Glutamine Complex

Goal

To supply the conditionally essential amino acid glutamine with co-factors (chromium/magnesium chelate) to be taken orally during periods when endogenous production may not keep up with the demand that would otherwise support health and skeletal muscle integrity/recovery and whole-body protein synthesis (WBPS). Proper dosing during times of bodily stress caused by injury, sickness, extended energy restricted diets and/or prolonged intense exercise regimens, is designed to maintain the free glutamine pool and subsequently reduce the stress-induced skeletal muscle proteolysis (catabolism) to help maintain the necessary glutamine homeostasis that normally supports overall immunity, antioxidant protection (glutamine – GSH* axis) and muscle protein synthesis and stores – i.e., proper supplementation would attenuate stress-induced muscle catabolism while strengthening immune defenses. Further, along with functioning as an effective immuno-nutrient (including supporting the integrity of the gastrointestinal tract where 70% of the immune system resides), and skeletal muscle defender, supplementation would bolster glutamine's important roles in cell growth and survival during times of depletion caused by rapid growth, tissue repair or the other high metabolic demands as named above compared to a non-supplemented state. Glutamine supplementation is necessary when the endogenous supply of glutamine becomes the limiting factor in the body's ability to recover to a healthy homeostatic state and maintain resilience.

Glutamine plays a crucial role in skeletal muscle metabolism. As the most abundant amino acid in the body and primarily manufactured, stored, and released as needed to other organs from skeletal muscle tissue, glutamine supplementation has been studied for its potential benefits in immune support, promoting muscle growth, enhancing exercise performance, and supporting recovery from exercise-induced muscle damage.

*The full name of glutathione is **gamma-glutamy-L-cysteinylglycine,** a tripeptide (three-amino-acid chain of glutamic acid, cysteine, and glycine). Technically, this state is referred to as **reduced glutathione (GSH).**

Rationale

Maintaining glutamine homeostasis is crucial to health and recovery because glutamine plays a variety of essential roles in nearly every cell in the body. Any bodily stressors such as rapid growth, injury, sickness, excessive exercise, or dietary restriction, deplete the naturally available glutamine, upsetting homeostasis (i.e., disordered respective cell functioning). Therefore, supplementing the body's natural glutamine pool during times of depletion would help support health (directly feeding the gut/immune system) and recovery, including protecting skeletal muscle from being forced to release resident glutamine and other amino acids for de novo glutamine synthesis to overcome the stress-induced losses that would otherwise compromise healing and daily recovery.

Glutamine (GLN) is the most abundant and versatile amino acid in humans, which is highlighted by the fact that in health and disease, the rate of glutamine consumption by immune cells is similar or greater than glucose and serves as the primary fuel source for the rapidly reproducing cells of the gastrointestinal (GI) tract. Studies have shown that glutamine is essential for lymphocyte proliferation and cytokine production, as well as for the phagocytic and secretory activities of macrophages and the bacterial killing capabilities of neutrophils. Related to the aforementioned, glutamine is probably the most widely recognized immunonutrient.[1] It plays indispensable roles in the tricarboxylic acid cycle (TCA, or Krebs cycle), heat shock protein responses, and antioxidant systems.[2] Moreover, glutamine is also involved in inter-organ ammonia transport, which is particularly important for both immune cells and the brain, especially in catabolic situations such as critical care, exhaustive exercise, and calorie-restricted diets.[3] The well-known fall in blood glutamine availability during stresses (see Figure 1) is the primary rationale for studies to explore the possible effects of glutamine replacement via supplementation during times of exercise and/or diet-induced stress to minimize these otherwise catabolic challenges to the body, including protecting skeletal muscle by directly delivering an exogenous source of glutamine. Currently, glutamine is routinely supplied as a component of clinical nutrition

supplementation for pre-and post-operative patients, and also for many elite athletes to restore immune functions and for its potential antioxidant and anti-inflammatory effects.[1,2,3,4] Athletes also use glutamine to help reduce fatigue.[5] Studies that evaluated glutamine supplementation observed improved fatigue markers, such as increased glycogen synthesis and reduced ammonia accumulation, while boosting antioxidant protection.[6,7]

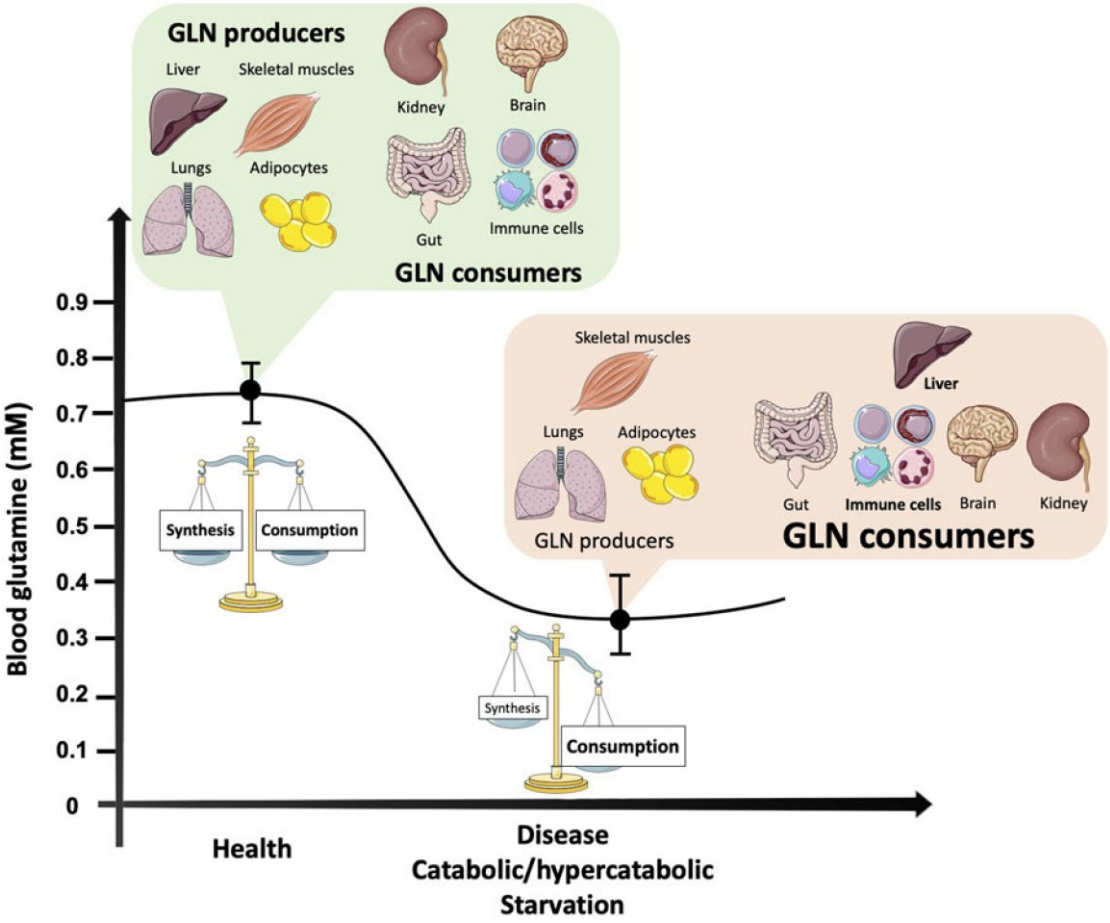

Figure 1 (from Newsholme et al.[1]) - Blood glutamine concentration changes according to the balance between major organ producers and consumers in health and catabolic situations.

As the most abundant and versatile amino acid in the body, glutamine (GLN) availability depends on the balance between its synthesis, release, and uptake by organs and tissues. In turn, multiple intracellular pathways require GLN as a substrate to maintain homeostasis. In normal health and diet, there is a balance between GLN synthesis and degradation, while in catabolic situations, organs responsible for GLN synthesis reduce their production, such as skeletal muscle tissue. Other GLN producers, such as the adipose tissue and the lungs, do not have the capability to replenish the needs of the amino acid during catabolism. Moreover, the liver, a primary glutamine producer under healthy conditions, becomes a major glutamine consumer under disease/stressed conditions, due to its role in supporting gluconeogenesis. At the same time, cells of the immune system increase their demand for both GLN and glucose. Although the brain and kidneys may have their GLN capabilities altered according to the disease/catabolic condition, no significant changes may counteract the fall in glutamine availability.

Background

Glutamine is the amide (an amide is any functional group containing a carbonyl group linked to a nitrogen atom) of glutamic acid and is uncharged under all biological conditions (neutral L-α-amino acid containing five carbons). Glutamine is the most abundant free amino acid (AA) in the body (up to 50% of the free AA pool in the blood and skeletal muscle).[8,9,10] GLN has two amino groups. The α-amino group and the easily hydrolysable side-chain amide group enable glutamine to play a role as a nitrogen transporter and NH3 carrier. Additionally, GLN is a proteinogenic amino acid (amino acids that are incorporated into proteins) and accounts for 5 to 6% of bound amino acids.[11] Healthy individuals weighing ~150 pounds have roughly 70 to 80 grams of GLN distributed in the whole body.[12] It has been estimated that GLN endogenous production is between 40 and 80 g/day.[13,14] Recorded in a fasting state, plasma GLN concentration varies between ~500 and 800 µM/L, representing ~20% of the total free amino acids pool in the blood.[11] In tissues, such as the liver and the skeletal muscles, GLN concentrations are higher, representing about 40% to 60% of the total amino acid pool.[15,16] Collectively, GLN concentration is 10- to 100-fold greater than that of any other amino acid.[2]

In the total body, GLN concentration and availability depend on the balance between its synthesis and/or release, as well as organ uptake/needs. The lungs, brain, skeletal muscles, liver, and adipose tissue have tissue-specific glutamine synthesis activity. Conversely, predominantly glutamine-consuming tissues, such as immune cells/leukocytes, intestinal mucosa, and renal tubule cells, have high glutaminase activity, thus capable of degrading glutamine.[2] However, the liver may become a glutamine-consuming site, causing tissues, such as muscle tissue, to reduce glutamine synthesis during conditions like reduced carbohydrate[17] and/or amino acid[18] intake, high catabolic situations (e.g., intense exercise), and/or diseases and stress.[1,3] Other components, primarily glucocorticoids,[19] thyroid hormones,[20] growth hormone,[21] and insulin,[22] will influence the activity of glutamine metabolism-regulating enzymes. There are two main intracellular enzymes involved in glutamine metabolism (**see Figure 2**), which are glutamine synthetase (GS) and phosphate-dependent glutaminase (GLS). GS triggers the reaction that synthesizes glutamine from ammonium ion (NH4+) and glutamate via ATP consumption. GLS, through hydrolysis, converts GLN into glutamate and NH4+ again[23] (Figure 2). The locations of these two enzymes align with their functions: GS produces GLN for the synthesis of cytoplasmic proteins and nucleotides. GLS catalyzes the conversion of GLN to glutamate, a crucial step in the tricarboxylic acid cycle (TCA)/Krebs cycle, serving as an energy source or a metabolic intermediate.[1,2]

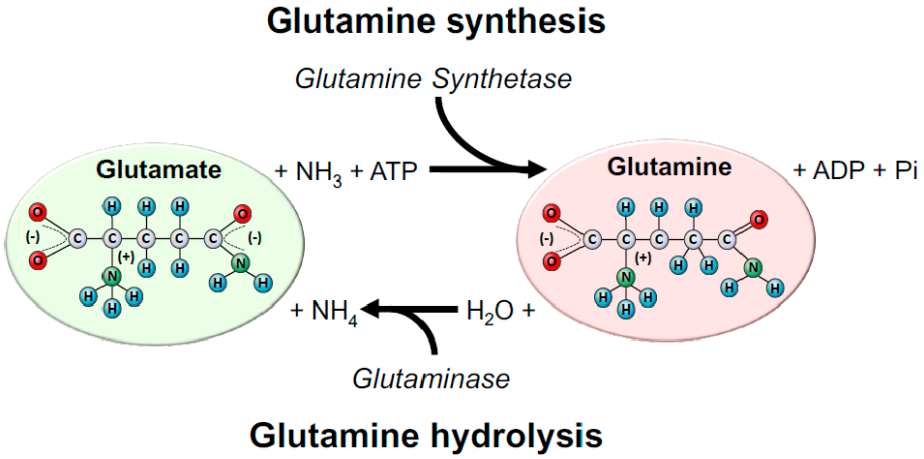

Figure 2 (from Cruzat et al.[2]) - Glutamine synthesis and hydrolysis. GLN is primarily synthesized by the enzyme glutamine synthetase (GS) and hydrolyzed by glutaminase (GLS). GS catalyzes GLN biosynthesis using glutamate and ammonia (NH3) as a source, in which one ATP is consumed. Glutamate can be donated by many amino acids obtained exogenously and/or from endogenous amino acid catabolism. GLS is responsible for the hydrolysis of glutamine to glutamate and an ammonium ion (NH4). Most cells in the body express GS and GLS, and their predominant expression and activity will determine if the tissue tendency is to produce or consume GLN in health and disease.

Under catabolic conditions (see Figure 3), such as infections, burns, surgeries, sickness, intense, prolonged physical activity, etc., endogenous GLN cannot meet the body's demands, giving rise to its classification as a conditionally essential amino acid and rationale for exogenous sources, including oral and intravenous supplementation.[1,2,6] Under these stressful conditions, a concomitant increase in GLS expression and inhibition of GS action occur. This stress- or sickness-related excessive tissue catabolism leads to reduced GLN concentrations (from 500-800 µmol/L to 300-400 µmol/L), primarily in muscle and liver, with the latter becoming a GLN consumer rather than a producer (Figure 3). While the blood glutamine concentration can fall by up to 30–50% under catabolic conditions, skeletal muscle GLN concentration can fall by up to 50%.[24,25] The low GLN concentration affects the entire body, as GN supplies nitrogen atoms for the synthesis of purines, pyrimidines, and amino sugars.[26] When this increase in GLN degradation persists, the many metabolic pathways and mechanisms that depend on GLN availability are negatively affected, resulting in immunosuppression.[1,2,3]

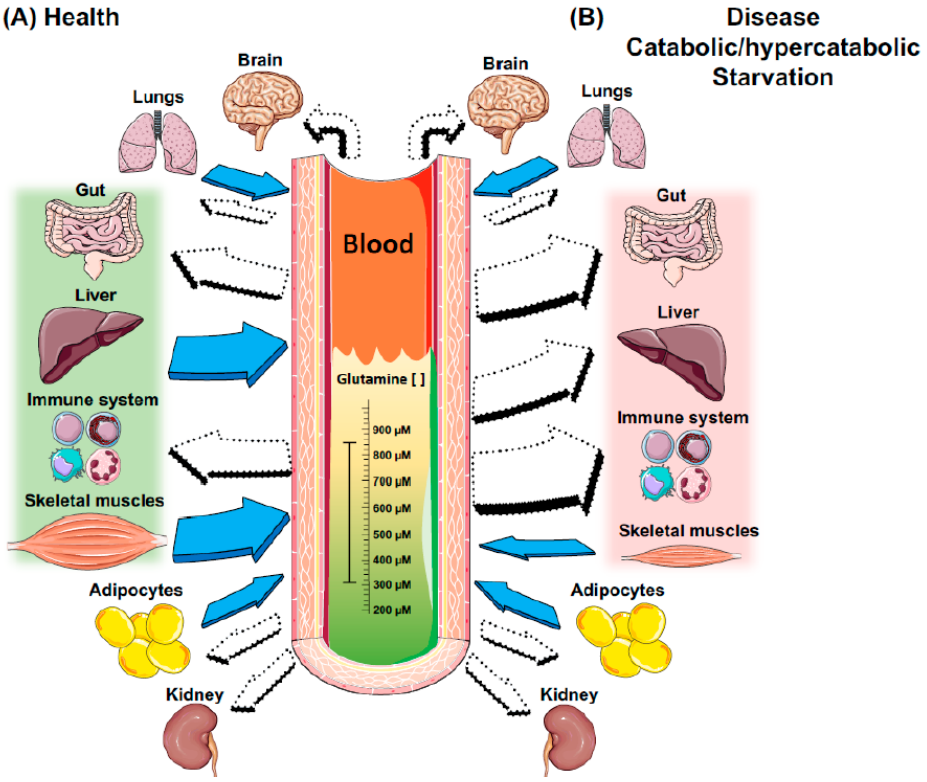

Figure 3 (from Cruzat et al.[2]) - Inter-tissue GLN production and utilization in health and catabolic/hypercatabolic situations. Filled arrows indicate tissues that exhibit GS activity producing glutamine; white arrows indicate tissues that express GLS activity, therefore consume GLN. In healthy and/or fed states, GLN stores are in equilibrium in the plasma/bloodstream and tissues. They are being continuously maintained primarily by the liver and skeletal muscles, the two major stores of glutamine in the body. As the figure depicts, cells of the immune system are incredibly dependent on glucose and glutamine in situation (**A**), and even more in situation (**B**). Although the gut is a major site of GLN consumption, in catabolic states (B), there is a significant increase in GLN consumption from both the luminal and basolateral membranes. Additionally, the liver transitions from being a major GLN producer to a major consumer to support gluconeogenesis, and the whole body now relies on the skeletal muscles' ability/stores to maintain glutamine levels. Nevertheless, this process is generally accompanied by significant increases in muscle proteolysis (breakdown), resulting in atrophy/cachexia. The lungs and adipose tissue express both GS and GLS enzymes; therefore, they can produce and consume glutamine in situations (**A**) and (**B**). The brain and the kidneys do not exhibit GS, only GLS, and thus are primarily dependent on plasma GLN availability in situations (**A**) and (**B**).

Role of Skeletal Muscle in Glutamine Metabolism

Skeletal muscle is central to glutamine metabolism, serving as the primary reservoir, synthesis site, and GLN release point. With 50-60% of total free amino acids in muscle being GLN, skeletal muscles house approximately 80% of the body's GLN, maintaining concentrations up to 30 times higher than plasma levels. The processes influencing GLN dynamics within muscle include hormonal regulation, active transport systems, and metabolic turnover.[2,27] During the post-absorptive state, approximately 50% of the GLN synthesis in the skeletal muscle happens via glutamate uptake from the bloodstream, a major part of the glutamine-glutamate cycle. Additionally, muscle protein catabolism directly produces GLN and causes the release of BCAAs, glutamate, aspartate, and asparagine. The carbon skeletons of these amino acids are used for GLN de novo synthesis.[2,28] GLN and alanine, make up 48% and 32% respectively, of the amino acids released by the skeletal muscle in the post-absorptive state. The GLN molecule, containing two nitrogen atoms, is the primary muscle nitrogen-release source. The GLN and alanine exchange rates exceed their body concentrations, and their abundance in muscle protein corresponds to 10–15%, indicating the continuous need for GLN and alanine de novo synthesis in the skeletal muscle.[2,3,27] The GLN synthesis rate in the skeletal muscle (approximately 50 mmol/h) is greater than that of any other amino acid. Therefore, GLN and alanine result from the interconversion of amino acids within the cell, in a process driven by the cell's metabolic conditions, which are affected by the host's nutritional and hormonal status, and physical activity/exercise.[2,4,6,7,10,29,30]

Summary of Metabolism and Mechanisms of Action:

1. **Synthesis and Release**:
    - Glutamine is synthesized in skeletal muscle primarily from glutamate and through protein catabolism.[31] Slow-twitch (type 1) muscle fibers exhibit higher glutamine levels than fast-twitch fibers due to increased glutamine synthetase (GS) activity and ATP availability.[2,29]
    - Hormones like insulin and IGFs promote intracellular glutamine transport, while glucocorticoids facilitate its release.[32]
2. **Transport**:
    - Glutamine is actively transported across cell membranes via sodium-dependent channels, consuming ATP.[33] Intracellular and extracellular concentrations, alongside competing amino acids, regulate transport efficiency.[2,9,34]
3. **Stress and Catabolic States**:
    - During severe catabolic conditions (e.g., sepsis), muscle glutamine concentrations decrease due to protein breakdown, while GS activity and glutamine synthesis increase.[2,35,36]
    - Glucocorticoids enhance GS mRNA transcription, though post-transcriptional mechanisms, fine-tune GS activity based on intracellular glutamine levels.[2,18,37,38]
4. **Gene Expression and Pathways**:
    - Glutamine influences the expression of muscle contractile proteins and activates pathways like mTOR, essential for regulating tissue size and mass.[2] Moreover, the use of essential amino acids, primarily leucine, as anabolic promoters in muscle cells has its influence compromised via mTOR when GLN is limited or not available.[18] Despite GLN's essential role in regulating the expression of muscle content-associated genes, no healthy human studies have found that GLN supplementation by itself (e.g., no supporting exercise, diet, etc.) can promote skeletal muscle increase.
    - GLN modulates stress responses by influencing the expression of heat shock protein (HSP) and antioxidant systems, such as glutathione synthesis.[1,2,39]
5. **Gut Health**
    - Promotion of intestinal integrity.[40,41,42] The importance of glutamine in intestinal physiology and management of several gastrointestinal diseases has been reported regularly,[43,44] as it has been shown to promote enterocyte proliferation (the intestines utilize about 30% of total glutamine[45]), regulate tight junction proteins, suppress proinflammatory signaling pathways, and confer protection

against apoptosis and cellular stresses during normal and pathological conditions.[46] Moreover, 70% of the immune system resides in the gut.[47] Therefore, the gut and the immune system support one another to promote homeostasis. Moreover, poor gut health can disrupt the balance of neurotransmitters, which can result in neuropsychiatric-based conditions such as depression. Glutamine supplementation may provide significant adjunctive nutritional support in cases of depression by promoting proper gut health and function.[41]

6. **In Exercise**
   - Muscle glutamine levels are critical for maintaining metabolic homeostasis during physical activity, as the availability of glutamine supports mTOR pathway activation, promoting muscle recovery and growth. Furthermore, GLN availability is a limiting step for this mTOR complex 1 activation pathway, a primary control point for cell size, including skeletal muscle. Conversely, a lack of availability caused by the stresses mentioned above, including chronic caloric restriction and prolonged intense exercise bouts, compromises MPS activities as well as immunity.[4,6,7,10,**Error! Bookmark not defined.**,29,**Error! Bookmark not defined.**,48,49] Glutamine acts as a fuel for rapidly dividing immune cells, while interleukin-6 (IL-6 is a signaling molecule that helps regulate immune responses) mediates inflammation and repair. Exercise-induced muscle contractions increase glutamine and IL-6 production, initiating a well-regulated immune response.[27] Therefore, regular balanced physical activity is important for maintaining immune health and metabolic balance (Figure 4). However, there are potential negative consequences from excessive activity/stress to immunity and muscle structure and function (intense, short-term exercise increases glutamine production, while prolonged or intense exercise reduces plasma glutamine levels. Post-exercise depletion leads to impaired immune function, including reduced lymphocyte and macrophage activity).[27,50,51]
   - Glutamine also serves as an osmolyte in regulating cell homeostasis in hyper- and hypo-osmolar conditions through cell shrinkage and swelling, conditions that may play a role in the regulation of protein synthesis.[52,53] However, under homeostatic conditions, supplementation alone does not directly induce muscle mass increases without combined nutritional and exercise interventions.

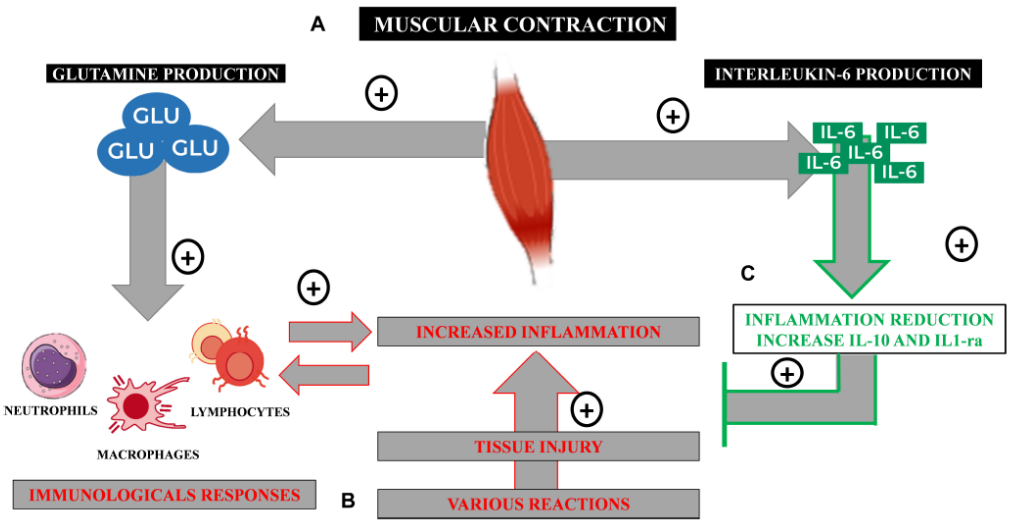

Figure 4 (from Rogeri et al.) - **Immunometabolic processes from the practice of physical exercises**. (A) Glutamine is synthesized by the active skeletal muscle in an ATP-dependent reaction and released to the plasma by a bidirectional Nm transportation system. (B) Under infectious or inflammatory conditions that lead to tissue injury, an inflammatory reaction takes place, activating immune cells, such as neutrophils, macrophages, and lymphocytes. These cells consume large amounts of glutamine to keep their function and immunological performance,

including pro-inflammatory cytokines' synthesis, such as IL-6. (C) The skeletal muscle is also capable of producing myokines*, such as IL-6, that, in this case, has an anti-inflammatory property, regulating inflammation and assisting on tissue healing processes.[27]

7. Immune System:

- GLN serves as a fuel for rapidly dividing and growing cells, such as the enterocytes (gut cells) and activated immune cells/lymphocytes[54,55] and aids in antioxidant defenses.[56] GLN mitigates oxidative stress by supporting glutathione production and heat shock protein (HSP) expression, both of which are crucial during inflammation and injury.[1,2,3,57, 58,59]
- The anti-inflammatory and cytoprotective properties of glutamine help modulate NF-κB pathways*, reducing apoptosis and tissue damage.[1,2,3]

* NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) plays a crucial role in both innate and adaptive immune responses, regulating the expression of genes involved in inflammation and pathogen defense.

Glutamine in Skeletal Muscle, Immunity, and Exercise Summary

Skeletal muscle's role in glutamine metabolism extends beyond a simple storage function, involving dynamic synthesis, transport, and regulatory mechanisms essential for exercise performance, immune defense, and overall metabolic stability. Because of the many important functions of glutamine (described throughout and below) there is a dramatic increase in the net release of glutamine from peripheral tissues, especially muscle, to central tissues (e.g. liver [switching from producer to consumer], immune system, etc.) during inflammatory and other physically stressful conditions, giving rise to the basis of supplementation during clinical (trauma, infection, wound healing, etc.) and non-clinical (intense prolonged exercise) situations.

Functions of Glutamine

- Substrate for protein, citrulline, and arginine synthesis
- Ammonia scavenger
- Nitrogen donor and transport mechanism
- Shuttle for glutamate for the central nervous system
- Provision of NADPH (stimulating intermediary metabolism and preventing apoptosis by supporting mitochondria function) to increase neutrophil and lymphocyte activity and function
- Substrate for glutathione production and redox balance (NADPH production)
- Activates heat shock factor 1 (HSF-1).* Tissue protection from enhanced heat shock expression by activating nutrient receptors (sirtuin 1/human antigen R), leading to the activation of heat shock transcription factor in the nucleus, favoring cell survival
    * Heat shock factor 1 (HSF-1) is a crucial transcription factor that plays a central role in the heat shock response (HSR, a cellular response that activates genes encoding heat shock proteins [HSPs], AKA molecular chaperones), a cellular mechanism activated by various stressors, including heat, to protect cells from damage by inducing the expression of HSPs, thus promoting cell survival and proper function.
- Stimulates glycogen synthesis
- Substrate for hepatic ureagenesis and hepatic and renal gluconeogenesis
- Participates in acid-base balance
- Fuel for intestinal enterocytes
- Nucleic acid precursor and involved in the generation of cytotoxic substances in immunocompetent cells
- Involved in cell volume through osmotic signaling, potentially related to protein synthesis and injury

Glutamine's Role in the Immune Response and Healing Process During Stressful Challenges

Glutamine plays a crucial role in various aspects of the immune response and healing process during stressful challenges. Below is a comprehensive list of its involvement:

1. Production and Supply of Glutamine[2,60,61]

Source: Skeletal muscle synthesizes and releases glutamine, especially during physical activity or stress, in an ATP-dependent process mediated by glutamine synthetase (GS). Glutamine is transported to the plasma through a bidirectional transportation system, influenced by glucocorticoids and insulin levels (Figure 4).

2. Glutamine as a Fuel for Immune Cells[54,55,62,63, 64,65]

Primary Energy Source: Glutamine serves as a key energy substrate for rapidly dividing immune cells like lymphocytes, macrophages, and neutrophils. Cell functions supported:

- **Lymphocytes**: Proliferation, interleukin-2 (IL-2) production, and antibody synthesis.
- **Macrophages**: Phagocytosis, antigen presentation, and cytokine production.
- **Neutrophils**: Oxidative burst and pathogen killing.

3. Stress-Induced Glutamine Dynamics[4,6,10,Error! Bookmark not defined.,29,30,27,28,30,48,49,66]

Exercise Impact: Intense, short-term exercise increases glutamine production, while prolonged or intense exercise reduces plasma glutamine levels. Post-exercise depletion leads to impaired immune function, including decreased lymphocyte and macrophage activity.

Stress Conditions:

Bodily stressors, including severe burns, sepsis, infections, undernourishment, excessive physical activity, or major surgeries, can cause a demand-supply imbalance, turning glutamine into a conditionally essential amino acid requiring an exogenous influx.

4. Regulation of the Healing Environment[1,2,3,29,56,57,67,68,]

Immune Cell Modulation: Glutamine enhances the immunological microenvironment by regulating cytokine synthesis, such as IL-6. It supports macrophage polarization from pro-inflammatory (M1) to anti-inflammatory (M2) phenotypes. Glutamine helps regulate heat shock proteins (HSPs) and neutralize reactive oxygen species (ROS), mitigating oxidative stress and preventing muscle catabolism. Through its conversion to glutamate, glutamine contributes to glutathione synthesis (a precursor), a powerful antioxidant critical for cellular protection and regeneration.

5. Role in Muscle and Immune System Crosstalk[27]

Competition for Glutamine: During intense muscle contractions, glutamine is consumed by the muscle itself, thereby limiting its availability for immune cells and potentially compromising their function. As markers for stress, plasma glutamine levels are used as an indicator of exercise severity and overtraining.

6. Glutamine Depletion Consequences[1,2,3,26,Error! Bookmark not defined.,48,60,71,]

Immune and Daily Recovery Impairment: Depleted/low GLN concentration affects the entire body, since GLN supplies nitrogen atoms for the synthesis of purines, pyrimidines, and amino sugars. When this increase in GLN degradation persists, the many metabolic pathways and mechanisms that depend on GLN availability are negatively affected, resulting in immunosuppression, including reduced oxidative burst in neutrophils, decreased T-cell proliferation, impaired macrophage phagocytosis, and increased susceptibility to infections (e.g., upper respiratory tract infections).

Furthermore, with delayed recovery, insufficient glutamine disrupts muscle repair and the function of related immune cells, as well as overall recovery from stress or injury.

7. Clinical and Supplementation Insights[1,2,3,4,30,39,48,49,69,70, 71,72,73]

Supplementation: Currently, glutamine is routinely supplied as a component of clinical nutrition supplementation for pre- and post-operative patients, burn victims, sepsis, etc., and for many elite athletes to restore immune functions and for its potential antioxidant and anti-inflammatory effects (i.e., recovery). In the latter group, while supplementation has shown some benefits (e.g., preventing post-exercise immune suppression and improving recovery parameters), results remain mixed and context-dependent (see the next section, "Glutamine in Exercise and Sport," for related studies). Additionally, branched-chain amino acids (BCAAs), precursors to glutamine, have demonstrated efficacy in enhancing glutamine availability and supporting immune responses.

In conclusion, glutamine is intricately involved in regulating energy metabolism, immune responses, and tissue repair during and after stressful challenges. It functions as a critical bridge between skeletal muscle and immune system activity, modulating both inflammatory and anti-inflammatory processes to promote healing. Under extended catabolic conditions (see Figure 3 and 5), such as infections, burns, surgeries, sickness, intense, prolonged physical activity, etc., endogenous GLN cannot meet the body's demands, compromising all areas of metabolism where GLN is active, especially the gut and immune system, giving the rationale for exogenous sources, including oral and intravenous supplementation.

Supplemental Data

For readers interested in current details on the roles and interactions of exercise, skeletal muscle, and glutamine during stressful challenges to the host, we refer you to the scientific publication by Rogeri et al., "Crosstalk Between Skeletal Muscle and Immune System: Which Roles do IL-1 and Glutamine Play?" [27] The following is a summary of interactions with all references contained within the published document.

Main Points on the Crosstalk Between Skeletal Muscle and the Immune System

1. **Glutamine's Role**:

Glutamine, a non-essential amino acid, serves as a key link between skeletal muscle and the immune system. Produced by active skeletal muscle, it provides energy for leukocytes, supporting their functions, such as phagocytosis, antigen presentation, and cytokine synthesis. Glutamine levels fluctuate in response to stress, exercise, or certain health conditions, and deficiencies can compromise immune function.

2. **Interleukin-6 (IL-6)**:

IL-6, a cytokine produced by skeletal muscles during exercise, has dual pro-inflammatory and anti-inflammatory roles. Acute IL-6 levels increase during exercise to support muscle repair, lipid oxidation, and insulin sensitivity, whereas chronic high levels are associated with inactivity and metabolic disorders.

3. **Lymphocytes and Other Immune Cells**:

Exercise induces transient leukocytosis followed by lymphocytopenia, involving T cells and macrophages. These immune cells are integral in managing the inflammatory response to muscle damage, transitioning from pro-inflammatory to anti-inflammatory state for tissue repair.

4. **Macrophage Dynamics**:

Macrophages play a central role in muscle repair, transitioning from M1 (pro-inflammatory) to M2 (anti-inflammatory) phenotypes. GLN is essential for maintaining proper macrophage balance, which is crucial in preventing excessive inflammation or fibrosis and ensuring effective tissue regeneration.

5. **Exercise and Immune Modulation (Figure 4)**:

Regular physical activity enhances immune-metabolic crosstalk, with skeletal muscle acting as an endocrine organ by releasing myokines, such as IL-6. Exercise-induced immune changes promote a controlled inflammatory response, preventing chronic inflammation while supporting muscle repair.

***Myokines are small proteins or peptides secreted by muscle cells in response to physical activity. They play a crucial role in inter-organ communication, influencing various physiological processes.**

6. **Therapeutic Implications**:

Understanding the roles of glutamine and IL-6 may lead to targeted interventions for conditions such as sarcopenia, metabolic syndrome, and chronic inflammation.

Summary:
The Rogeri et al. review[27] explores the intricate communication between skeletal muscles and the immune system, focusing on the roles of GLN and interleukin-6 (IL-6). Skeletal muscle, beyond its biomechanical role, functions as an endocrine organ, producing myokines like IL-6 and GLN during activity. These molecules influence immune cell behavior, particularly lymphocytes and macrophages. GLN acts as a fuel for rapidly dividing immune cells, while IL-6 mediates inflammation and repair. Exercise-induced muscle contractions increase the production of GLN and IL-6, initiating a well-regulated immune response (Figure 4). Acute exercise triggers a pro-inflammatory phase essential for clearing debris and activating satellite cells. This is followed by an anti-inflammatory phase that promotes tissue repair and regeneration. Macrophages transition from M1 to M2 phenotypes, balancing inflammation and repair processes. Chronic disorders and stresses, including physical or prolonged diet restrictions, disrupt this balance, often leading to excessive inflammation (or fibrosis in severe cases). Interventions targeting GLN metabolism or IL-6 signaling may be appropriate therapeutic strategies for these conditions. Overall, the review highlights the dual role of skeletal muscle as a physical and immunological regulator, emphasizing the importance of regular balanced physical activity for maintaining immune health and metabolic balance, while describing the potential negative consequences from excessive activity/stresses to immunity and muscle structure and function (Figure 5), which supplemental glutamine may mitigate under specific related conditions. Therefore, delivering exogenous sources of GLN (either IV or orally) may assist in halting or reversing the effects of GLN depletion, including supporting immunity and skeletal muscle in highly stressed individuals.

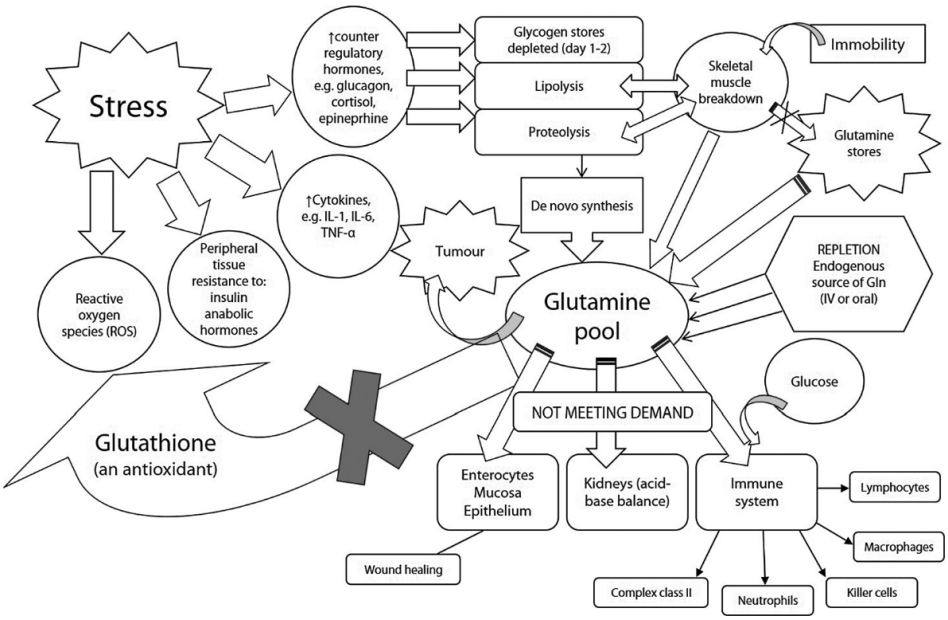

Figure 5 (From Tydeman-Edwards.[56]) - Depletion of Glutamine and Its Consequences During Stress
The enzyme glutamine synthetase, in skeletal muscle, responds to the increase in cortisol by up-regulating GLN release from skeletal muscle. Normally, GLN will be released to the glutamine pool, but, in catabolism/long-term stress, proteolysis leads to the *de novo* synthesis of GLN from other amino acids in support of energy needs and other functions. When demand exceeds supply, the GLN pool becomes depleted and normal GLN-dependent biological functions are compromised, leading to poor wound healing, acid-base imbalance, impaired muscle function/activity recovery, and compromised immunity.

Glutamine in Exercise and Sport

While glutamine's mechanisms of action and clinical success using supplementation as described above makes glutamine attractive to athletes, the evidence at this time supporting purported benefits is equivocal and probably explains why it's generally a "no-show" on expert lists (other than lessening the incidence of exercise-induced upper respiratory tract infection [URTI][50,73,74,75,76,77]) of effective *ergogenic* aids for healthy athletes.[74,78,79,80,81] That said, glutamine supplementation has survived the test of time. Many athletes continue to use it during intense training and long-duration activities, and/or for competitions, believing it helps recovery, gut health, and immune function (lessening viral infections/sick days), especially when combined with severe or prolonged energy restriction.[82,83] An explanation for the aforementioned phenomenon may be that athletes who perceive success may, through their specific diets and activities, actually deplete enough glutamine stores or surpass endogenous glutamine's ability to function optimally in respective protective pathways. Additionally, when L-glutamine is ingested, the amino acid is largely metabolized in the rapidly reproducing gut tissues (~70%)[84,85] potentially leaving less available for other dependent systems, including its role in reducing skeletal muscle breakdown, immune cell function, antioxidant production, etc., thus causing confusion on proper dosing.[27,86] To avoid this fate and to increase glutamine's potential effectiveness in other target pathways (e.g. glutathione synthesis, immune, heat shock and anabolic signaling, etc.), free-form glutamine is often supplied in larger amounts, whereas in dipeptide form (attached to another amino acid) such as alanine or glycine/bisglycinate chelate, which is currently common in clinical practice, may require lesser amounts. However, both free form and dipeptides have been shown to raise plasma glutamine concentrations within two hours.[73,87] In a dipeptide form, glutamine remains highly soluble and stable, allowing lower dosing than free-form FF in achieving desired levels in circulation because of the glycopeptide transport protein (PepT-1) in the enterocytes,

which has greater efficiency in transporting small peptides for absorption than free form AAs.[Error! Bookmark not defined.,88,89] In this sense, besides varied dosing protocols,[42] the form in which glutamine supplementation is ingested may also be a factor in potential desired (or claimed) efficacy – i.e., reaching target tissues in greater amounts (see di-peptide insert below in this section).[89,90,91,92] In summary, both free-form and dipeptide GLN can raise the body's GLN pool to desired levels, with the free-form possibly requiring higher dosing as shown in clinical studies. Furthermore, free-form GLN is significantly less expensive than many dipeptide clinical forms, making it a more cost-effective option in reaching desired levels through supplementation.

Glutamine Studies in Sport & Exercise

It should be noted that earlier studies found the oral dosage of L-glutamine that may attenuate the exercise-induced decrease in plasma glutamine and lymphocytes, thus lowering the risk of URTIs,[73] was approximately ~0.05 g/lb of body weight (10 g for a 200 lb person).[71,93] Other studies using fixed (20-30 g/day) found contrary results.[94] The latter may be due to the specific study designs, including the number of subjects, since current dosages that produced positive results are generally administered at 4-30 g/day or by body weight. Sticking with the above-stated goal of glutamine supplementation supporting the immune system, muscle metabolism, and overall recovery during intense, prolonged training regimens, the following are related clinical trials.

- Agostini F. et al. investigated the effect of physical activity on glutamine metabolism and suggested that following exercise, the reduced glutamine availability may be a marker of overreaching; thus, supplementation may decrease inflammation and enhance otherwise compromised immunocompetence after strenuous activity.[95]
- Sasaki E et al. tested 3,000 mg/day of glutamine supplementation on neutrophil function in 26 judoists during two weeks of intense training. The results showed that the glutamine-supplemented group prevented excessive muscle damage and suppressed neutrophil function, particularly in reactive oxygen species (ROS) production activity, during the strenuous training period.[96]
- Ga Hee Koo, et al. had subjects perform 2,000 meters of rowing at high intensity and take three different tests following completion on three separate occasions: using a placebo, branched chain amino acids (3.15 g/day), and glutamine (6 g/day) separately in each test. They found that, compared to the placebo, groups supplemented with BCAAs or glutamine showed a lower level of blood phosphorus during the recovery stage after maximal-intensity exercise. The glutamine group alone appeared to have a lower concentration of blood creatine kinase (CK), suggesting a positive effect on reducing factors that contribute to fatigue. Differences in measurements of blood IL-6 and IL-15 were found between the resting stage and the end of exercise in both placebo and BCAA groups, but not in GLN-only test groups. The authors concluded that glutamine supplementation could be beneficial for enhancing immune function and mitigating the inflammatory response after exercise.[97]
- Song QH, et al. had athletes performing heavy training loads for six weeks. During that time, the experimental group took 10 g of glutamine orally once a day, three weeks after the initial testing, while athletes in the control group received a placebo. Immune function was assessed by measuring the following immunity markers: CD4 and CD8 T cell counts, serum IgA, IgG, and IgM levels, and natural killer (NK) cell activity both before and after the completion of training. While there were no observed differences in serum IgA, IgG, or IgM levels, all other tested levels in the experimental group were positively affected, leading to the conclusion that "glutamine supplementation may be able to restore immune function and reduce the immunosuppressive effects of heavy-load training."[98]
- Rahmani et al. found that glutamine administered daily at .045 g/lb of body weight had no effect on muscle injury markers following six sets to exhaustion of eccentric leg extensions at 75% of 1RM. However, glutamine supplementation appeared to attenuate delayed onset muscle soreness (DOMS).[99]
- Legault et al. tested the effects of glutamine (GLN) and placebo supplementation on quadriceps muscle strength and soreness ratings following exhaustive eccentric exercise. The GLN group used .136 g/lb/d of GLN with equal maltodextrin. The placebo was isocaloric at .272 g/lb/d. L-glutamine resulted in greater relative peak torque both immediately after (71% vs. 66%) and 72 hours (91% vs. 86%) post-exercise. In the entire sample (men and

women), L-glutamine resulted in lower soreness ratings at 24 (2.8 vs. 3.4), 48 (2.6 vs. 3.9), and 72 (1.7 vs. 2.9) hours post-exercise. The authors concluded, "Glutamine supplementation resulted in faster recovery of peak torque and diminished muscle soreness following eccentric exercise. The effect of L-glutamine on muscle force recovery may be greater in men than women."[100]

- It is well known that intense exercise is associated with an increase in intestinal permeability, also known as "leaky gut," and can lead to negative inflammatory responses.[101,102] Micah N. Zuhl et al. tested the effects of seven days of 0.4 g/lb/d/fat free mass of glutamine supplementation vs. placebo on exercise-induced gastrointestinal permeability and tight junction (TJ) protein expression (up-regulation of heat shock response/ HSF-1 activation). Supplementation raised plasma glutamine levels by 128%. They found that glutamine supplementation in response to exercise stress: 1) prevented exercise-induced intestinal permeability; 2) enhanced the peripheral blood mononuclear cells (PBMC) level IκBα (suggesting a blunted inflammatory response; 3) increased HSF-1 and HSP70 in response to heat; 4) preserved the stability of occludin (typically declines with heat) at the TJ. The authors suggested the protective effects of glutamine on the gut during vigorous exercise may be multi-pronged: *1*) through preserving the intestinal TJ barrier and reducing permeability; and *2*) via modulation of the inflammatory response through activation of HSP70 and cytosolic housing of NF-κB, thus inactivating its pro-inflammatory pathway.[72]
- Favano et al. used 50 g of maltodextrin (carbohydrate [CHO]) combined with glutamine peptide (CHO/GP), supplying 3.5 g of glutamine vs. 50 g of CHO alone and given 30 minutes before the event, to investigate potential soccer performance enhancement. The conclusion was that the CHO/GP increased athletes' distance and duration of tolerance to intermittent exercise, and lowered feelings of fatigue in players compared to CHO alone. Thus, supplementation with both carbohydrate and peptide glutamine improved the physical performance of these soccer players.[103]
- The Coqueiro et al. review found that most of the studies observed that glutamine supplementation improved some fatigue markers, such as increased glycogen synthesis and reduced ammonia accumulation, but this intervention did not increase physical performance. Thus, despite improving some fatigue parameters, glutamine supplementation seems to have limited effects on performance.[6]
- Ma et al. found that cystine and glutamine supplementation alleviated fatigue by decreasing ratings of perceived exertion (RPE) and enhanced fatty acid oxidation during a 60-minute endurance exercise in human trials – summarizing these positive effects on ameliorating exercise-induced fatigue can be attributed to the enhancement of fatty acid utilization.[5]
- Amirato et al. demonstrated that 10 g/d of glutamine supplementation versus placebo in elderly women (60-80 years), when combined with exercise, improves strength and power of knee muscles (muscle measured endpoint) and glycemia control while boosting their plasma antioxidant capacity.[7]
- A review by Newsholme et al. found that overall, the current data indicates that glutamine supplementation may provide important metabolic and immunological support in catabolic situations, including critical care and elite athletes. However, any lack of consensus is likely related to the fact that the quantity, dosage, and frequency of L-glutamine supplementation, as well as the presence or absence of other conditions such as amino acids metabolized by enterocytes, significantly impact the desired amino acid supplementation outcomes.[1]
- Córdova-Martínez et al. in a double-blind, placebo-controlled trial, analyzed the effect of glutamine on exercise-induced muscle damage by determining muscle blood markers in a team of professional basketball players during a very demanding competition period. Twelve participants were supplemented with 6 g/day of glutamine (G group) or placebo (P group) for 40 days in a crossover study design (20 days with glutamine + 20 days with placebo and vice versa). They concluded that: "the data showed that glutamine supplementation results in a decrease of circulating muscle damage markers accompanied by an adequate balance between the response of the catabolic and anabolic hormones and the stability of leucocyte cell numbers. We hypothesize that controlling these specific parameters could help prevent the inflammation and stress provoked by highly strenuous exercise. From a

practical point of view, glutamine supplementation (GS) could help in recovery after intense and demanding eccentric exercises that produce muscle damage with a high risk of lesions."[Error! Bookmark not defined.] This study highlights the primary rationale for athletes' use of GS, which is enhanced recovery and immune support that hopefully helps to reduce injuries or sickness and allows not just improved readiness for subsequent training bouts, but also leads to a longer competitive career or prolonged ability to remain active.

- In line with the Córdova-Martínez et al. study and further support for the athlete's rationale for GS, Lu et al. reported that three weeks of supplementation with L-glutamine (0.3 g/kg/d {~20-25 g/d]) after combat training significantly increased the immunoglobulin A (IgA), nitric oxide and testosterone/cortisol (T/C) ratio in saliva, decreased the incidence of upper respiratory tract infections (URTI), and led to better mood status. Conclusion: "These findings suggest that habitual or intense supplementation of L-glutamine has the potential to prevent anabolic/catabolic hormonal disturbances caused by prolonged and intensive training and enhance the mucosal immunity, thereby helping athletes maintain their health, enhance recovery, and improve sports performance".[50]

Dipeptides

Note: Although it may require a higher dose of free-form GLN to achieve the same level as a lower dose dipeptide, such as alanine-glutamine, the cost-to-benefit ratio favors using a free-form GN supplement. Meaning, using FF GN at higher doses is still less expensive to achieve equal levels of GLN in the body and subsequent results.

As described above, glutamine supplementation in a dipeptide form also raises bodily GLN levels. GLN combined with alanine or glycine[104,105] including glycine chelates (often combined with minerals to enhance their absorption, including avoiding phytate sequestering[106,107,108]), may allow lower doses to achieve the same result as higher doses of FF GLN, due to a combination of greater stability (especially in low pH),**Error! Bookmark not defined.** and an enhanced rate of absorption via specific ion transporters within intestinal epithelia.[109] Notably, acute ingestion of an alanine-glutamine dipeptide (AG) was found to enhance fluid uptake and attenuate performance loss during exercise to exhaustion under hypohydrated conditions, compared to water alone.[110]

- Hoffman et al. examined the efficacy of L-alanyl-L-glutamine (AG) ingestion on basketball performance, including jump power, reaction time, shooting accuracy, and fatigue. Female basketball players participated in four trials, each consisting of a 40-minute basketball game with controlled time-outs for rehydration. The first trial (DHY) subjects were not allowed to rehydrate, and the weight lost was used to establish fluid replenishment during the subsequent three trials. In one trial, participants consumed only water (W), while during the other two trials, subjects consumed the AG supplement mixed in water using either a low dose of 1 g/500 ml for a total of 6 g AG (AG1) or a high dose of 2 g/500 ml for a total of 12 g AG (AG2) concentration. The results showed subjects in the DHY trial lost 2.3% of body mass. No differences in fluid intake were seen between rehydration trials. A 12.5% difference in basketball shooting performance was shown between DHY and AG1, and an 11.1% difference between AG1 and W. Visual reaction time was significantly greater following AG1 compared to DHY. Differences in fatigue, determined by player loads, were seen only between AG2 and DHY. No differences were noted in peak or mean vertical jump power during any trial. The authors concluded that rehydration with AG appears to maintain basketball skill performance and visual reaction time to a greater extent than water alone.[111]
- In the same vein as Hoffman et al., McCormack et al. examined the use of l-alanyl-l-glutamine (AG) in a sports drink versus a sports drink alone on time to exhaustion and physiological measures during prolonged endurance exercise. Twelve endurance-trained men performed four trials, each consisting of a one-hour treadmill run at 75% of their VO2 peak, followed by a run to exhaustion at 90% of their VO_2 peak. The first trial was with no hydration (NHY); the second consisted of ingestion of only a sports drink (ED); the third trial utilized a low dose of AG (LD) of 300 mg/500 ml, and the fourth trial utilized a high dose of AG (HD) with 1 g/500 ml added to the sports drink. During the fluid ingestion trials, 250 mL was consumed every 15 minutes, resulting in a total of 600 mg AG in LD and 2 g in HD. Time to exhaustion was significantly longer during the LD and HD trials compared to NHY, while there were no differences in time to exhaustion between ED and NHY. Plasma glutamine concentrations were significantly elevated at 45 minutes in both LD and HD trials and remained elevated at 60 minutes during the HD

trial. At 60 minutes, plasma sodium was significantly lower in all trials compared to NHY. These results indicate that even a relatively low dose of an alanine-glutamine dipeptide can significantly improve time to exhaustion during high-intensity exercise compared to a sports (electrolyte) drink alone.[112] Pruna GJ, et al., using the same dosages and basic testing protocol, found similar results related to upper and lower body reaction times following exhaustive exercise.[113]

- Mahdi Khorshidi-Hosseini, et al. tested glutamine peptide supplementation with the carbohydrate maltodextrin (CHO), without CHO, and CHO alone on its ability to prevent anaerobic power decrease in repeated competitions. The four groups in this trial were as follows: 1) G group - GLN at .11 g/lb body mass, 2) M group – 50 g of maltodextrin, 3) GM group - 50 g of maltodextrin + GLN at .11 g/lb body mass and 4) Placebo - 250 ml of water and 30 g sweetener. Each participant performed Running-based Anaerobic Sprint Tests (RAST) three times, with one-hour intervals between each test. Max power, minimal power (min power) and fatigue were assessed for each subject. The study demonstrated that acute supplementation of GLN peptide with CHO, taken two hours before exercise, is more effective in preventing a decrease in anaerobic power than placebo, pure carbohydrate, or glutamine alone in repeated bouts of the RAST protocol, thereby improving performance.[114]
- In a pilot study, de Souza et al. tested 30 g/day for 14 days of oral GLN supplementation for its ability to favorably modify the gut microbiota composition in overweight and obese adults. The outcome was that the GLN group had altered the composition of the gut microbiota in overweight and obese subjects, reducing the Firmicutes to Bacteroidetes ratio (a biomarker for obesity), resembling the results of weight loss programs currently seen in science.[115]

Dosing and Composition

It has been established that both oral ingestion of free-form and peptide glutamine supplementation can raise the body's glutamine levels, and both have demonstrated safety and efficacy. The dosing amounts recommended here are based on positive studies using glutamine in free-form, which may also include mineral cofactors for added synergy, as there is a clear cost/efficacy benefit versus most peptide forms.

Amounts that have yielded positive results in supporting the immune system, intestinal integrity, and recovery related to exercise-induced stresses, range from approximately 5 to 40 g (or .05-0.2 g/lb of body weight) taken always before and sometimes split before, during, and after exercise. Based on the rapid depletion of endogenous glutamine during prolonged, demanding stress, it is logical that higher doses may be more appropriate, especially during extended periods of energy restriction, as in weight- or fat-conscious athletes attempting to "make weight" or achieve extremely low body fat. All considered, the optimal suggested dosing for stated goals may be 0.1 g/lb of body weight split three times daily, with half the dose 40 minutes before the exercise, a quarter of the dose immediately following, and the last quarter spaced at least eight hours from other doses, to get full daily coverage. For example, a 175 lb athlete would use ~18 g/day (0.1 g X 175 lb) of GLN with activity taking place at 8:00 AM:

- 9 g (1/2 of daily dose) at 7:20 AM (with pre-workout protein and carbohydrate formula/shake)
- 4.5 g (1/4 of the daily dose) immediately following activity
- 4.5 g (1/4 of the daily dose) before bed or mid-evening

Note: *long-duration activities (>3 hours) or continuous daily bouts with intermittent rest periods may require dosing during the span of all activities.*

Data Summary

Glutamine is the most abundant amino acid in the human body, playing vital roles in muscle metabolism, immune system function, gut integrity, and cellular energy. GLN becomes conditionally essential during times of physiological stress—such as intense exercise, illness, injury, or prolonged caloric restriction—when natural production cannot meet increased demand. Supplementing glutamine helps maintain homeostasis, preventing muscle breakdown, supporting immune cells, enhancing gut health, and aiding recovery. The rationale for supplementation is based on its role as a

primary fuel for immune and intestinal cells, precursor for antioxidants like glutathione, and modulator of key signaling pathways such as mTOR, critical for muscle growth and repair, all areas that will be compromised when the natural supply cannot meet the demand for establishing homeostasis.* Athletes, individuals under physical stress, and those with immune or gut challenges may benefit most. Dosing recommendations vary, but a common effective protocol is approximately 0.1 g per pound of body weight daily, split into three doses: half pre-workout, a quarter post-workout, and a quarter later in the day.

Supplementing GLN may be especially important for athletes or individuals undergoing intense training, as well as for anyone seeking to improve resilience and recovery under physical stress, particularly when combined with energy intake restrictions.

***The process by which the body maintains a stable internal environment despite external changes**

Typical Use

- Athletes and exercisers under prolonged demanding physical stress, and especially combined with extended periods of energy restriction, as in weight/body fat conscious athletes attempting to "make weight" or attain extremely low body fat.
- Anyone attempting to support the immune system, intestinal health/integrity, and/or recovery related to exercise/physical-induced stresses, including reducing the likelihood of overtraining/reaching or attenuating its general effects, and mitigating exercise-induced immune suppression.
- General instructions to support immunity, gut health, and overall exercise recovery:
    - Take 5 grams (1-scoop) three times daily, split evenly throughout the day. If exercising, take one dose before activity, one after, and one before bed (total 15 g/day)
- Strategic instructions to maximize all product goals, especially in hyperactive or stressed athletes, including ultra-endurance competitors:
    - Take approximately 0.1 g/lb of body weight split three times daily with half the dose 40 minutes before the exercise, one quarter of the dose immediately following, and the last quarter spaced at least eight hours from other doses to get full daily coverage. Example of 175 lb athlete: ~18 g/day with activity taking place at 8:00 AM:
        - 9 g at 7:20 AM (with pre-workout protein and carbohydrate formula/shake)
        - 4.5 g immediately following activity (ex, 11:00 AM)
        - 4.5 g before bed or mid-evening
- Long-duration activities (>3 hours) or continuous daily bouts with intermittent rest periods may require dosing during the span of all activities

Safety

As for all amino acids, there is no Upper Limit (UL) established for glutamine. Chronic use of very high doses (>30 g/day), as often used because of clinical necessity, may have adverse side effects, especially in clinically dependent subjects.[116] However, a systematic review assessing safety and efficacy for chronic high doses (≥30 g/day) used in cancer or burn patients found side effects similar to control groups and no signals of harm.[117,118] Large doses used in exercise-related studies have reported no toxicity; however, use should be restricted to intense training periods that can be cycled strategically throughout a competitive season/year.[1,5,6,7,**Error! Bookmark not defined.**,50,48,72]

Qualified practitioners needing more information related to these "Safety" categories (below), including drug interactions, are referred to the TRC Natural Medicine Data Base (TRCNMD), which is continually updated with emerging evidence-based data.[119] Glutamine supplementation is considered safe when used orally and appropriately and has been safely used in clinical research in doses up to 40 grams per day or 1 gram/kg daily. (TRCNMD References: 2334,2337,2338,2365,5029,5462,7233,7288,7293.)

Precautions

Presently, insufficient data exists to use the risk assessment model for determining an upper limit (UL) for any of the amino acids, including glutamine. Furthermore, it is well-tolerated orally, even in high doses, for healthy exercisers.[1,2,3,4,6,7,Error! Bookmark not defined.,27,Error! Bookmark not defined.,73,81,83,48,72] As with any amino acid supplementation, individuals with liver or kidney disease should avoid supplementation without the supervision of a medical professional.[120]

Contraindications

Glutamine supplementation is contraindicated in those with kidney problems or at risk for kidney disease because of possible increased kidney stress.[121] Unless supervised by a qualified health professional, glutamine supplementation should be avoided in cancer patients (both normal healthy and cancer cells use glutamine as an energy source[122,123]), and by children and pregnant or lactating women because of the lack of studies done in these populations. Any person using anticonvulsants (or any drug used for epilepsy)[124] and Lactulose should avoid glutamine supplementation. Theoretically, glutamine might antagonize the anti-ammonia effects of lactulose because glutamine can be metabolized to ammonia.[125]

Adverse Events

Orally and intravenously, glutamine is generally well tolerated.[119] Doses up to 40 grams/day of glutamine supplementation have not shown any significant adverse effects.[126] Significant side effects have not been reported in clinical studies.[48,72,116,117,125] Although rare, the most common adverse events from oral ingestion are belching, bloating, constipation, cough, diarrhea, flatulence, gastrointestinal pain, headache, musculoskeletal pain, and nausea.[119]

Upper Limit (UL)/Toxicity

Currently, glutamine does not have an established upper limit and has not been shown to elicit toxic effects in high amounts.[119,124,125]

Summary

Purpose

To supply glutamine with stabilizing co-factors (chromium/magnesium chelates) during times of depletion caused by rapid growth, tissue repair, or other high metabolic demands to help maintain health (immune support), including the integrity of the intestinal tract, reducing muscle breakdown, and enhancing recovery. Supplementation may be especially important when prolonged energy restriction (dieting) is combined with demanding physical stresses to restore body GLN to homeostasis.

Potential Beneficiaries

- Athletes and exercisers under prolonged demanding physical stress, especially when combined with extended periods of energy restriction or shortages, as in weight/body fat conscious athletes attempting to “make weight” or attain extremely low body fat, and ultra-endurance athletes.
- Anyone attempting to support:
    - Immune system (especially during seasonal high health risk periods) to lessen and shorten sick periods.
    - Intestinal integrity (gastrointestinal health, including reducing the potential intestinal permeability, also known as “leaky gut.”
    - Recovery related to exercise/physical-induced stresses, including reducing the likelihood of overtraining/reaching or attenuating its general effects, while mitigating exercise-induced immune suppression.

Unique Features

- Easy-to-mix powder that can be added to other desired nutrition products, including sports drinks and shakes.
- Effective and safely synergistic with all other dotFIT products.
- NSF Certified for Sport (NSFCS), which is an additional product guarantee for drug-tested athletes. Click here for the dotFIT NSFCS section.
- Formulated and manufactured for taste and pleasing texture in a regularly inspected NSF-certified facility, in compliance with Good Manufacturing Practices (GMPs) exclusively for dotFIT, LLC.

Supplement Facts Panel

Ingredient	Amount Per Serving	% Daily Value*
Magnesium (as Magnesium Bisglycinate Chelate) (Albion®)‡	34 mg	8%
Chromium (as Chromium Nicotinate Glycinate Chelate (Albion®)‡	150 mcg	429%
L-Glutamine	5 g	*

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