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Muscle Inflammation Susceptibility: A Potential Phenotype for Guiding Precision Rehabilitation After Total Hip Arthroplasty in End-Stage Osteoarthritis

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Abstract

The progression of osteoarthritis of the hip to its end stage and ultimately to total hip arthroplasty (THA) is complex; the multifactorial pathophysiology involves myriad collaborating tissues in and around the diseased joint. We have named the heightened state of periarticular muscle inflammation at the time of surgery "muscle inflammation susceptibility" (MuIS) because it is distinct from systemic inflammation. In this review article, we discuss how MuIS and heightened atrophy-associated signaling in the periarticular skeletal muscles may contribute to reduced muscle mass, impaired muscle quality (ie, through fibrosis), and a muscle microenvironment that challenges regenerative capacity and thus functional recovery from THA. We also review directions for future research that should advance understanding of the key determinants of precision for optimized success of THA for each individual.

Keywords

rehabilitation, total hip arthroplasty, osteoarthritis, muscle, inflammation

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Introduction

The prevalence of osteoarthritis (OA) is substantially increasing, with cases more than doubling over the past 30 years worldwide to 528 million in 2019; by anatomic site, the highest rate of increase appears to be for hip OA [13]. Consequently, the number of total hip arthroplasties (THAs), an effective approach to manage pain and improve physical function and quality of life for most patients with end-stage hip OA, has been increasing (0.11%, 0.42%, 0.57%, and 0.83% of the U.S. population in 1980, 1990, 2000, and 2010, respectively) [14]. In 2010, there were an estimated 2.5 million adults living with artificial hips in the United States [14]. Over 450,000 THA surgeries are performed annually in the United States alone, and recent projections suggest this will increase 284% by 2040 [23]. Although successful surgery often improves patients' life quality, 30% to 35% of THA recipients experience muscle atrophy, long-term pain, and significant mobility limitation and disability for several years after surgery [24]. Postoperative recovery and long-term rehabilitation to reduce the burden of subsequent complications and reoperation are significant concerns in the current health care system.

The etiology and pathophysiology of OA progression are incompletely understood. While OA has generally not been considered a genetic disease, OA-associated genetic variation at 10 loci in the genome have recently been identified [15]. The degree to which genetic variants influence risk and ultimately disease progression at the individual level is modulated by epigenetic influences, as recently summarized [20].

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Although often referred to as degenerative arthritis, it is now widely recognized that OA is an inflammatory disease with a complex pathophysiology. Pro-inflammatory signaling and its deleterious consequences are thought to involve interactions between the affected articular cartilage and other structures in the joint (subchondral bone, synovium, menisci, and ligaments) and in the periarticular and neighboring support structures including tendons, skeletal muscles, nerves, and adipose tissue [12].

We are particularly interested in the periarticular musculature as a key factor in THA outcomes. During THA, some damage to periarticular structures including skeletal muscles surrounding the joint is unavoidable. While pro-inflammatory processes play roles in the early phase of muscle regeneration following injury, heightened muscle inflammation prior to injury and/or prolonged inflammation postinjury impair regenerative processes. In a significant subset of end-stage OA patients electing THA, we have found a heightened state of periarticular muscle inflammation at the time of surgery that we named "muscle inflammation susceptibility" (MuIS) because it is distinct from systemic inflammation [1,5]. We strongly suspect MuIS in this subset may impair regenerative capacity, leading to failed restoration of high-quality skeletal muscle and ultimately to disability and reduced quality of life. We therefore think it is important to study the cellular and molecular mechanisms of MuIS and viable mitigation strategies, and to identify THA patients positive for MuIS (ie, $MuIS^{(+)}$) to optimize the outcomes of THA.

In this article, we discuss how MuIS and heightened atrophy-associated signaling in the periarticular skeletal muscles are likely drivers of reduced muscle mass, impaired muscle quality (eg, greater fibrosis), and a muscle microenvironment that challenges regenerative capacity and thus THA functional recovery. We also highlight our clinical trial (NCT02628795) in end-stage OA, testing the hypothesis that an intensive, 16-week exercise rehabilitation program (progressive resistance training and functional mobility training) would be superior to usual care rehabilitation for the restoration of muscle mass and mobility after THA or total knee arthroplasty (TKA) [5]. The molecular basis underlying the trial was that the more intensive intervention would overcome the inflammatory burden of MuIS to facilitate muscle regeneration and functional recovery. Finally, we summarize current findings of various other rehabilitation approaches that have been tested to speed and enhance recovery after THA.

The Impact of Chronic Inflammation on Skeletal Muscle

Skeletal muscle regeneration following injury (including periarticular muscle injured during THA surgery) depends on a coordinated immune response involving both innate and adaptive immune systems. There is a highly regulated transition from an initial inflammatory phase to a later anti-inflammatory phase [29]. The pro-inflammatory phase driven by migrating neutrophils and M1 macrophages promotes phagocytosis of damaged cells and associated necrotic cell debris and activates proliferation of the resident muscle stem cell pool (satellite cells [SCs]). This inflammatory environment is furthered by CD4 T helper 1 (Th1) cells and cytotoxic CD8 T cells recruited to the damaged region that secrete pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin (IL)-1β, IL-6, and IL-8 (neutrophil chemotactic factor), which facilitate activation/proliferation of the nominally quiescent SCs. The subsequent anti-inflammatory phase, facilitated by M2 macrophages, CD4 T helper 2 (Th2) cells, and regulatory T cells, promotes SC differentiation, leading to myofiber repair and/or replacement (dependent on the degree of damage), along with extracellular matrix (ECM) remodeling and angiogenesis. Moreover, the intrinsic capacity of skeletal muscle for tissue regeneration including self-renewal of a quiescent pool of SCs (in preparation for the next demand) is quite impressive but relies on a precisely orchestrated series of events. These events are highly regulated and thus sensitive to subtle changes that can drive aberrant signaling or otherwise disrupt normal biological processes.

Surgical procedures such as THA disrupt periarticular muscles. Local signaling that reduces myogenic potential, tilts protein metabolism in favor of net catabolism, and/or increases fibrogenic potential will impair the regeneration of high-quality muscle tissue. When compounded by the local muscle atrophy that can occur as OA progresses [1,2], there is a need to optimize the muscle environment so that proanabolic and proregenerative effects might restore high-quality muscle postsurgery.

While an initial inflammatory response stimulates regeneration following muscle damage, chronic elevation of pro-inflammatory signaling in local muscle inhibits regeneration and may impair postsurgical rehabilitation. IL-6, TNF-α, and TNF-like weak inducer of apoptosis (TWEAK) signaling cascades are potent, pro-inflammatory pathways in skeletal muscle. TNF-α and IL-6 are major cytokines produced by first-response neutrophils, macrophages, and T cells traveling to surgical sites. TWEAK is a relatively new player found in the local environment. IL-6 induces pro-inflammatory signaling ultimately via activation of the transcription factor signal transducer and activator of transcription 3 (*STAT3*), whereas TNF and TWEAK promote inflammatory and catabolic signaling primarily via activation of the transcription factor nuclear factor-κB (NF-κB). TNF-α initiates such signaling via binding 1 of 2 receptors, TNF receptor (TNFR) type 1 (p55) or type 2 (p75). TNF-α binding to TNFR1, a death domain–containing protein, can activate TRADD/FADD/Caspase 8 cascades or NF-κB via RIP1/TRAF2/IKK, leading to muscle

cell apoptosis or protein degradation; whereas binding to TNFR2 initiates NF-κB activation via NF-κB–inducing kinase. Both cascades can inhibit expression of the myogenic regulatory factor MyoD.

TWEAK belongs to the TNF superfamily of cytokines. TWEAK binds to the fibroblast growth factor–inducible 14 (Fn14 or TWEAK-R) receptor and activates NF-κB via TRAF6. TWEAK/Fn14 signaling regulates several cell processes such as cell survival, proliferation, angiogenesis, cell migration, and apoptosis. Chronically elevated TWEAK/Fn14 is associated with the pathogenesis of disease including rheumatoid arthritis [11,19], systemic lupus erythematosus [8,28], multiple sclerosis [27], and some cancers [7]. Chronic elevations in any of the 3 major cascades (IL-6, TNF, and TWEAK) have been linked to muscle atrophy and impaired regenerative potential, but the strongest and most consistent evidence is for TNF [26] and TWEAK [10]; IL-6 effects are context dependent [17].

Muscle Inflammation Susceptibility and End-Stage OA

In 2013, we defined MuIS in the context of human aging and suggested it may impair muscle regenerative capacity [16]. In this study, we binned 87 women and men into 3 groups by mean age: AGE40, AGE61, and AGE76. The older groups and particularly AGE76 had heightened gene expression and cell signaling in resting skeletal muscle for several factors central to IL-6, TNF, and TWEAK signaling, including activation of downstream pro-inflammatory transcription factors STAT3 (IL-6 pathway) and NF-κB (TNF and TWEAK pathways). We also showed here and in earlier work using the same protocol [25] that the degree of modest muscle damage in response to a standardized mechanical loading stress (unaccustomed resistance loading) was similar across age groups; yet, the muscle transcriptomic profile was much more sensitive to the damage protocol among older adults, revealing damage-induced upregulation of stress and cellular compromise, inflammation and immune responses, necrosis, and protein degradation [25]. Moreover, the exaggerated inflammatory profiles noted in basal/resting muscle of older adults combined with the exaggerated pro-inflammatory transcriptomic responses to modest muscle damage [16,25] were noted *in the absence of differences in circulating cytokines* [25]; hence, the term "muscle inflammation susceptibility" (MuIS) was born.

These data strongly suggested MuIS would impair muscle regenerative capacity. Also in 2013, we confirmed MuIS in vitro by comparing control conditions and TNF treatment responses in primary SCs isolated from young and aging human muscle [16]. In standard growth media, SCs differentiate to myoblasts, and in differentiation media, these cells fuse to form myotubes. In growth media, the cells isolated from aging muscle expressed substantially higher TNFR expression. When treated with TNF, the older donor cells demonstrated much higher sensitivity to TNF than young adult donor cells [16], as seen by heightened TNF cell signaling across a titration of TNF doses. Furthermore, both in standardized differentiation media and in response to TNF, the older donor myoblasts showed an impaired fusion index, indicative of impaired muscle regeneration capacity.

Initial identification of MuIS with aging led to questions on MuIS status among adults with end-stage OA undergoing THA or TKA. In the first of these studies, we profiled end-stage OA patients undergoing THA (N = 15) versus 2 comparator groups based on expected inflammation status: nonsurgical, negative controls (CON; N = 19) and hip fracture/trauma-positive controls (HFX; N = 11) [1]. As expected, only the positive control HFX group showed systemic inflammation based on circulating cytokines, and HFX had the most robust induction of pro-inflammatory signaling in periarticular skeletal muscle surrounding the fractured hip and pro-inflammatory signaling in muscle from the contralateral limb (another indication of systemic inflammation). We then dichotomized the THA patients into MuIS$^{(+)}$ (n = 7) or MuIS$^{(-)}$ (n = 7) groups based on expression of the TWEAK receptor (Fn14) in periarticular muscle surrounding the hip with end-stage OA. Fn14 mRNA expression was 5-fold higher in the MuIS$^{(+)}$ group than in either the CON or the MuIS$^{(-)}$ group. This was accompanied by exaggerated pro-inflammatory signaling on the surgical side among MuIS$^{(+)}$ patients and by suppressed muscle protein synthesis compared with MuIS$^{(-)}$ patients. Muscle from the contralateral limb of both MuIS$^{(+)}$ and MuIS$^{(-)}$ patients was unaffected, suggesting a true MuIS localized to the muscle surrounding the diseased hip with end-stage OA among a subset of THA candidates.

We followed this initial work with a larger cohort study (N = 70) of end-stage OA THA and TKA patients [5] and confirmed the surgical versus contralateral muscle phenotype, again with heightened inflammatory signaling and greater fibrosis in periarticular muscle of the surgical limb. In a subset of women, we performed RNA sequencing of surgical versus contralateral muscles and found an exaggerated pro-inflammatory gene expression signature on the surgical versus contralateral limb [4]. This analysis focused solely on the protein-coding transcriptome. Our next steps include integrated analyses of the non–protein-coding muscle transcriptome (noncoding long RNAs and the various structural classes of small RNAs) along with microRNA profiling of serum exosomes. In the initial paper [5], we performed a secondary analysis after dichotomizing the cohort based on MuIS status, which yielded mRNA indices of heightened inflammation and muscle protein catabolism among MuIS$^{(+)}$ versus MuIS$^{(-)}$ patients, along with a strong trend toward greater muscle fibrosis. Interestingly, in this study of N = 70, 34% were found to be MuIS$^{(+)}$, which closely mirrors the percentage of patients in large-scale

epidemiological studies found to suffer pain and disability for several years post-THA [24] or TKA [6]. We suspect MuIS may be an important factor in determining success of muscle restoration and functional recovery following THA or TKA.

Muscle Phenotype and Compromised Functional Capacity in OA

Human skeletal muscle is composed of slow-twitch (type I) and fast-twitch (types IIa and IIx) myofibers, along with hybrid myofibers (eg, I/IIa, IIax) typically classified based on the predominant myosin heavy chain isoform(s) expressed by a given fiber. Fast-twitch type II fibers produce greater power and force, and type II motor units have a high threshold for recruitment; type I motor units are recruited readily and are more resistant to fatigue. Aging and chronic diseases are associated with predominant type II atrophy, while disuse or chronically low activity drive type II atrophy in addition to a shift in myofiber type distribution toward more highly fatigable IIax/IIx myofibers. Other key changes in the muscle phenotype linked to aging and chronic disease often include increased prevalence of fibrosis, reduced microvasculature (ie, capillary supply), increased content of resident pro-inflammatory cells (eg, M1 macrophages), and reduced density of SCs. Osteoarthritis is no exception, as impaired muscle quality in OA has been associated with a shift toward IIax/IIx myofibers, higher collagen/ECM content, and lower SC density [18]. Among human OA studies, the shift toward fatigable IIax/IIx myofibers is a common finding [2,18,22], as is impaired muscle functional capacity. However, whether OA exaggerates the rate of type II myofiber atrophy beyond the well-established type II atrophy of aging remains equivocal. Based on our work demonstrating substantial sex differences in aging myofiber atrophy [21], whereby atrophy of both type IIa and type IIax/IIx myofibers is more severe among women, inconsistency among studies in OA could stem from sex effects and/or differences in OA disease stage at the time of muscle tissue analysis.

Rehabilitation After THA: Time for Precision Strategy?

Several trials have tested interventions attempting to improve the magnitude of functional recovery and muscle mass restoration following THA or TKA. For THA rehabilitation, a 2022 systematic review concluded that the studies are highly heterogeneous and the strength of evidence is low; thus, data are insufficient to determine the most effective aspects of THA rehabilitation [9]. A 2019 systematic review of TKA rehabilitation protocols reached a similar conclusion, although the authors indicated some evidence supported the value of higher intensity exercise rehabilitation [3]. While substantial heterogeneity among trials and their implemented rehabilitation interventions certainly contribute to a lack of consensus, we argue that interindividual response heterogeneity among participants due to MuIS or other underlying differences can be a major disruptor in meta-analyses or systematic reviews.

We therefore recently completed a single-blind, randomized controlled clinical trial (NCT02628795) in end-stage OA testing the hypothesis that an intensive, 16-week exercise rehabilitation program (progressive resistance training and functional mobility training) would be superior to usual care rehabilitation for the restoration of muscle mass and mobility after THA or TKA. While elective THA and TKA relieve pain and improve mobility function for thousands with end-stage OA, up to 35% endure persistent muscle atrophy and mobility limitations for several years that affect life quality, increase morbidity, and burden the health care system. Given that THA/TKA volumes are increasing annually, refractory mobility impairment is a major public health problem. Available data raise important knowledge gaps in THA/TKA rehabilitation: (1) poorly understood factors that limit responsiveness of many patients to current highly variable usual care and (2) the absence of rehabilitation programs proven to overcome these limitations. We designed this trial to fill these gaps. Our fundamental tenet was that restoration of mobility function following THA/TKA requires both regeneration of surgically damaged muscle and regrowth of muscles that have atrophied over years of OA and limited use. The molecular basis underlying the trial was the presence of significant MuIS in about one third of these individuals and the expectation that the more intensive intervention would overcome this inflammatory burden to facilitate muscle regeneration and functional recovery. Trial results will be published soon.

The restoration of full mobility function and the mitigation of pain following THA are not guaranteed. We suspect interindividual differences in the inflammatory profile of periarticular muscle and other support structures may strongly influence recovery. Our current work and future directions should advance our understanding of determinants and how they can be assessed to augment precision rehabilitation strategies that maximize success for each person recovering from THA.

Declaration of Conflicting Interests

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Human/Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

Informed Consent

Informed consent was not required for this review article.

Required Author Forms

Disclosure forms provided by the authors are available with the online version of this article as supplemental material.

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