \geq 0.093$). The CON demonstrated a

**TABLE 3 |** Measures related to skeletal muscle mass of the lower extremities during the prehabilitation- and post-operative period.

| | CON (*N* = 10) | BFR (*N* = 10) | AC (*N* = 10) | One-way ANOVA/rANOVA ($p/\eta_p^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Time | | | Group | | | | | Time x group |
| | | | | CON | BFR | AC | Baseline | 3w-Prehab | Pre-OP | 3m-Post-OP | 6m-Post-OP | |
| Femoral circumference OP (cm) | | | | | | | | | | | | |
| Baseline | 58.2 (7.4) | 53.2 (4.2) | 52.0 (7.3) | <0.001/0.728 | <0.001/0.754 | 0.078/0.266 | 0.092/0.162 | 0.224/0.105 | 0.331/0.079 | 0.524/0.047 | 0.592/0.038 | <0.001/0.494 |
| 3w-Prehab | 57.7 (7.5) | 55.6 (4.6)[a] | 52.5 (7.2) | | | | | | | | | |
| Pre-OP | 57.6 (7.6) | 57.0 (5.2) [ab] | 53.4 (7.1) | | | | | | | | | |
| 3m-Post-OP | 55.9 (7.1) [abc] | 55.0 (3.9) [ac] | 52.8 (6.9) | | | | | | | | | |
| 6m-Post-OP | 55.5 (7.6) [abc] | 56.6 (4.0) [ad] | 53.7 (6.4) | | | | | | | | | |
| Femoral circumference NonOP (cm) | | | | | | | | | | | | |
| Baseline | 58.5 (7.2) | 55.0 (4.0) | 53.6 (7.3) | 0.001/0.627 | <0.001/0.674 | 0.192/0.178 | 0.229/0.103 | 0.311/0.083 | 0.365/0.072 | 0.502/0.050 | 0.510/0.049 | <0.001/0.350 |
| 3w-Prehab | 58.5 (7.2) | 56.8 (4.4)[a] | 54.0 (7.4) | | | | | | | | | |
| Pre-OP | 58.5 (7.2) | 57.6 (4.5)[a] | 54.5 (7.3) | | | | | | | | | |
| 3m-Post-OP | 57.2 (7.2) [abc] | 56.9 (4.3)[a] | 54.2 (6.7) | | | | | | | | | |
| 6m-Post-OP | 57.4 (7.2) [abc] | 58.0 (4.3) [ad] | 55.0 (6.7) | | | | | | | | | |
| %Difference in femoral circumference NonOP - OP | | | | | | | | | | | | |
| Baseline | -0.49 (3.24) | -3.44 (1.48)[e] | -3.09 (2.85) | 0.002/0.469 | 0.059/0.254 | 0.271/0.135 | 0.037/0.217 | 0.523/0.047 | 0.802/0.016 | 0.748/0.021 | 0.654/0.031 | 0.014/0.186 |
| 3w-Prehab | -1.43 (3.54) | -2.29 (0.94) | -2.86 (3.16) | | | | | | | | | |
| Pre-OP | -1.64 (3.73) | -1.15 (2.74) | -2.11 (3.17) | | | | | | | | | |
| 3m-Post-OP | -2.27 (4.18) | -3.44 (2.71) | -2.67 (3.44) | | | | | | | | | |
| 6m-Post-OP | -3.44 (3.50)[a] | -2.54 (2.61) | -2.24 (2.80) | | | | | | | | | |
| Calf circumference OP (cm) | | | | | | | | | | | | |
| Baseline | 39.2 (3.5) | 38.3 (3.9) | 36.7 (2.7) | | 0.682/0.014 | | | | 0.054/0.201 | | | 0.412/0.072 |
| 3w-Prehab | 39.2 (3.5) | 38.8 (3.6) | 36.8 (2.7) | | | | | | | | | |
| Pre-OP | 39.2 (3.5) | 38.8 (3.7) | 37.0 (2.7) | | | | | | | | | |
| 3m-Post-OP | 38.7 (3.8) | 38.9 (3.8) | 36.7 (2.7) | | | | | | | | | |
| 6m-Post-OP | 38.9 (4.0) | 39.1 (3.4) | 37.1 (2.7) | | | | | | | | | |
| Calf circumference NonOP (cm) | | | | | | | | | | | | |
| Baseline | 40.2 (3.5) | 39.2 (3.4) | 37.9 (3.4) | 0.013/0.426 | 0.502/0.053 | 0.202/0.169 | 0.333/0.078 | 0.366/0.072 | 0.476/0.054 | 0.549/0.043 | 0.524/0.047 | 0.018/0.205 |
| 3w-Prehab | 40.2 (3.5) | 39.3 (3.4) | 38.0 (3.4) | | | | | | | | | |
| Pre-OP | 40.2 (3.5) | 39.4 (3.5) | 38.3 (3.4) | | | | | | | | | |
| 3m-Post-OP | 39.3 (3.9) | 39.5 (3.5) | 37.9 (3.3) | | | | | | | | | |
| 6m-Post-OP | 39.4 (3.8) | 39.4 (3.6) | 37.8 (3.3) | | | | | | | | | |
| %Difference in calf circumference NonOP - OP | | | | | | | | | | | | |
| Baseline | -2.63 (3.34) | -2.53 (2.20) | -3.16 (4.46) | | 0.612/0.019 | | | | 0.241/0.104 | | | 0.406/0.030 |
| 3w-Prehab | -2.63 (3.34) | -1.36 (1.42) | -3.20 (3.92) | | | | | | | | | |
| Pre-OP | -2.63 (3.34) | -1.54 (2.79) | -3.54 (4.04) | | | | | | | | | |
| 3m-Post-OP | -1.63 (5.23) | -1.36 (2.84) | -3.02 (4.99) | | | | | | | | | |
| 6m-Post-OP | -1.55 (2.93) | -0.67 (1.51) | -1.93 (4.22) | | | | | | | | | |

*Data are provided as mean (standard deviation). CON, control group; BFR = BFR-training group; AC, active control group; rANOVA, repeated-measures analysis of variance; OP, operated leg; NonOP, non-operated leg.*
[a]*$p < 0.05$, significantly different to baseline within the respective group.*
[b]*$p < 0.05$, significantly different to 3w-Prehab within the respective group.*
[c]*$p < 0.05$, significantly different to Pre-OP within the respective group.*
[d]*$p < 0.05$, significantly different to 3m-Post-OP within the respective group.*
[e]*$p < 0.05$, significantly different to CON within the respective time point.*

greater increase in the upper knee swelling with higher level at 3m-Post-OP compared to the BFR-group ($p = 0.046$), which significantly decreased again at 6m-Post-OP ($p = 0.044$). Despite being statistically non-significant, both BFR- and AC-groups demonstrated decreased knee swelling values at 6m-Post-OP compared to the baseline level (**Table 4**).

## Functionality Measurements

**Table 5** summarizes the ROM assessed during active extension and flexion. For all ROM measurements, there were no significant time × group interaction effects ($p \geq 0.403$, $0.043 < \eta_p^2 < 0.073$). Further, significant time effects were detected only for OP leg (extension: $p = 0.012$, $\eta_p^2 = 0.138$; flexion: $p < 0.001$, $\eta_p^2 = 0.468$) indicating a continually improved ROM during overall study period. No main group effects were found for all ROM measures ($p \geq 0.169$, $0.048 < \eta_p^2 < 0.128$).

For 6-MWT (**Figure 2A**), we found a significant time × group interaction effect ($p = 0.012$, $\eta_p^2 = 0.209$). Further analyses revealed a significant time effect only in BFR-group ($p < 0.001$, $\eta_p^2 = 0.677$). *Post hoc*-tests for BFR-group indicated a significant improvement in 6-MWT already at 3w-Prehab compared to baseline (390 ± 82 m to 431 ± 69 m, $p = 0.034$), which increased further after the prehabilitation (to 456 ± 58 m) with a significantly higher level to the baseline- and 3w-Prehab-level ($p \leq 0.048$). At 3m-Post-OP, the BFR-group showed a significant deterioration in 6-MWT compared to Pre-OP (to 426 ± 73 m, $p = 0.05$), but it pronounced recuperated at 6m-Post-OP (to 464 ± 58 m, $p = 0.002$). Consequently, the BFR-group demonstrated a significantly higher ability in 6-MWT at 6m-Post-OP compared to baseline- ($p = 0.004$) and 3w-Prehab-level ($p = 0.007$).

Regarding the CRT (**Figure 2B**), there was a significant time x group effect ($p = 0.007$, $\eta_p^2 = 0.205$). In addition, we found significant time effects in BFR- ($p < 0.001$, $\eta_p^2 = 0.671$) and AC-group ($p < 0.001$, $\eta_p^2 = 0.596$), whereas no changes occurred in the CON. According to *Post hoc*-tests, the patients in the BFR-group significantly improved in the CRT already at 3w-Prehab compared to the baseline (8.90 ± 2.08 reps. to 11.20 ± 2.35 reps., $p = 0.012$). In comparison, the AC-group showed a significant improvement only after the prehabilitation period (9.90 ± 2.51 reps. to 12.00 ± 2.49 reps., $p = 0.006$). At 3m-Post-OP, the AC-group exhibited a significant deterioration in the CRT compared to Pre-OP (to 10.00 ± 2.98 reps., $p = 0.002$), which pronounced improved at 6m-Post-OP again (to 11.30 ± 2.50 reps., $p = 0.019$), and was significantly higher to baseline level ($p = 0.026$). In contrast, the BFR-group indicated no statistically significant change in the CRT at 3m-Post-OP (12.10 ± 2.73 reps. to 10.90 ± 2.77 reps., $p = 1.00$), which was still higher compared to the baseline level ($p = 0.038$). At 6m-Post-OP, the BFR-group improved again (to13.30 ± 2.31 reps., $p = 0.003$) remaining above the baseline- and 3w-Prehab level ($p \leq 0.004$).

## Muscular Strength of the Lower Extremities

The results regarding the muscular strength of both OP and NonOP legs and their percent difference during the prehabilitation and post-operative period are presented in **Table 6**. Significant interaction effects were observed for all measured muscle strength indices ($p < 0.001$, $0.567 < \eta_p^2 < 0.625$). Further analyses revealed a significant main time effect for all muscle strength measures in all groups ($p < 0.05$, $0.298 < \eta_p^2 < 0.916$). In addition, there were significant group effects for all measured leg strength indices ($p \leq 0.046$, $0.204 < \eta_p^2 < 0.676$) excepting for leg extension of OP leg at baseline ($p = 0.077$, $\eta_p^2 = 0.173$) and at 3w-Prehab ($p = 0.230$, $\eta_p^2 = 0.103$). *Post hoc*-tests revealed that both training groups significantly improved in all measured leg strength indices already at 3w-Prehab (BFR-group: $p \leq 0.01$; AC-group: $p \leq 0.026$). At Pre-OP, the BFR-group indicated more pronounced improvements in all leg strength measures (i.e., 3w-Prehab to Pre-OP: $p < 0.001$) with significantly higher values compared to other groups ($p < 0.05$). No changes occurred in the CON during the prehabilitation period ($p = 0.100$). At 3m-Post-OP, significant reductions in leg strength measures were observed in BFR-group ($p \leq 0.01$) except for the leg extension of the NonOP leg ($p = 0.308$), which were still above the baseline level ($p \leq 0.01$). The AC-group indicated significantly decreased muscular strength in both leg-extension (only in NonOP leg) and -curl (in both legs) at 3m-Post-OP even to the baseline level ($p \leq 0.05$). Similarly, the patients in the CON showed a significant decrement in leg extension of both OP and NonOP legs at 3m-Post-OP with a lower value compared to the pre-operative level ($p \leq 0.031$). At the same time, no changes occurred in leg curl ($p \geq 0.187$). At 6m-Post-OP, both training groups significantly improved again in all leg strength measures (BFR-group: $p \leq 0.029$; AC-group: $p \leq 0.031$) with a significant difference to baseline- (BFR-group: $p < 0.001$ for all measures; AC-group: $p \leq 0.029$ only for leg curl of both legs) and to 3w-Prehab-level (only in BFR-group: $p \leq 0.038$ for all measures). The CON also indicated significant improvements but only in muscular strength of OP leg (leg extension: $p = 0.005$; leg curl: $p = 0.007$). Consequently, there were significant differences in leg strength between BFR-group and other groups during the overall post-operative period (AC-group: $p \leq 0.032$; CON: $p \leq 0.020$) excepting for the leg extension of OP leg at 3m-post-OP between BFR-group and CON ($p = 0.265$).

Regarding the strength deficit of the OP leg accessed by the percent difference between OP and Non-OP leg during leg-extension and -curl, we found no significant interaction ($p \geq 0.063$, $0.134 < \eta_p^2 < 0.150$) and time effects ($p \geq 0.105$, $0.038 < \eta_p^2 < 0.081$). There were significant main group effects ($p \leq 0.003$, $0.366 < \eta_p^2 < 0.481$) with lower values in BFR-group compared to other groups.

## Subjective Surveys and Questionnaires

The analysis on the KOOS (**Figure 3**) demonstrated significant time × group interaction effects for all evaluated dimensions ($p \leq 0.004$, $0.268 < \eta_p^2 < 0.416$). Further analyses revealed a significant main time effect for all measures of KOOS in all groups (CON: $p \leq 0.004$, $0.475 < \eta_p^2 < 0.907$; BFR-group: $p < 0.001$, $0.869 < \eta_p^2 < 0.978$; AC-group: $p \leq 0.001$, $0.571 < \eta_p^2 < 0.951$). In addition, there were significant group effects for all measures of KOOS ($p \leq 0.049$, $0.200 < \eta_p^2 < 0.581$) excepting for the dimension *symptoms* at baseline, 3w-Prehab, 3m-Post-OP, and 6m-Post-OP ($p \geq 0.207$, $0.029 < \eta_p^2 < 0.110$) and *quality of life-related to the affected knee* at baseline ($p = 0.398$, $\eta_p^2 = 0.066$).

**TABLE 4 |** Measures related to knee swelling during the prehabilitation- and post-operative period.

| | CON (*N* = 10) | BFR (*N* = 10) | AC (*N* = 10) | One-way ANOVA/rANOVA ($p/\eta_p^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Time | | | Group | | | | | Time x group |
| | | | | CON | BFR | AC | Baseline | 3w-Prehab | Pre-OP | 3m-Post-OP | 6m-Post-OP | |
| Upper knee circumference OP (cm) | | | | | | | | | | | | |
| Baseline | 45.0 (4.5) | 44.0 (3.1) | 43.9 (4.1) | | 0.686/0.014 | | | | 0.323/0.083 | | | 0.505/0.060 |
| 3w-Prehab | 45.0 (4.5) | 43.7 (3.4) | 43.4 (4.0) | | | | | | | | | |
| Pre-OP | 45.0 (4.5) | 43.7 (3.8) | 43.3 (4.2) | | | | | | | | | |
| 3m-Post-OP | 46.0 (5.0) | 44.3 (3.3) | 43.8 (4.2) | | | | | | | | | |
| 6m-Post-OP | 44.8 (5.1) | 43.9 (3.4) | 43.6 (4.2) | | | | | | | | | |
| Upper knee circumference NonOP (cm) | | | | | | | | | | | | |
| Baseline | 44.5 (3.8) | 43.3 (3.0) | 42.2 (3.1) | 0.057/0.287 | 0.069/0.209 | 0.278/0.129 | 0.485/0.052 | 0.509/0.049 | 0.600/0.037 | 0.793/0.017 | 0.805/0.016 | 0.010/0.213 |
| 3w-Prehab | 44.5 (3.8) | 43.2 (3.3) | 42.4 (4.0) | | | | | | | | | |
| Pre-OP | 44.5 (3.8) | 43.8 (3.8) | 42.6 (4.2) | | | | | | | | | |
| 3m-Post-OP | 44.0 (5.5) | 43.6 (3.1) | 42.7 (4.1) | | | | | | | | | |
| 6m-Post-OP | 43.7 (5.3) | 43.7 (3.3) | 42.6 (4.1) | | | | | | | | | |
| %Difference upper knee NonOP - OP | | | | | | | | | | | | |
| Baseline | 1.22 (2.04) | 1.78 (1.81) | 3.90 (2.01)[e] | 0.017/0.445 | 0.073/0.239 | 0.093/0.250 | 0.012/0.280 | 0.181/0.119 | 0.076/0.174 | 0.049/0.200 | 0.097/0.159 | 0.049/0.172 |
| 3w-Prehab | 1.22 (2.04) | 1.62 (1.48) | 2.65 (1.63) | | | | | | | | | |
| Pre-OP | 1.22 (2.04) | 0.31 (1.04) | 1.96 (1.40) | | | | | | | | | |
| 3m-Post-OP | 4.39 (2.31)* | 1.77 (1.51) | 2.84 (2.79) | | | | | | | | | |
| 6m-Post-OP | 2.64 (1.78)[d] | 1.09 (0.74) | 2.79 (2.59) | | | | | | | | | |
| Middle knee circumference OP (cm) | | | | | | | | | | | | |
| Baseline | 43.8 (4.5) | 42.7 (3.2) | 42.7 (3.2) | | 0.172/0.065 | | | | 0.096/0.165 | | | 0.134/0.123 |
| 3w-Prehab | 43.8 (4.5) | 42.4 (2.5) | 42.2 (3.2) | | | | | | | | | |
| Pre-OP | 43.8 (4.5) | 42.4 (2.9) | 42.1 (3.3) | | | | | | | | | |
| 3m-Post-OP | 44.8 (4.1) | 42.7 (2.7) | 42.6 (3.0) | | | | | | | | | |
| 6m-Post-OP | 43.6 (4.0) | 41.8 (2.9) | 42.4 (2.9) | | | | | | | | | |
| Middle knee circumference NonOP (cm) | | | | | | | | | | | | |
| Baseline | 42.9 (4.5) | 41.5 (3.4) | 41.0 (3.9) | | 0.563/0.024 | | | | 0.264/0.097 | | | 0.555/0.058 |
| 3w-Prehab | 42.9 (4.5) | 41.8 (3.6) | 41.2 (3.9) | | | | | | | | | |
| Pre-OP | 42.9 (4.5) | 41.7 (3.7) | 41.2 (4.1) | | | | | | | | | |
| 3m-Post-OP | 42.7 (5.4) | 41.8 (3.2) | 41.2 (4.0) | | | | | | | | | |
| 6m-Post-OP | 42.3 (5.2) | 41.6 (3.3) | 41.1 (4.1) | | | | | | | | | |
| %Difference middle knee NonOP - OP | | | | | | | | | | | | |
| Baseline | 1.87 (1.74) | 2.85 (2.24) | 4.20 (1.41) | | 0.140/0.072 | | | | 0.046/0.211 | | | 0.107/0.133 |
| 3w-Prehab | 1.87 (1.74) | 1.54 (2.24) | 2.58 (1.78) | | | | | | | | | |
| Pre-OP | 1.87 (1.74) | 1.82 (2.67) | 2.05 (1.75) | | | | | | | | | |
| 3m-Post-OP | 4.86 (2.94) | 2.27 (1.75) | 3.25 (4.00) | | | | | | | | | |
| 6m-Post-OP | 3.14 (2.18) | 0.75 (2.65) | 3.19 (2.96) | | | | | | | | | |
| Lower knee circumference OP (cm) | | | | | | | | | | | | |
| Baseline | 39.4 (3.5) | 38.5 (3.4) | 39.0 (3.2) | | 0.017/0.149 | | | | 0.067/0.188 | | | 0.059/0.164 |
| 3w-Prehab | 39.4 (3.5) | 37.8 (3.1) | 38.7 (3.3) | | | | | | | | | |
| Pre-OP | 39.4 (3.5) | 37.7 (3.8) | 38.6 (3.3) | | | | | | | | | |
| 3m-Post-OP | 40.3 (4.1) | 38.6 (3.4) | 38.6 (3.3) | | | | | | | | | |
| 6m-Post-OP | 39.4 (4.0) | 38.3 (3.7) | 38.8 (3.2) | | | | | | | | | |
| Lower knee circumference NonOP (cm) | | | | | | | | | | | | |
| Baseline | 39.0 (3.6) | 37.5 (3.1) | 37.5 (3.3) | | 0.335/0.008 | | | | 0.335/0.081 | | | 0.384/0.076 |
| 3w-Prehab | 39.0 (3.6) | 37.3 (2.8) | 37.4 (3.3) | | | | | | | | | |
| Pre-OP | 39.0 (3.6) | 37.3 (3.0) | 37.7 (3.3) | | | | | | | | | |
| 3m-Post-OP | 38.8 (4.1) | 37.3 (2.7) | 37.7 (3.3) | | | | | | | | | |
| 6m-Post-OP | 38.7 (3.9) | 37.4 (2.8) | 37.7 (3.1) | | | | | | | | | |
| %Difference lower knee NonOP - OP | | | | | | | | | | | | |
| Baseline | 0.76 (3.51) | 2.60 (1.89) | 3.83 (2.16) | | <0.001/0.373 | | | | 0.573/0.042 | | | 0.282/0.091 |
| 3w-Prehab | 0.76 (3.51) | 1.39 (2.00) | 3.49 (2.58) | | | | | | | | | |
| Pre-OP | 0.76 (3.51) | 1.04 (1.89) | 2.54 (1.78) | | | | | | | | | |
| 3m-Post-OP | 4.06 (2.42) | 3.51 (2.65) | 2.32 (3.30) | | | | | | | | | |
| 6m-Post-OP | 1.90 (1.55) | 2.30 (2.25) | 2.94 (2.21) | | | | | | | | | |

*Data are provided as mean (standard deviation). CON, control group; BFR, BFR-training group; AC, active control group; rANOVA, repeated-measures analysis of variance; OP, operated leg; NonOP, non-operated leg.*

[a]*$p < 0.05$, significantly different to baseline within the respective group.*

[b]*$p < 0.05$, significantly different to 3w-Prehab within the respective group.*

[c]*$p < 0.05$, significantly different to Pre-OP within the respective group.*

[d]*$p < 0.05$, significantly different to 3m-Post-OP within the respective group.*

[e]*$p < 0.05$, significantly different to CON within the respective time point.*

*Post hoc*-tests for the KOOS related to *symptoms* (**Figure 3A**) revealed a significant improvement only in the BFR-group during (45.0 ± 5.4 to 54.2 ± 3.9, $p < 0.001$) and after the prehabilitation period (to 60.8 ± 3.7, $p < 0.001$) with a significant higher value compared to other groups at Pre-OP (CON: 51.7 ± 4.7; AC-group: 48.6 ± 9.5, $p \leq 0.01$). No difference was observed between CON and AC-group ($p = 0.893$). At 3m-Post-OP, the BFR-group indicated a significant lower KOOS related to *symptoms* (47.2 ± 3.0) compared to 3w-Prehab- ($p = 0.021$) and Pre-OP-level ($p < 0.001$), but still similar level to other groups (CON: 45.0 ± 4.5; AC-group: 46.1 ± 7.7). At 6m-Post-OP, the KOOS related to *symptoms* increased in all groups (CON: 63.4 ± 5.1; BFR-group: 67.1 ± 3.6; AC-group: 65.2 ± 9.0) with a significantly higher value compared to previous level ($p \leq 0.05$).

The KOOS related to *pain* (**Figure 3B**) in the CON was significantly higher at baseline compared to other groups (CON: 48.7 ± 3.9; BFR-group: 41.1 ± 4.3; AC-group: 44.2 ± 3.8, $p \leq 0.048$), but there was no difference between both training groups ($p = 0.299$). The BFR-group significantly improved the KOOS related to *pain* during (to 52.8 ± 4.1, $p < 0.001$) and after the prehabilitation period (to 57.6 ± 3.4, $p < 0.001$), while no changes occurred in the CON (at 3w-Prehab: 48.0 ± 4.1; at Pre-OP: 47.6 ± 5.4, $p = 1.00$). The AC-group showed an improvement in the KOOS related to *pain* only after the prehabilitation (i.e., at Pre-OP to 49.8 ± 5.2) with a significant difference to baseline ($p = 0.033$). Consequently, the BFR-group exhibited significant higher KOOS related to *pain* compared to other groups both at 3w-Prehab ($p \leq 0.048$) and at Pre-OP ($p \leq 0.003$). During the post-operative period, all groups indicated further improvements in the KOOS related to *pain* with a significant higher value to all pre-operative time points (at 3m-Post-OP: 60.8 ± 6.9 vs. 67.8 ± 3.5 vs. 61.7 ± 6.8; at 6m-Post-OP: 70.0 ± 4.7 vs. 76.2 ± 3.6 vs. 71.1 ± 7.9 in CON, BFR-, AC-group, respectively). In addition, the BFR-group indicated a significant higher KOOS related to *pain* during the post-operative period compared to the CON ($p \leq 0.050$ at both 3m- and 6m-Post-OP), whereas the AC-group did not differ to any other groups ($p \geq 0.10$).

The analysis on the KOOS related to the *activities of daily living* (**Figure 3C**) revealed a continuous improvement in both training groups during the overall study period (BFR-group: 45.5 ± 4.2 to 53.5 ± 6.1 to 57.9 ± 3.7 to 63.7 ± 5.1 to 71.9 ± 3.1; AC-group: 46.7 ± 3.5 to 50.5 ± 3.8 to 52.8 ± 3.4 to 59.0 ± 3.5 to 67.8 ± 3.1; $p \leq 0.047$), while the CON showed a significant improvement only during the post-operative period (49.2 ± 4.2 to 49.0 ± 4.4 to 49.4 ± 6.0 to 58.7 ± 4.5 to 65.6 ± 4.6; $p < 0.001$). Moreover, the BFR-group indicated significant higher KOOS related to activities of daily living compared to other groups at Pre-OP ($p \leq 0.05$), 3m- ($p \leq 0.05$), and 6m-Post-OP ($p \leq 0.05$), whereas no differences were observed between CON and AC-group ($p \geq 0.325$).

Regarding the functionality in sports and recovery (**Figure 3D**), the CON showed a higher KOOS compared to BFR-group at the baseline (24.0 ± 3.2 vs. 19.5 ± 3.7; $p = 0.024$), but the AC-group indicated no difference to any other groups (20.5 ± 3.7; $p \geq 0.105$). Only in the BFR-group, the functionality in sports and recovery already improved at 3w- Prehab (to 27.5 ± 3.5; $p = 0.001$) with a significant higher value compared to AC-group (22.5 ± 3.5; $p = 0.024$). At the Pre-OP, both training groups demonstrated higher sports and recovery functionality than the baseline level (BFR-group: to 29.5 ± 3.7; AC-group: to 24.0 ± 3.9; $p \leq 0.013$). No changes occurred in the CON during (to 25.0 ± 4.1) and after (to 25.0 ± 4.1) the prehabilitation period. At the 3m-Post-OP, only in the BFR-group, the functionality in sports and recovery was higher compared to the baseline level (to 31.0 ± 5.7; $p < 0.001$). At the 6m-Post-OP, the functionality in sports and recovery in the BFR-group was significant higher compared to each of all other time points (38.5 ± 3.4; $p \leq 0.003$), whereas the CON (32.0 ± 6.7) and AC-group (29.5 ± 6.0) demonstrated a significant higher value only compared to the baseline- ($p \leq 0.031$) and 3m-Post-OP-level ($p \leq 0.037$). After the Pre-OP until 6m-Post-OP, the functionality in sports and recovery was higher in the BFR-group compared to other group ($p \leq 0.05$).

The KOOS related to the quality of life-related to the affected knee (**Figure 3E**) increased in both training groups already at 3w-Prehab (BFR-group: 21.9 ± 3.3 to 33.8 ± 4.4; AC-group: 24.5 ± 5.3 to 28.5 ± 5.5; $p \leq 0.017$), and thus the BFR-group indicated higher value compared to the CON (25.5 ± 8.6; $p = 0.024$). At Pre-OP, the BFR-group demonstrated a more pronounced improvement in the quality of life-related to the affected knee (to 40.0 ± 3.2; $p = 0.011$) with a higher value compared to other groups (CON: to 25.6 ± 10.0; AC-group: 30.9 ± 5.2; $p \leq 0.017$). During the post-operative period, all groups demonstrated an increased quality of life-related to the affected knee compared to each of other previous time points (CON: to 45.6 ± 9.2 to 54.4 ± 8.99; BFR-group: to 52.5 ± 6.8 to 69.4 ± 4.6; AC-group: to 44.4 ± 4.6 to 55.0 ± 4.0; $p \leq 0.032$), whereas the BFR-group still exhibited higher values compared to other groups ($p \leq 0.05$) except for 3m-Post-OP in the CON ($p = 0.119$).

## DISCUSSION

The present study aimed to investigate the impact of a 6-week prehabilitation with BFRE on skeletal muscle mass and strength before and after elective primary TKA. The main findings were, that BFR prehabilitation can reduce perceived pain and increase muscle mass and strength significantly more than prehabilitation without BFR before elective TKA surgery. Furthermore, BFR prehabilitation shows a positive influence on postoperative regeneration of skeletal muscle mass, strength and functionality compared to AC and CON, with supportive effects on subjective pain perception and QoL as well.

The present findings at baseline show that muscle mass and strength of patients receiving primary TKA is highly affected by OA. In addition to the subjectively perceived and objectively measurable decrease in functionality, the difference between the patients' extremities is particularly remarkable. Our data show significant differences between the muscle mass as well as muscle strength between the OP and NonOP leg at baseline (**Table 3**, **6**). These results are of particular significance, since it is known that the most important predictive parameters concerning a successful rehabilitation after surgery are preoperative strength, ROM, perceived pain and the ability to complete functional tasks (Topp et al., 2009). This condition is expected to be caused by preoperative immobility and OA-induced arthrogenic muscle inhibition (Mayer et al., 2017). Since comparative literature show similar preoperative deficits (Ikeda et al., 2005; Dreyer et al., 2013), this circumstance could contribute to the dissatisfaction rate of approximately 20% after primary TKA (Bourne et al., 2010; Canovas and Dagneaux, 2018). Therefore, preoperative modification of physical capacities could be a tool to increase rehabilitation success and satisfaction after TKA.

Several studies supported preoperative well-being and postoperative rehabilitation through prehabilitation (Walls et al., 2010; Shaarani et al., 2013; Calatayud et al., 2017). However, current meta-analyses show only a slight to moderate influence of previous prehabilitation concepts on pre- and postoperative clinical outcomes (Wang et al., 2016; Moyer et al., 2017). These results are essentially influenced by the fact that existing methods of exercise led to increased pain, have been simplified and thus do no longer provide the necessary stimulus for muscle development. BFR training avoids this problem by using metabolic rather than mechanical stimuli to increase muscle mass and strength.

The present study suggests that prehabilitation with a 6-week cycling ergometer protocol is sufficient to enhance muscle mass, strength and subjective pain significantly before surgery. In comparison, BFRE was able to increase muscle mass already after 3 weeks of prehabilitation (**Table 3**), enhance muscle strength (**Table 6**) and functional performance (**Figure 1**) superior to AC. These findings are well in line with the literature, illustrating that a 6-week knee extensor-based prehabilitation protocol with BFR induce significant improvements in muscle mass and strength in patients receiving ACL-reconstruction (Kacin et al., 2021). Even though only an indirect measurement tool was chosen to represent muscle mass in the present study, these results allow the interpretation that changes in leg circumference are primarily explained by muscular gains. Furthermore, comparison between the OP and NonOP legs revealed, that BFR-prehabilitation can address successfully preoperative muscular disbalances (**Table 3**, **6**). In addition to the choice of exercise technique, the duration of the prehabilitation is also very important. In a study by Grapar Zargi and colleagues (Grapar Zargi et al., 2016), five times of BFRE within 10 days before an elective ACL reconstruction could not show any influence on the muscle mass and muscle strength. Considering the present results, a prehabilitation duration between three and 6 weeks with strength or endurance BFRE seems to be able to induce significant muscular effects before an elective joint surgery.

The improvements in muscle mass and strength of the BFR-group during and after the prehabilitation phase were associated with an equal enhancement in all five different subparameters of the KOOS score (**Figure 3**). These findings are well in line with previous literature reporting the positive influence of increased muscle mass and strength on subjective pain perception and QoL in OA-affected patients (Davison et al., 2017; Kemnitz et al., 2017). A meta-analysis by Ferlito et al. (2020)) was able to show that BFRE leads to similar gains in muscle mass and strength with concurrent reductions in perceived pain like high-intensity training. Although there is no high-intensity comparison group in the current study, our data are well in line with previous reports showing that low-intensity exercise with BFR is superior to low-intensity exercise alone (Segal et al., 2015). Especially the effects on pain perception during and after the prehabilitation protocol makes BFR training particularly interesting for patients with degenerative joint diseases. Our results show a significant reduction in pain during the 6-week prehabilitation period in patients with terminal gonarthrosis. These findings are well in line with the literature, showing significant reductions in pain in traumatic and degenerative triggered joint diseases by BFR (van Cant et al., 2020; Pitsillides et al., 2021). Since pain is one of the main symptoms in gonarthrosis (Jones et al., 2000) and can serve as a predictor of mortality during a 10-years post-surgery period (Dennis et al., 2016), the present results of pre- and postoperative pain reduction through BFR-prehabilitation are of particular importance.

Although, scientific knowledge about the underlying mechanisms and safety of BFRE is rising in the last years, a regular implementation of BFRE in clinical settings is not given at present. Therefore, it is important to note that the BFR application in this study was done without evoking adverse effects or leading to a drop out by concurrent rising patient compliance to this training method. The study protocol consists of an individual approach in BFR application (Patterson et al., 2019) by measuring the LOP before prehabilitation and applying a pneumatic-controlled pressure individualized to the LOP of the patient with a tourniquet of 11.5 cm wide. Regarding the necessary BFR pressure to induce muscular effects, there is an ongoing debate. While results from Ilett and colleagues (Ilett et al., 2019) show that most beneficial acute effects are induced by a pressure application of ≥60% of LOP, Counts et al. (2016) reported by regular application, that pressures of 40% LOP are also sufficient for hypertrophy effects. In our study, a BFR pressure of 40% LOP was applied to ensure high patient compliance to the exercise. Based on the positive results of this study, it can be concluded that in case of a reduced training status of the muscles of a subject, low BFR pressures such as 40% LOP are sufficient enough to induce significant effects on muscle mass and strength. Based on this individualized approach of BFRE, it is possible to provide a safe, patient compliant and efficient training for patients with end-stage gonarthrosis.

Although BFRE has demonstrated positive results in postoperative rehabilitation after anterior cruciate ligament reconstruction or conservative therapy of degenerative diseases of the knee joint (Charles et al., 2020), its use as a prehabilitation strategy in degenerative joint diseases has not been previously investigated. As the participating patients of the prehabilitation groups underwent surgery with enhanced muscle mass and strength, we could thereby also address the issue of the "better in, better out" principle.

First of all, the present study reported the classical course of regeneration of skeletal muscle mass and strength after primary TKA in all groups with an initial decrease after surgery (**Table 3**, **6**), and inverse improvement in perceived pain (**Figure 3**) (Mizner R. L. et al., 2005). However, even if the BFR-group follows this trend as well, our results show that the drop in muscle mass and strength 3 months after surgery does not fall below the baseline values. In comparison to the AC-group,

**TABLE 5 |** Active range of motion of knee joint during the prehabilitation- and post-operative period.

| | CON (*N* = 10) | BFR (*N* = 10) | AC (*N* = 10) | One-way ANOVA/rANOVA ($p/\eta_p^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Time | | | Group | | | | | Time x group |
| | | | | CON | BFR | AC | Baseline | 3w-Prehab | Pre-OP | 3m-Post-OP | 6m-Post-OP | |
| ROM extension OP (°) | | | | | | | | | | | | |
| Baseline | 2.60 (1.90) | 3.40 (3.20) | 2.40 (2.76) | | 0.012/0.138 | | | | 0.169/0.128 | | | 0.723/0.043 |
| 3w-Prehab | 2.60 (1.90) | 2.70 (2.83) | 2.30 (2.83) | | | | | | | | | |
| Pre-OP | 2.60 (1.90) | 2.70 (2.41) | 2.30 (2.83) | | | | | | | | | |
| 3m-Post-OP | 3.30 (2.98) | 1.50 (3.24) | 2.00 (1.63) | | | | | | | | | |
| 6m-Post-OP | 2.00 (2.58) | 0.70 (1.57) | 1.20 (1.14) | | | | | | | | | |
| ROM extension NonOP (°) | | | | | | | | | | | | |
| Baseline | 3.90 (4.23) | 0.30 (0.95) | 1.20 (1.75) | | 0.607/0.022 | | | | 0.699/0.027 | | | 0.580/0.056 |
| 3w-Prehab | 3.90 (4.23) | 0.70 (1.49) | 0.90 (1.52) | | | | | | | | | |
| Pre-OP | 3.90 (4.23) | 0.50 (1.08) | 1.70 (2.67) | | | | | | | | | |
| 3m-Post-OP | 2.60 (3.57) | 1.20 (2.10) | 1.30 (1.49) | | | | | | | | | |
| 6m-Post-OP | 1.10 (1.45) | 0.20 (0.63) | 0.60 (1.07) | | | | | | | | | |
| ROM flexion OP (°) | | | | | | | | | | | | |
| Baseline | 116.5 (14.8) | 113.7 (11.5) | 113.1 (4.2) | | <0.001/0.468 | | | | 0.513/0.048 | | | 0.403/0.073 |
| 3w-Prehab | 116.4 (14.3) | 116.2 (10.8) | 112.7 (3.5) | | | | | | | | | |
| Pre-OP | 117.0 (14.4) | 116.0 (10.7) | 112.4 (3.1) | | | | | | | | | |
| 3m-Post-OP | 114.7 (7.1) | 117.9 (6.0) | 113.3 (10.1) | | | | | | | | | |
| 6m-Post-OP | 122.0 (8.5) | 119.5 (6.6) | 115.3 (7.9) | | | | | | | | | |
| ROM flexion NonOP (°) | | | | | | | | | | | | |
| Baseline | 127.3 (9.8) | 128.1 (9.1) | 126.4 (7.7) | | 0.337/0.043 | | | | 0.342/0.082 | | | 0.820/0.033 |
| 3w-Prehab | 127.3 (9.8) | 130.3 (8.5) | 127.7 (6.9) | | | | | | | | | |
| Pre-OP | 127.3 (9.8) | 128.5 (8.6) | 126.4 (8.0) | | | | | | | | | |
| 3m-Post-OP | 126.8 (9.5) | 130.5 (10.5) | 126.6 (9.2) | | | | | | | | | |
| 6m-Post-OP | 127.3 (10.1) | 128.5 (8.6) | 126.6 (9.2) | | | | | | | | | |

*Data are provided as mean (standard deviation). CON, control group; BFR, BFR-training group; AC, active control group; rANOVA, repeated-measures analysis of variance; OP, operated leg; NonOP, non-operated leg.*

[a]*p < 0.05, significantly different to baseline within the respective group.*

[b]*p < 0.05, significantly different to 3w-Prehab within the respective group.*

[c]*p < 0.05, significantly different to CON within respective the time point.*

which showed a reduction in muscle mass and strength to baseline, or CON, which partly dropped below the baseline levels, patients of the BFR-group remain consistently better 3 months after TKA than before the start of the prehabilitation-phase (**Table 3**, **6**). Since these results are associated with an improved CRT 3 months post-surgery of the BFR-group in comparison to the other groups, it can be concluded that prehabilitation with BFRE shows a supportive impact on muscle and functional maintenance after TKA surgery. These changes lead to improved outcomes in the early rehabilitation

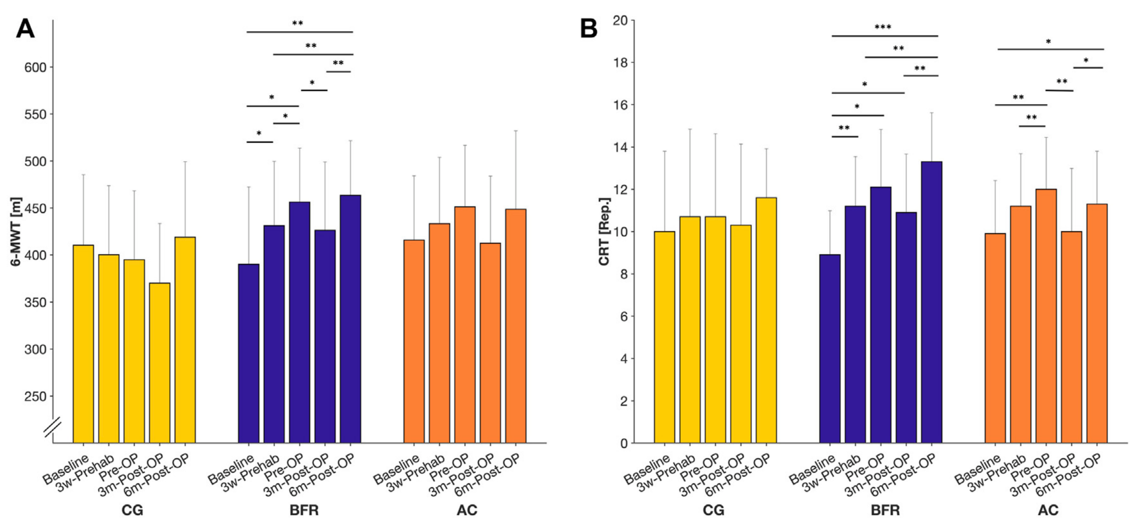


**FIGURE 2 |** Measures related to the 6-min walking test (6-MWT; **(A)** and chair-rising test (CRT; **(B)** during prehabilitation- and post-operative period. Data are provided as mean (standard deviation). CON = control group; BFR = BFR-training group; AC = active control group. ***$p$ < 0.001, **$p$ < 0.01, *$p$ < 0.05, significant difference within the respective group.

**TABLE 6 |** Measures related to muscular strength of lower extremities during the prehabilitation- and post-operative period.

| | CON ($N$ = 10) | BFR ($N$ = 10) | AC ($N$ = 10) | One-way ANOVA/rANOVA ($p/\eta_p^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Time | | | | | Group | | | Time x group |
| | | | | CON | BFR | AC | Baseline | 3w-Prehab | Pre-OP | 3m-Post-OP | 6m-Post-OP | |
| Leg extension OP (kg) | | | | | | | | | | | | |
| Baseline | 20.3 (8.1) | 13.8 (9.1) | 11.8 (7.8) | 0.001/0.591 | <0.001/0.863 | 0.014/0.392 | 0.077/0.173 | 0.230/0.103 | 0.003/0.351 | 0.033/0.223 | 0.002/0.364 | <0.001/0.614 |
| 3w-Prehab | 20.3 (7.1) | 21.9 (9.1)a | 15.3 (9.8)a | | | | | | | | | |
| Pre-OP | 20.3 (7.1)$^{f}$ | 31.5 (10.4) $^{ab}$ | 16.0 (10.2)$^{a}$f | | | | | | | | | |
| 3m-Post-OP | 15.0 (6.3) $^{abc}$ | 22.1 (10.4) $^{ac}$ | 11.1 (9.5)f | | | | | | | | | |
| 6m-Post-OP | 18.5 (7.0)$^{d}$f | 30.8 (11.1) $^{abd}$ | 15.3 (9.4)$^{d}$f | | | | | | | | | |
| Leg extension NonOP (kg) | | | | | | | | | | | | |
| Leg extension NonOP (kg) | | | | 0.018/0.404 | <0.001/0.851 | 0.003/0.503 | 0.026/0.237 | 0.021/0.250 | 0.003/0.348 | 0.002/0.379 | 0.000/0.445 | <0.001/0.587 |
| Baseline | 28.3 (10.4) | 24.3 (7.3) | 17.5 (7.1)e | | | | | | | | | |
| 3w-Prehab | 28.5 (10.5) | 31.8 (7.6)a | 20.3 (8.1)$^{a}$f | | | | | | | | | |
| Pre-OP | 28.3 (10.7)f | 38.4 (9.7) $^{ab}$ | 22.0 (8.7)$^{a}$f | | | | | | | | | |
| 3m-Post-OP | 22.5 (8.6) $^{abc}$f | 34.1 (8.5)a | 18.8 (9.2)$^{c}$f | | | | | | | | | |
| 6m-Post-OP | 27.0 (9.5)f | 39.6 (9.7) $^{abd}$ | 20.8 (8.3)$^{d}$f | | | | | | | | | |
| %Difference leg extension NonOP - OP | | | | | | | | | | | | |
| Baseline | -34.4 (36.0) | -64.6 (31.9) | -51.0 (31.3) | 0.367/0.038 | | | | | | 0.003/0.366 | | 0.063/0.150 |
| 3w-Prehab | -33.1 (26.2) | -40.3 (23.2)a | -39.6 (35.9) | | | | | | | | | |
| Pre-OP | -31.9 (28.5) | -21.0 (16.2) $^{ab}$ | -44.1 (42.5) | | | | | | | | | |
| 3m-Post-OP | -39.5 (34.0) | -46.7 (29.2)c | -69.1 (40.7) | | | | | | | | | |
| 6m-Post-OP | -37.0 (28.4) | -27.3 (23.9) $^{abd}$ | -38.1 (26.8) | | | | | | | | | |
| Leg curl OP (kg) | | | | | | | | | | | | |
| Baseline | 10.8 (3.1) | 9.0 (4.6) | 6.4 (3.4)e | 0.038/0.334 | <0.001/0.916 | 0.003/0.502 | 0.046/0.204 | 0.017/0.260 | <0.001/0.557 | 0.001/0.416 | <0.001/0.645 | <0.001/0.625 |
| 3w-Prehab | 10.8 (3.1) | 14.2 (4.6)a | 9.0 (3.6)$^{a}$f | | | | | | | | | |
| Pre-OP | 11.0 (2.9)f | 19.1 (4.8) $^{ab}$ | 9.8 (3.6)$^{a}$f | | | | | | | | | |
| 3m-Post-OP | 8.8 (2.7)f | 14.6 (5.3) $^{ac}$ | 6.4 (4.6)$^{c}$f | | | | | | | | | |
| 6m-Post-OP | 11.0 (1.7)$^{d}$f | 19.6 (4.1) $^{abd}$ | 9.0 (4.3) $^{ad}$f | | | | | | | | | |
| Leg curl NonOP (kg) | | | | | | | | | | | | |
| Baseline | 13.3 (4.6) | 14.6 (3.9) | 10.0 (3.1)f | 0.049/0.298 | <0.001/0.815 | <0.001/0.617 | 0.039/0.213 | 0.011/0.286 | <0.001/0.550 | <0.001/0.597 | <0.001/0.676 | <0.001/0.567 |
| 3w-Prehab | 13.8 (4.3)f | 19.0 (4.3)a | 13.3 (4.4)$^{a}$f | | | | | | | | | |
| Pre-OP | 13.5 (4.3)f | 23.1 (3.7) $^{ab}$ | 14.5 (4.2)$^{a}$f | | | | | | | | | |
| 3m-Post-OP | 11.3 (2.7)f | 19.5 (3.1) $^{ac}$ | 10.8 (4.4) $^{bc}$f | | | | | | | | | |
| 6m-Post-OP | 12.8 (4.0)f | 22.6 (2.6) $^{abd}$ | 12.5 (3.5) $^{ad}$f | | | | | | | | | |
| %Difference leg curl NonOP - OP | | | | | | | | | | | | |
| Baseline | -19.8 (25.97) | -54.5 (35.5) | -54.4 (40.3) | 0.105/0.081 | | | | | | <0.001/0.481 | | 0.100/0.134 |
| 3w-Prehab | -24.5 (18.5) | -30.8 (27.5) | -39.9 (27.0) | | | | | | | | | |
| Pre-OP | -19.8 (18.9) | -20.4 (17.3) | -40.9 (23.0) | | | | | | | | | |
| 3m-Post-OP | -26.5 (19.3) | -33.0 (29.5) | -67.5 (38.4) | | | | | | | | | |
| 6m-Post-OP | -12.0 (19.9) | -15.8 (18.7) | -40.2 (28.5) | | | | | | | | | |

*Data are provided as mean (standard deviation). CON, control group; BFR, BFR-training group; AC, active control group; rANOVA, repeated-measures analysis of variance; OP, operated leg; NonOP, non-operated leg.*
*[a]$p < 0.05$, significantly different to baseline within the respective group.*
*[b]$p < 0.05$, significantly different to 3w-Prehab within the respective group.*
*[c]$p < 0.05$, significantly different to Pre-OP within the respective group.*
*[d]$p < 0.05$, significantly different to 3m-Post-OP within the respective group.*
*[e]$p < 0.05$, significantly different to CON within the respective time point.*
*[f]$p < 0.05$, significantly different to BFR-group within the respective time point.*

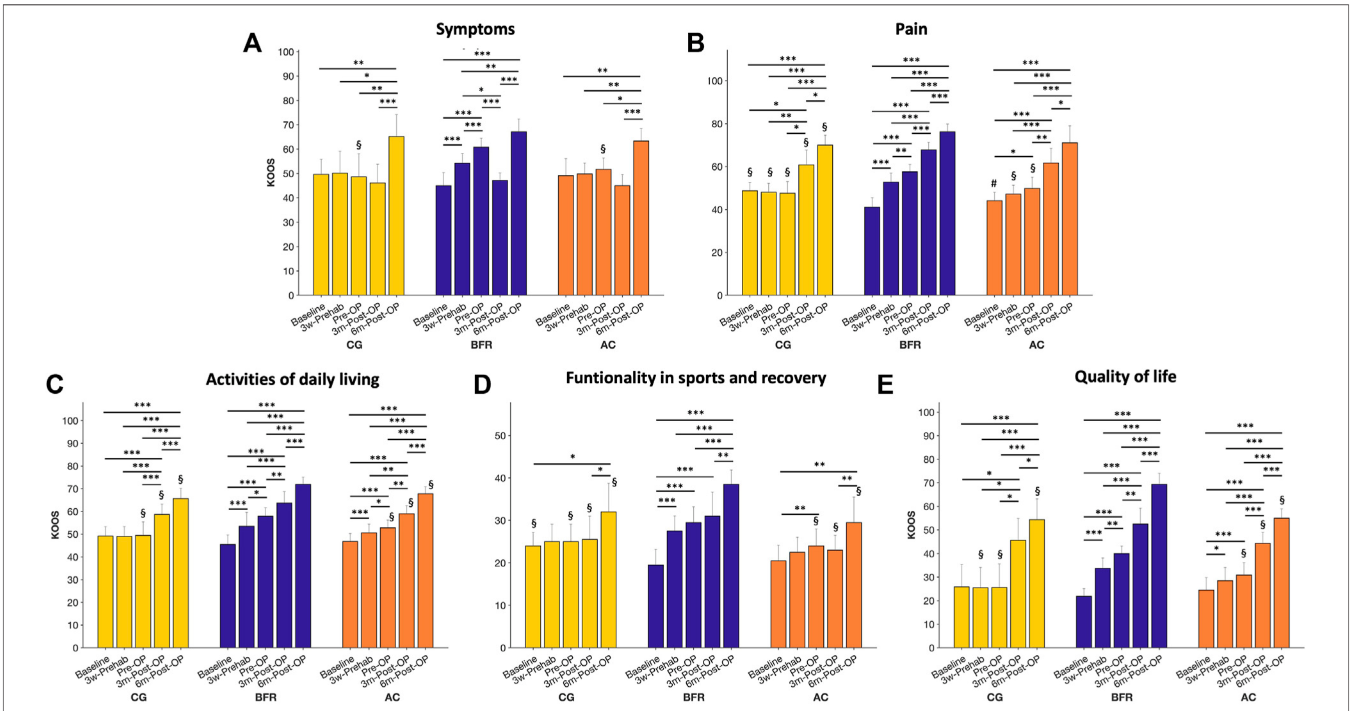


**FIGURE 3 |** Presentation of the five subparameters (Symptoms, Pain, Activities of daily living, Functionality in sports and recovery, Quality of life) of the Knee Injury and Osteoarthritis Outcome Score (KOOS) during prehabilitation- and post-operative period. Data are provided as mean (standard deviation). CON, control group; BFR, BFR-training group; AC, active control group. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, significant difference within the respective group. $^{§}p < 0.05$, significantly different to BFR-group within the respective timepoint. $^{\#}p < 0.05$, significantly different to CON within the respective timepoint.

phase which is also illustrated by higher scores in the KOOS (**Figure 3**).

After 6 months post-surgery, all groups showed a significant increase in muscle strength in comparison to 3 months post-surgery. However, the BFR-group exclusively achieves additional improvements in muscle mass and strength to baseline values already 6-month after surgery (**Table 3**, **6**). Whereas no significant change in muscle mass and strength to baseline for the AC group was revealed, CON showed significant decreased outcomes after 6 months (**Table 3** and **6**). These findings are well in line with previous literature, illustrating persistent reductions in muscle mass and strength post TKA for patients without prehabilitation (Bade et al., 2010). Our results suggest that prehabilitation with BFRE enables patients to recover postoperative muscular deficits faster than control groups and were able to improve skeletal muscle mass, strength and disbalances to the contralateral leg within the first 6 months postoperatively. This result stands in contrast to previous prehabilitation concepts, which showed only a minor impact on postoperative rehabilitation (Moyer et al., 2017).

## LIMITATIONS

The following limitations should be considered when interpreting our findings. Firstly, the methodology of measuring muscle mass by extremity circumference used in this study should be considered as an index of change in muscle size. Since these kinds of measurements includes soft-, adipose- connective- and muscle-tissue, only an estimation of the muscle mass and its change in the course of the study can be done. Future studies should use more valid methods of muscle mass calculation, such as body composition analysis by DXA measurements or MRI scans. Secondly, a possible interference in our results could be caused by a missing matching of the groups to baseline characteristics such as level of physical activity, preoperative muscular deficits, or leg-dominance. Thirdly, there is a possible risk of attention bias, as prehabilitation groups had more visitations to supervisors through the weekly training than the CON, which may have influenced the results preoperatively. Fourthly, level of activity and intensity of activity of the patients after the surgery was not recorded. Future studies should try to monitor postoperative patient activity to get valid data about the effects of prehabilitation on postoperative daily activity.

## CONCLUSION

The present study is the first one describing the supporting impact of BFRE on skeletal muscle mass, strength, subjective pain perception and QoL pre-as well as post-TKA surgery. BFR prehabilitation appears to be a safe, patient compliant, easy-to-perform and effective tool to improve pre-as well as postoperative clinical outcomes and patient satisfaction in TKA. In a highly standardized clinical intervention such as TKA, BFR prehabilitation allows to prepare the patient physical capacities in the best possible way for surgery. Furthermore, in contrast to previous findings, the present study shows that prehabilitation with BFR is able to support rehabilitation after primary TKA in a "better in, better out"-manner.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Comittee of the University Hospital Dusseldorf, Moorenstraße 5, 40223 Düsseldorf. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

AF was responsible for study conception, conduction, evaluation and manuscript preparation. SJ collected and interpretated the data and was involved in the realization of the study. BB and CZ collected and interpretated the clinical data and were involved in the realization of the study. SJ and MB were responsible for statistical analyzation of the obtained data and writing the manuscript. All authors read and approved the final manuscript.

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