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# The Role of Glutamine in Muscle Regeneration and Recovery: A Literature Review

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# ABSTRACT

#### **Purpose:**

The purpose of this review is to analise current scientific literature regarding the impact of glutamine supplementation on muscle repair, post-exercise recovery, and skeletal muscle preservation. It also examines the biological pathways through which glutamine may exert its effects, including modulation of inflammation and enhancement of protein turnover.

#### Methodology:

A review of scientific literature was performed, focusing on studies investigating the effects of glutamine supplementation on skeletal muscle recovery and function. The review includes experimental studies, clinical trials, and narrative reviews involving both athletic and clinical populations, with attention to various training conditions, health statuses, and supplementation strategies.

#### **Findings:**

The evidence indicates that glutamine can support recovery processes by mitigating muscle inflammation, improving redox balance, and promoting anabolic signalling. However, the degree of effectiveness varies, with more pronounced benefits observed in clinical and stress-related conditions compared to healthy individuals. The influence of dosage, supplementation timing, and individual variability remains a key consideration.

#### **Conclusions:**

Glutamine shows potential as a supportive agent in muscle regeneration, particularly in contexts of physical stress, illness, or injury. Further studies are needed to define its role in athletic, healthy populations and to optimize administration strategies based on individual needs and health status.

**Keywords:** glutamine, muscle regeneration, muscle recovery, protein metabolism, oxidative stress, amino acid supplementation, skeletal muscle

#### **1. Introduction**

Glutamine is the most abundant free amino acid in the human body, involved in numerous biological processes such as nitrogen transport, acid-base balance, immune cell function, and redox regulation (1,2). While it is classified as a non-essential amino acid under normal conditions, it becomes conditionally essential during metabolic stress such as trauma, infection, or intense physical exertion (3,4).

The role of glutamine in skeletal muscle regeneration has gained increasing attention due to its possible benefits in reducing inflammation, muscle soreness, and promoting protein synthesis after damage or exercise (5,6). However, results from both clinical and experimental studies remain inconclusive and context-dependent. This review aims to critically analyze the recent literature on glutamine's effects on muscle recovery.

#### 2. Methodology

The research was based on a comprehensive review of existing literature, with studies sourced from databases including PubMed, Scopus, and Google Scholar. The review prioritized clinical trials, experimental research, and narrative reviews that examined the effects of glutamine supplementation on skeletal muscle recovery, regeneration, strength, and protein metabolism. The review included a broad range of studies involving both human participants - such as athletes, older adults, and patients in clinical settings - and animal models used to investigate relevant physiological mechanisms.

Key factors considered were supplementation dosage, treatment duration, and demographic variables like age, training status, and health condition.

Relevant studies were carefully reviewed and compared in terms of their methodologies, outcomes, and scientific quality. Their conclusions were then interpreted in the context of practical applications in clinical nutrition and sports recovery.

## 3. Physiological Functions of Glutamine with a Focus on Skeletal Muscle

Glutamine is crucial for multiple metabolic pathways, particularly in rapidly dividing cells like lymphocytes and enterocytes (2). In skeletal muscle, it functions both as a fuel and a regulator of anabolic processes. Glutamine's involvement in glutathione synthesis helps control oxidative stress post-exercise (7), and its influence on mTORC1 signalling has been linked to muscle protein synthesis (8,9).

Skeletal muscle plays an underappreciated systemic role in glutamine metabolism, acting as a reservoir that becomes depleted in catabolic conditions (10). Furthermore, glutamine's regulatory effect on autophagy and protein degradation adds another layer of relevance to muscle regeneration processes (8,11).

### 4. Mechanisms of Action in Muscle Recovery and Regeneration

Glutamine supplementation has been proposed to support muscle regeneration through several interconnected physiological and cellular mechanisms. One of its primary functions is the modulation of inflammatory responses. Research indicates that glutamine can reduce the production of pro-inflammatory cytokines and oxidative damage in both injured and immobilized skeletal muscle tissues, thereby limiting secondary damage and supporting the regenerative process (6,7).

Another important mechanism involves its influence on protein metabolism. Glutamine contributes to the stimulation of protein synthesis and may suppress muscle protein breakdown. This is thought to occur through the activation of anabolic pathways, particularly the mammalian target of rapamycin complex 1 (mTORC1), which is a key regulator of muscle growth and repair (8,9). Glutamine plays a role in restoring intracellular amino acid balance, which supports muscle anabolism after catabolic stress (12).

Additionally, glutamine has been shown to enhance antioxidant defence mechanisms. It is a key precursor for glutathione, one of the most important intracellular antioxidants. By improving redox balance, glutamine can protect muscle cells from oxidative stress, a common consequence of both intense exercise and injury (1,2).

Emerging evidence also points to glutamine's ability to influence muscle contractile function. In animal models, supplementation has led to improvements in the functional recovery of damaged muscle fibers, suggesting that glutamine may support not only structural regeneration but also neuromuscular performance (11). Together, these mechanisms underline glutamine's multifaceted role in the recovery of skeletal muscle.

#### 5. Evidence from Experimental and Clinical Studies

A growing body of evidence, derived from both preclinical and clinical studies, has investigated the effects of glutamine supplementation on muscle recovery. In animal models, glutamine has consistently demonstrated beneficial outcomes. For example, Koike et al. (2022) reported improved contractile function in regenerating rat soleus muscles following glutamine administration. Similarly, Petry et al. (2019) observed reduced oxidative stress and preservation of muscle protein content in immobilized rats, accompanied by an upregulation of protective proteins such as HSP70. Boza et al. (2001) further confirmed that glutamine supplementation can enhance tissue protein synthesis rates, especially under glucocorticoid-induced catabolic stress (7,11,12).

Human studies, although more variable in their outcomes, provide additional insight. In controlled trials involving trained individuals, glutamine supplementation has been associated with reductions in muscle soreness and improved recovery after eccentric exercise (13,14). Córdova-Martínez et al. (2021) reported decreased levels of muscle damage biomarkers in professional athletes who supplemented with glutamine during intensive training periods (15). However, other studies by Antonio et al. (2002) and Candow et al. (2001) found limited or no significant impact on muscle mass or performance, particularly in well-nourished, healthy participants (16,17).

In clinical and aging populations, glutamine appears to hold greater promise. Studies by Maykish (2020), and Negro et al. (2024) emphasize glutamine's utility in conditions such as sarcopenia, immobilization, and critical illness, where muscle wasting is accelerated. In these contexts, glutamine may help preserve lean body mass, support immune function, and facilitate recovery. Notably, when glutamine is combined with other anabolic agents like leucine or HMB, synergistic effects on muscle maintenance and regeneration are often observed (18,19). Altogether, the evidence supports a context-dependent role for glutamine in muscle recovery, with stronger and more consistent results in clinical or catabolic states than in athletic or healthy populations.

#### 6. Potential Adverse Effects and Safety Considerations

Although glutamine is generally considered safe and well-tolerated when used in moderate doses, the available literature indicates that certain safety concerns may arise in specific contexts or with prolonged supplementation. It is considered safe for short-term use in healthy individuals but note that long-term effects remain insufficiently studied. Impaired renal and hepatic function can disrupt glutamine metabolism, leading to excessive ammonia accumulation and metabolic complications. Therefore, patients with severe organ failure, particularly in the early phase of acute liver failure or AKI with low creatinine clearance, should be excluded from glutamine may still be used safely under proper clinical conditions (20). Gleeson (2022) highlights the lack of standardization in dosing and the scarcity of long-term human trials, which limits the ability to conclusively determine the safety of chronic glutamine use in sports settings. He also points out that the popularity of high-dose supplementation in athletic circles is often not supported by robust safety data (21).

Maykish (2020), in the context of older adults and individuals at risk for metabolic disorders, emphasizes the importance of individualized assessment before recommending glutamine, particularly when combined with other amino acids. Although not directly reporting adverse events, the study raises questions about the metabolic impact of multi-amino acid regimens in vulnerable populations (18).

While some in vitro studies have suggested that glutamine could support tumour cell growth due to its role in cellular metabolism (22), such effects have not been confirmed in living organisms (23). In fact, animal research has shown that glutamine supplementation may reduce tumour size and enhance immune activity, including increased natural killer (NK) cell function (24). The evidence suggests that glutamine may influence tumours differently depending on the context-potentially supporting immune-mediated anti-tumour responses despite its role in cell proliferation.

In summary, while no serious adverse effects have been consistently documented in the reviewed literature, the lack of long-term safety data, especially in healthy individuals using high doses, remains a relevant limitation. Further research is needed to clarify the metabolic consequences of prolonged glutamine use, particularly in populations with comorbidities or altered renal function.

#### 7. Discussion

The analysis of current literature supports the view that glutamine plays a multifunctional role in skeletal muscle recovery and regeneration, particularly in response to physiological stress. Its biological functions-ranging from modulation of inflammatory signalling to antioxidant defence and promotion of protein synthesis-suggest its importance in preserving muscle integrity after injury, immobilization, or intense physical exertion (1,2,7). Mechanistic studies have highlighted glutamine's capacity to support anabolic pathways such as mTORC1 signalling (8,9) and its role as a precursor for glutathione, which helps protect muscle tissue from oxidative stress (7).

In animal models, glutamine supplementation has shown positive effects on muscle contractile function, inflammation resolution, and protein preservation (6,11,12). These findings have also been partially reflected in human studies, where certain trials have reported reductions in delayed-onset muscle soreness and improved recovery of muscle strength following eccentric exercise (13,14). Moreover, in clinical populations facing catabolic stress-such as critically ill patients or older adults with sarcopenia-glutamine has been shown to help preserve lean mass and support functional recovery, especially when combined with other nutrients like leucine or HMB (18, 19).

Despite these promising outcomes, the evidence for glutamine's effectiveness in healthy, physically active individuals remains inconsistent. Several studies have failed to demonstrate significant improvements in performance, muscle mass, or strength in this population (16,17). This may be due to sufficient endogenous glutamine availability under normal physiological conditions, reducing the need for exogenous supplementation. Furthermore, study designs, participant characteristics, and supplementation protocols vary greatly, making it difficult to compare outcomes directly or derive standardized recommendations.

An important limitation in the existing body of literature is the frequent reliance on animal studies. Although these models provide valuable mechanistic insights, physiological and metabolic differences between species limit the extent to which such findings can be extrapolated to humans. Additionally, many human trials do not adequately account for individual variability related to age, sex, baseline nutritional status, or training background, all of which may influence the body's response to glutamine supplementation.

Another concern is the heterogeneity in dosing strategies, duration of supplementation, and forms of glutamine used across studies. Without standardization, drawing conclusions about optimal intake or timing is challenging. Moreover, few studies examine the long-term safety or metabolic consequences of chronic glutamine use, especially in non-clinical populations.

While positive effects have been observed in individuals with glutamine deficiency, these outcomes may not apply to healthy populations. There is concern that prolonged intake may alter metabolic and cellular pathways, potentially affecting the body's response to stress, illness, or even tumor development. However, current research offers limited data on the side effects or risks of long-term use (25).

These concerns underline the importance of further studies examining the metabolic effects and long-term safety of glutamine supplementation, especially in athletic or clinical contexts.

#### **Future Research Directions:**

To address these limitations, future studies should prioritize well-designed, placebo-controlled human trials with clearly defined dosing regimens and standardized outcome measures. There is a particular need for research focusing on personalized supplementation strategies, taking into account sex, age, training status, and metabolic profiles. More work is also required to determine the synergistic potential of glutamine in combination with other anabolic nutrients in both athletic and clinical populations. Finally, long-term studies are necessary to assess the safety, efficacy, and sustainability of glutamine supplementation over extended periods.

#### 8. Conclusions

This review demonstrates that glutamine supplementation may offer significant benefits in supporting skeletal muscle recovery, particularly under conditions of physiological or clinical stress. Its ability to reduce inflammation, support antioxidant defence, and stimulate anabolic signalling highlights its multifactorial role in muscle regeneration. Experimental studies in animal models and clinical trials involving catabolic states consistently show favourable outcomes, including preservation of muscle mass, improved contractile function, and reduced protein degradation.

However, evidence for similar benefits in healthy, physically active individuals remains inconsistent. While some studies report reduced soreness and faster strength recovery, others suggest minimal or no effect, likely due to sufficient endogenous glutamine levels and variations in supplementation protocols. The widespread use of animal models and the limited personalization of supplementation strategies further restrict the generalizability of current findings.

Although glutamine appears safe for most individuals, limited evidence exists regarding its long-term use, and potential adverse effects may arise at high doses or in individuals with compromised organ function. This highlights the need for cautious application and further research into its safety profile.

Overall, glutamine appears to be a valuable adjunct in the nutritional support of muscle recovery in specific populations, particularly in clinical or catabolic settings. Further human research is required to clarify its effectiveness in athletic contexts and to determine optimal dosing, duration, and combinations with other nutrients.

#### **Disclosure:**

#### Authors' contribution:

All authors contributed to the article.

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The authors declare no conflict of interest.

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