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Effects of Nonsteroidal Anti-Inflammatory Drugs on Muscle Hypertrophy, Connective Tissue Remodeling and Exercise Adaptation: A Narrative Review

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Abstract:

Introduction and Purpose

Exercise-induced inflammation plays a fundamental role in skeletal muscle regeneration and physiological adaptation to training. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in sports medicine to reduce pain and inflammation; however, increasing evidence suggests that chronic suppression of inflammatory pathways may interfere with selected adaptive mechanisms associated with exercise. The aim of this review was to analyze current evidence regarding the effects of NSAIDs on skeletal muscle hypertrophy, connective tissue remodeling, and exercise adaptation in physically active individuals.

Materials and Methods

A narrative review of the literature was conducted using PubMed, Scopus, and Web of Science databases. Publications concerning NSAIDs, exercise physiology, muscle hypertrophy, satellite cells, mTOR signaling, tendon remodeling, and gut-muscle axis interactions were analyzed. Particular attention was paid to experimental studies, systematic reviews, and meta-analyses evaluating molecular and physiological mechanisms associated with exercise recovery and adaptation.

Results

Available evidence suggests that prolonged NSAID use may influence selected pathways involved in muscle regeneration and connective tissue remodeling. Chronic inhibition of cyclooxygenase activity may affect prostaglandin synthesis, satellite cell activation, mTORC1 signaling, collagen remodeling, and intestinal barrier integrity. The observed effects appear to depend on dosage, duration of use, timing of administration, age, and type of physical activity. The greatest potential impact on adaptive processes may occur in young individuals exposed to high training loads and chronic prophylactic NSAID use.

Conclusions

NSAIDs remain important agents in short-term pain management in sports medicine; however, routine long-term use as a recovery strategy should be approached with caution. Current evidence suggests that chronic pharmacological suppression of exercise-induced inflammation may influence physiological mechanisms responsible for muscle and connective tissue adaptation. Further long-term studies involving athletic populations are required to clarify the clinical significance of these findings.

Keywords: NSAIDs; exercise adaptation; muscle hypertrophy; skeletal muscle regeneration; mTOR; satellite cells; connective tissue remodeling; tendons; sports medicine; gut-muscle axis

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used pharmacological agents in sports medicine. Medications such as ibuprofen, diclofenac, naproxen, and selective cyclooxygenase-2 (COX-2) inhibitors are widely used by both professional athletes and recreationally active individuals to reduce pain and alleviate symptoms of inflammation following exercise and musculoskeletal injuries [1,2]. Increasing attention has also been directed toward the prophylactic use of NSAIDs before competitions or intensive training sessions, particularly in endurance sports and contact disciplines [3,4].

The mechanism of action of NSAIDs is primarily based on inhibition of cyclooxygenase enzymes COX-1 and COX-2, which are responsible for prostaglandin synthesis and participate in the regulation of inflammatory, nociceptive, and regenerative processes [5]. Despite their analgesic and anti-inflammatory efficacy, growing evidence suggests that chronic NSAID use may influence not only clinical symptoms but also physiological adaptive processes occurring within skeletal muscle and connective tissue following exercise [6,7].

Contemporary exercise physiology emphasizes that acute exercise-induced inflammation constitutes an essential component of tissue regeneration and remodeling. Post-exercise activation of inflammatory mediators contributes to satellite cell activation, regulation of anabolic signaling pathways, and extracellular matrix remodeling [8,9]. Consequently, prolonged suppression of inflammatory responses by NSAIDs may potentially interfere with mechanisms responsible for muscle hypertrophy, tendon regeneration, and adaptation of the musculoskeletal system to training loads [10,11].

Recent studies have also highlighted the potential influence of NSAIDs on connective tissue remodeling and the gut-muscle axis. Evidence suggests that chronic use of these agents may affect collagen synthesis, biomechanical properties of tendons, and intestinal barrier integrity, which may indirectly influence regenerative processes in athletes [12–14]. At the same time, available findings remain partially inconsistent, and the observed effects may depend on age, dosage, timing of administration, and type of physical activity [15].

The aim of this review is to analyze current evidence regarding the effects of NSAIDs on skeletal muscle and connective tissue regeneration, muscle hypertrophy, and exercise adaptation in physically active individuals. Particular attention is given to molecular mechanisms of NSAID action, their influence on skeletal muscle and tendon physiology, and practical implications for sports medicine.

2. Methodology

This study constitutes a narrative review of the literature concerning the effects of nonsteroidal anti-inflammatory drugs on skeletal muscle and connective tissue regeneration as well as exercise adaptation in physically active individuals. The analysis was based on scientific publications indexed in PubMed, Scopus, and Web of Science databases.

The search strategy included combinations of keywords such as “NSAIDs”, “sports medicine”, “exercise adaptation”, “muscle hypertrophy”, “satellite cells”, “mTOR”, “tendon healing”, “connective tissue remodeling”, “gut-muscle axis”, “intestinal permeability”, “exercise

recovery", and "cyclooxygenase inhibitors". Additionally, references cited in selected publications were screened to identify further relevant studies.

The analysis primarily included studies published between 2018 and 2025, with particular emphasis on experimental studies, systematic reviews, and meta-analyses concerning molecular mechanisms of regeneration and exercise adaptation associated with NSAID use. Both studies involving athletes and recreationally active individuals were included.

Publications unrelated to muscle regeneration, connective tissue remodeling, or exercise physiology were excluded, as were isolated case reports and studies of limited methodological quality. Particular emphasis was placed on studies investigating the effects of NSAIDs on muscle protein synthesis, satellite cell activation, collagen remodeling, and gut-muscle axis function.

3. Physiological Role of Inflammation in Exercise Adaptation

Contemporary exercise physiology recognizes acute post-exercise inflammation as an essential component of tissue regeneration and adaptation. Exercise-induced microdamage to muscle fibers triggers the activation of numerous inflammatory mediators involved in tissue remodeling and adaptation to training loads [8,9].

A central role in this process is played by the arachidonic acid pathway and the prostaglandins produced through its metabolism. In response to mechanical stress, cyclooxygenase enzymes become activated, contributing to the synthesis of prostaglandins that regulate inflammatory responses, satellite cell activation, and regenerative processes within skeletal muscle [5,10].

Prostaglandins are increasingly recognized as important mediators of anabolic signaling. Experimental evidence suggests that prostaglandin F2α may participate in the regulation of muscle protein synthesis and activation of pathways associated with skeletal muscle hypertrophy [13,14]. Furthermore, the inflammatory response following exercise facilitates the recruitment of immune cells responsible for the removal of damaged cellular structures and the initiation of tissue repair.

Satellite cell activation represents another key component of muscle regeneration. These muscle stem cells normally remain quiescent; however, mechanical stress and inflammatory mediators stimulate their proliferation and participation in the repair of damaged muscle fibers [15]. Consequently, satellite cell activation is considered one of the primary mechanisms underlying adaptation to resistance training.

Evidence also indicates that a tightly regulated inflammatory response contributes to the activation of anabolic pathways associated with mTORC1 signaling. This pathway plays a crucial role in the regulation of muscle protein synthesis and hypertrophic adaptations following resistance exercise [14,16]. Therefore, chronic suppression of inflammation through NSAID use may potentially influence physiological processes involved in muscle recovery and training adaptation in physically active individuals.

3.1. Molecular Mechanisms of NSAID Influence on Muscle Hypertrophy

The influence of nonsteroidal anti-inflammatory drugs on muscle hypertrophy remains an area of considerable interest in exercise physiology and sports medicine. Available evidence suggests that prolonged inhibition of cyclooxygenase activity may affect not only pain and

inflammation but also molecular pathways involved in skeletal muscle regeneration and adaptation to training stimuli [10,12].

One of the most important components of the regenerative response to exercise is satellite cell activation. These cells are responsible for the repair of damaged muscle fibers and contribute to muscle hypertrophy following resistance training. Experimental studies indicate that prostaglandins synthesized through COX-dependent pathways may regulate satellite cell proliferation and activity [14,15]. Consequently, chronic NSAID use may attenuate some of the regenerative processes occurring after intensive physical exercise.

Another critical regulator of muscle adaptation is mTORC1, which serves as a central controller of muscle protein synthesis. Activation of this pathway is influenced by mechanical loading, amino acid availability, and inflammatory mediators generated in response to exercise [16]. Several studies have reported that high doses of NSAIDs may partially suppress mTORC1 activation and blunt the early anabolic response following resistance exercise [13,16]. However, available findings remain inconsistent, and the observed effects appear to depend on factors such as age, training modality, and duration of drug administration.

The role of macrophages has also emerged as an important area of investigation in muscle regeneration research. Following exercise-induced muscle damage, immune cells infiltrate the affected tissue. In the early phase of recovery, pro-inflammatory M1 macrophages predominate and facilitate the removal of damaged cellular components. Subsequently, a shift toward the anti-inflammatory and regenerative M2 phenotype occurs, supporting muscle fiber repair and extracellular matrix remodeling.

Current evidence suggests that chronic suppression of inflammation by NSAIDs may alter the balance between these stages of the immune response, potentially disrupting physiological muscle remodeling [12,13]. Such alterations may contribute to less favorable muscle fiber organization and reduced efficiency of adaptive responses to training.

Importantly, the effects of NSAIDs on muscle hypertrophy do not appear to be uniform across different populations. In young physically active individuals, chronic suppression of inflammation may impair anabolic adaptations associated with resistance training [10,18]. In contrast, several studies involving older adults have reported that reduction of chronic low-grade inflammation may enhance the anabolic response to exercise [19]. This phenomenon has been described as the “age-related paradox” of NSAID action in skeletal muscle adaptation.

Despite the growing body of evidence, current literature does not allow for definitive conclusions regarding the overall impact of NSAIDs on muscle hypertrophy. Nevertheless, available findings suggest that prolonged use of high-dose NSAIDs, particularly during periods of intensive training, may influence selected mechanisms involved in skeletal muscle regeneration and adaptation.

4. Effects of NSAIDs on Connective Tissue and Collagen Remodeling

Regenerative processes occurring within connective tissue differ substantially from those observed in skeletal muscle. Tendons, ligaments, and other components of the musculoskeletal system are characterized by relatively poor vascularization, lower metabolic activity, and slower tissue turnover. As a result, the healing of collagen-rich structures is typically prolonged and particularly susceptible to disturbances associated with mechanical overload and chronic inflammation [11,23].

Evidence from both experimental and clinical studies suggests that NSAIDs may influence collagen synthesis and the biomechanical properties of tendons. Prostaglandins generated through cyclooxygenase activity participate not only in the regulation of inflammatory responses but also in extracellular matrix remodeling and the activity of tenocytes responsible for collagen production [23,25].

Several studies have demonstrated that prolonged NSAID use may reduce type I collagen synthesis, the primary structural component of tendons and ligaments [24,25]. In addition, suppression of tenocyte proliferation and alterations in extracellular matrix remodeling have been reported following exercise. These changes may affect the biomechanical properties of connective tissue and its ability to adapt to repetitive training loads.

This issue may be particularly relevant in sports requiring the generation of high explosive forces and rapid changes in movement direction, such as tennis, padel, football, and strength-based disciplines. Adequate tendon stiffness plays a crucial role in the storage and release of elastic energy during movement, thereby contributing to biomechanical efficiency and athletic performance [24]. Impairment of collagen remodeling may therefore increase susceptibility to overuse injuries and chronic tendinopathies.

Current evidence further suggests that the effects of NSAIDs on connective tissue may depend on both the duration of administration and the timing of drug intake relative to exercise. The most unfavorable outcomes have generally been observed with prolonged use of high doses and with NSAID administration before physical activity [12,13]. Under such conditions, the initial inflammatory response required for activation of regenerative pathways may be attenuated.

From a sports medicine perspective, the masking of overuse-related pain by NSAIDs represents an additional concern. Short-term pain relief may encourage athletes to continue training despite incomplete recovery of tendinous and ligamentous structures. Over time, this may contribute to the progression of microdamage and the development of chronic degenerative changes within the musculoskeletal system [7,23].

Although interest in this topic continues to grow, available evidence regarding the effects of NSAIDs on connective tissue remodeling remains limited. Most studies involve relatively short observation periods and small sample sizes, making it difficult to determine the long-term consequences of NSAID use on tendon and ligament function in athletic populations.

5. Gut-Muscle Axis and NSAID-Associated Enteropathy

The concept of the gut-muscle axis has emerged as an important area of research within exercise physiology. This concept describes the complex interactions between gastrointestinal function, systemic inflammation, and skeletal muscle regeneration. Growing evidence suggests that intestinal barrier integrity may play a significant role in recovery processes and adaptation to physical training [27,29].

Intense physical exercise, particularly endurance exercise, results in redistribution of blood flow from the gastrointestinal tract toward working muscles. This physiological response may induce transient intestinal ischemia and increase intestinal permeability [29]. Simultaneous NSAID use may further exacerbate these effects by reducing the protective functions of prostaglandins within the gastrointestinal mucosa [27,28].

Prostaglandins contribute to the maintenance of intestinal blood flow, mucus production, and epithelial barrier integrity [5]. Inhibition of cyclooxygenase activity by NSAIDs may therefore increase intestinal permeability and compromise mucosal defense mechanisms. This phenomenon is commonly referred to as NSAID-associated enteropathy [28].

Increased intestinal permeability may facilitate the translocation of bacterial endotoxins, including lipopolysaccharides (LPS), into the systemic circulation. These molecules can stimulate systemic inflammatory responses and influence immune system function [27,29]. Some studies suggest that chronic low-grade inflammation may negatively affect muscle regeneration and anabolic processes following exercise.

Disruption of gastrointestinal function may also impair the absorption of nutrients essential for post-exercise recovery. This particularly concerns amino acids, electrolytes, and micronutrients involved in muscle protein synthesis and tissue repair [27,30]. Such effects may be especially relevant in endurance athletes who regularly perform prolonged exercise while frequently using NSAIDs.

Despite increasing scientific interest, knowledge regarding the gut-muscle axis remains relatively limited. Most available studies rely on experimental models or indirect markers of intestinal barrier dysfunction, while large-scale clinical investigations in athletic populations remain scarce. Nevertheless, current evidence suggests that chronic NSAID use may affect not only local regenerative processes within the musculoskeletal system but also systemic mechanisms involved in recovery and exercise adaptation.

6. Influence of Dosage, Timing of Administration, and Age on the Response to NSAIDs

The effects of nonsteroidal anti-inflammatory drugs on recovery and adaptive processes appear to depend on multiple factors, including dosage, timing of administration relative to exercise, duration of use, and the age of the individual. Consequently, interpretation of the available evidence remains complex, and the observed outcomes are not consistent across all athletic populations [12,13].

One of the most frequently investigated issues concerns the impact of prolonged high-dose NSAID use on the anabolic response to resistance training. Studies involving young physically active individuals suggest that regular consumption of high doses of ibuprofen or other non-selective COX inhibitors may partially impair muscle hypertrophy and strength adaptations associated with resistance exercise [10,13]. This effect has been attributed to reduced satellite cell activation, decreased prostaglandin synthesis, and partial suppression of anabolic signaling pathways involving mTORC1.

The timing of NSAID administration may also be of considerable importance. Several studies indicate that taking these medications before exercise may exert a greater suppressive effect on physiological inflammatory responses than administration after training [12]. Under such circumstances, early signaling processes activated immediately following mechanical loading of muscle and connective tissue may be attenuated.

Current evidence nevertheless suggests that short-term use of low-dose NSAIDs after acute injuries or particularly demanding training sessions may have a less pronounced impact on adaptive processes than chronic pharmacological suppression of inflammation. However,

available findings remain inconsistent, and the magnitude of the observed effects varies between studies [18].

Another important consideration is the influence of age on the physiological response to NSAID administration. In young athletes, exercise-induced inflammation plays a crucial role in anabolic and regenerative processes. Consequently, chronic suppression of inflammatory responses may interfere with normal training adaptations in this population [10,13]. In contrast, different outcomes have been reported in older adults.

Aging is associated with the presence of chronic low-grade inflammation, commonly referred to as inflammaging. Under such conditions, partial suppression of inflammatory mediators may enhance the anabolic response of skeletal muscle to resistance exercise [19,31]. This phenomenon has been described in the literature as the "age-related paradox" of NSAID action and remains an active area of investigation.

It should be emphasized that most available studies include relatively short follow-up periods and limited sample sizes. Furthermore, differences in training protocols, drug dosages, and participants' training status contribute to substantial heterogeneity, making definitive interpretation of current findings difficult.

7. Limitations of Current Research on NSAIDs and Exercise Adaptation

Despite the growing number of publications addressing the influence of NSAIDs on recovery and exercise adaptation, several methodological limitations continue to hinder definitive conclusions regarding their effects on muscle hypertrophy and connective tissue remodeling.

One of the major challenges is the considerable heterogeneity of the populations studied. Available investigations have included both recreationally active individuals and elite athletes representing different sports disciplines and training backgrounds [9,18]. These factors may substantially influence both the physiological response to exercise and the effects of pharmacological suppression of inflammation.

Additional limitations arise from differences in training and pharmacological protocols. Some studies have examined the effects of NSAIDs following a single exercise session, whereas others have evaluated long-term resistance or endurance training interventions [10,13]. Moreover, various drug dosages, administration schedules, and both selective and non-selective cyclooxygenase inhibitors have been investigated, making direct comparison of findings challenging.

A substantial proportion of the available evidence is based on experimental models or indirect markers of anabolic activity, including signaling kinase activation, inflammatory mediator expression, and short-term changes in muscle protein synthesis. In contrast, relatively few studies have assessed clinically relevant long-term outcomes such as muscle mass development, tendinopathy risk, or the incidence of overuse injuries [12,23].

Interpretation of the findings is further complicated by limited control of factors known to influence post-exercise recovery. Dietary intake, sleep quality, supplementation practices, psychological stress, training volume, and individual genetic predisposition may all substantially affect both exercise adaptation and the physiological response to NSAID use. In many studies, these variables were not fully standardized.

Another important limitation concerns the relatively short duration of observation in most available studies. Potential effects of chronic NSAID use on tendon biomechanics, connective tissue remodeling, and long-term muscular adaptations may only become apparent after many months or years of repeated training exposure.

Given these limitations, current evidence does not support definitive recommendations regarding complete avoidance of NSAIDs in sports. Nevertheless, available findings suggest that routine and prolonged use of these medications as part of a recovery strategy should be approached with caution, particularly when long-term adaptation to training is a primary objective.

8. Practical Implications for Sports Medicine

Current evidence suggests that NSAID use in sports should be considered not only in the context of short-term pain relief but also with regard to its potential influence on long-term adaptation to training. This issue is particularly relevant in competitive sports, where recovery is an integral component of the training process and directly affects performance development and training continuity.

Studies investigating chronic NSAID use indicate that the routine administration of these medications to accelerate post-exercise recovery may not provide the expected adaptive benefits [12,18]. This concern is especially relevant in individuals exposed to high training volumes who regularly consume high doses of anti-inflammatory drugs. Under such conditions, pharmacological suppression of inflammation may interfere with physiological mechanisms involved in muscle hypertrophy, collagen remodeling, and tissue regeneration [10,13,23].

The timing of NSAID administration may also have important practical implications. Taking these medications before training sessions or competitions may reduce the perception of pain and physical strain, potentially encouraging continued exercise despite incomplete tissue recovery [7,33]. Over time, this behavior may increase the risk of overuse injuries and contribute to the development of chronic musculoskeletal disorders, particularly in sports characterized by repetitive loading and high training volumes.

At the same time, NSAIDs remain valuable therapeutic agents in the management of acute pain and selected sports-related injuries. Short-term administration under appropriate medical supervision may improve athlete comfort and facilitate symptom control [2,7]. However, current evidence does not support the routine long-term use of NSAIDs as a standard recovery strategy in physically active populations.

Contemporary sports medicine increasingly emphasizes comprehensive approaches to post-exercise recovery. Appropriate training design, adequate energy and protein intake, sufficient sleep, periodization of training loads, and monitoring of fatigue and recovery status remain fundamental components of successful adaptation to exercise [30,39,40]. In many cases, individualized therapeutic strategies that consider age, sport-specific demands, and injury characteristics may be more beneficial than routine pharmacological interventions.

Another important issue concerns the prophylactic use of NSAIDs in the absence of clear medical indications. Epidemiological studies indicate that some athletes routinely consume anti-inflammatory medications before competitions or intensive training sessions [9,31]. Increasing awareness of the potential effects of chronic NSAID use on recovery and adaptation may therefore represent an important aspect of health promotion and injury prevention in sport.

9. Conclusions

Exercise-induced inflammation is a fundamental component of the regenerative and adaptive processes occurring within skeletal muscle and connective tissue. Current evidence suggests that nonsteroidal anti-inflammatory drugs may influence not only pain perception and inflammatory symptoms but also molecular pathways involved in muscle hypertrophy, collagen remodeling, and long-term adaptation to training.

Available studies indicate that chronic suppression of inflammatory responses may affect satellite cell activation, mTORC1 signaling, extracellular matrix remodeling, and collagen synthesis. These mechanisms are closely associated with tissue regeneration and adaptation to repeated mechanical loading. Consequently, prolonged NSAID use may have implications for athletes and physically active individuals engaged in regular resistance or endurance training.

Growing attention has also been directed toward the influence of NSAIDs on connective tissue physiology and the gut-muscle axis. Experimental evidence suggests that chronic use of these medications may affect collagen turnover, tendon biomechanical properties, and intestinal barrier integrity. Nevertheless, the number of long-term clinical studies investigating these effects in athletic populations remains limited.

The impact of NSAIDs on adaptive processes appears to depend on several factors, including age, dosage, duration of use, timing of administration, and type of physical activity. The greatest potential risk of impaired training adaptation may be associated with chronic high-dose NSAID consumption, particularly when used prophylactically before exercise.

Although current evidence does not justify a recommendation for complete avoidance of NSAIDs in sport, routine long-term use of these medications as a recovery strategy should be approached with caution. Further well-designed longitudinal studies involving athletic populations are needed to clarify the clinical significance of these observations and to establish evidence-based recommendations for NSAID use in sports medicine.

10. Disclosure

Author's Contributions

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