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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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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:
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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

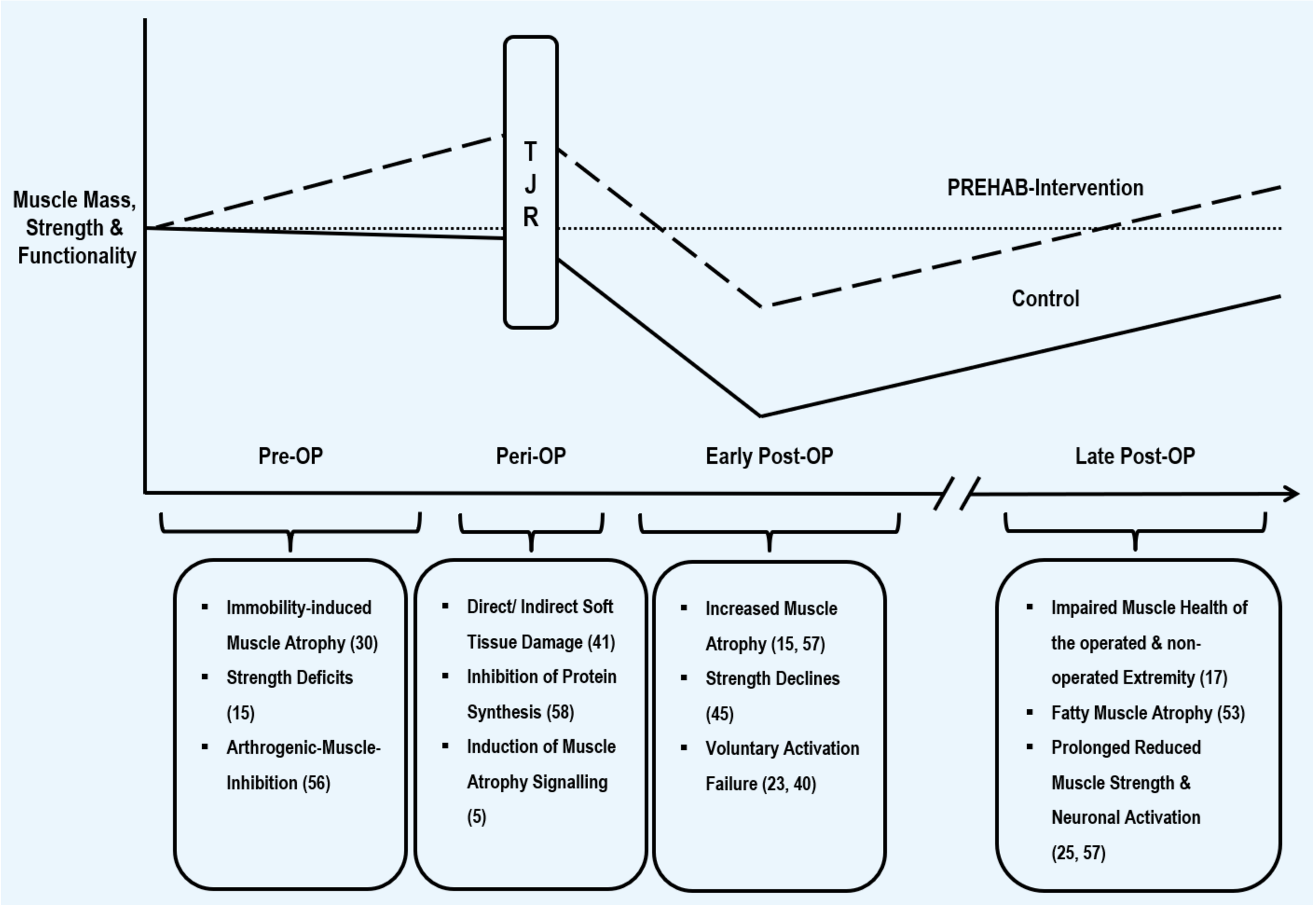

Figure 1

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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