L-Glutamine
Nutritional therapy

DESCRIPTION

L-Glutamine is the most abundant free amino acid in the body and is involved in more metabolic processes than any other amino acid. Cellular concentrations are roughly four times higher than they are in the plasma. Most tissues are capable of producing glutamine of their own accord. Nonetheless, only the skeletal muscles, lungs, brain and adipose tissue are capable of producing large quantities of glutamine that can subsequently enter the bloodstream. Due to their considerable mass, the skeletal muscles easily account for the majority of glutamine supply. Around 50% of glutamine in circulation is used as an energy substrate and is oxidized, 10-20% is used for gluconeogenesis, and the rest is used (or reused) for the purposes of protein synthesis. Due to the fact that virtually all cells in the body (especially muscle cells) are capable of producing glutamine, glutamine has long been considered to be irrelevant when it comes to supplements. It is partly because of this that it has not been the subject of much research.

However, it turns out that L-glutamine can be semi-essential, because the body's own production of it can be deficient under certain circumstances. Deficiencies can easily arise during stress, fasting, strenuous exertion (e.g. during sport), cirrhosis of the liver and serious diseases, including severe infections. Glutamine-enriched parenteral nutrition has now proven its value in intensive care units. Research indicates that administering L-glutamine supplements can be regarded as a life-saving intervention in many a serious disease process.

EFFECT

Function

L-glutamine is implicated in a very high number of metabolic processes, including acid-base homeostasis; protein, fat and carbohydrate metabolism; regulation of cell volume; glutathione production; and regulation of the equilibrium between catabolism and anabolism. It is an important substrate for rapidly dividing cells, such as those of the intestinal mucosa and the immune system. For that reason it could also be an important nutrient in wound healing and formation of muscle tissue.

Virtually all amino acids have one amino group. By contrast, glutamine contains two. Partly as a result of this glutamine occupies a central place in the metabolism of amino acids. By means of glutamic acid, all other amino acids can be produced. In addition, glutamic acid (glutamate) and glutamine can easily be converted to one another.

Furthermore, purines, pyrimidines (nucleic acids, the building blocks of DNA), amino-glucose compounds, hormones and coenzymes can also be synthesized from glutamine.

The most important functions of glutamine are explained point by point below:

- **Energy provision:** in the liver, the carbon skeleton of glutamine is an important building block for glucose molecules. And by means of conversion to alpha-ketoglutaric acid, glutamine can be burned in the citric acid cycle. Glutamine is the most important source of energy for the small intestine. It is also an important source of energy for immune cells.

- **Immune cells** (particularly lymphocytes and macrophages) use significant quantities of glutamine, even at times when there is no major demand on the immune system. Nonetheless, consumption of glutamine increases dramatically during an immune response, when immune cells have to multiply rapidly and all manner of antibodies need to be produced. Where immune stress is short-lived, the body's own production of glutamine, partly from branched-chain amino acids (BCAAs) in muscle tissue, is usually sufficient to fulfill the need. Where the stress situation persists, endogenous production proves insufficient, resulting in the breakdown of muscle tissue and weak immunity. L-glutamine is particularly essential for the Common Mucosal Immune System (CMIS), the immune function in the body's mucous membranes, as found in the trachea, the sexual organs and the gastrointestinal tract. In the mucosa of these tissues, glutamine aids production of secretory IgA (s-IgA). This type of antibody is specific to the immune system in the body's mucous membranes. A glutamine shortage could therefore result in reduced immunity to pathogens in the intestines and trachea. Researchers have associated diminished s-IgA levels in saliva with an increased incidence of Candida and other infections.

- **Glutamine supplements** are more potent than glucose or other amino acids in terms of stimulating secretion of the gut hormone glucagon-like peptide-1 (GLP-1). This inhibits glucagon and increases the glucose sensitivity of the beta cells in the pancreas, stimulating secretion of insulin and resulting in a fall in the blood sugar level. GLP-1 also inhibits beta cell apoptosis and encourages the proliferation and differentiation of these insulin-producing cells. GLP-1 also suppresses the appetite. Glutamine is an interesting substance for the treatment of diabetes and obesity, and is now being used in clinical studies.

- **Acid-base homeostasis:** in the event of acidosis, the kidneys' consumption of glutamine increases dramatically. The surplus hydrogen atoms are bound to the NH3 group (ammonia) of glutamine and are excreted as ammonium ions (NH4+). The burning of glutamine also produces bicarbonate ions (HCO3−), which helps to neutralize an excessively low pH.

- **Building block for proteins:** as an amino acid, glutamine can naturally be incorporated into a variety of proteins.
Neurotransmitter synthesis: glutamine is the most abundant amino acid in cerebrospinal fluid, which indicates that it plays an important role in brain metabolism. Glutamic acid (glutamate), which is related to glutamine, is itself an important excitatory neurotransmitter. It is also possible for this glutamic acid to be converted (with the aid of vitamin B6, vitamin B12 and manganese) to GABA (gamma-aminobutyric acid), which is an inhibitory neurotransmitter. To illustrate, tranquilizers such as valium unleash their calming effect by way of the GABA receptors in the brain. The ratio between GABA and glutamate (GABA/glutamate index) is a measure of the equilibrium between excitation and inhibition of the nervous system.

Glutathione production: glutamine can also be used to make glutathione (an important detoxifier and antioxidant). Glutathione is a tripeptide comprising glycine, glutamine and cysteine. Normally the amino acid cysteine is the limiting factor in glutathione synthesis. In cases of glutamine deficiency - e.g. due to stress, fasting, strenuous exertion (e.g. during sport) and serious illnesses - glutamine can become the limiting factor. In such cases, taking supplements for both cysteine (best source: N-acetylcysteine) and L-glutamine can provide marked stimulation of glutathione synthesis.

Production of purines and pyrimidines: these are the building blocks of DNA and RNA. This role of glutamine is extremely important for rapidly dividing cells, such as those of the immune system and the intestinal epithelium.

Nitrogen transport and ammonia removal: around one third of all nitrogen (N) stemming from the breakdown of proteins is transported between the organs in the form of glutamine. When the body is using glutamine, nitrogen is released in the form of ammonia. This then enters the bloodstream. Subsequently in the liver the remaining ammonia (NH3) is removed from the body by means of the urea cycle so as to remedy the nitrogen surplus. This ammonia can also be used to convert glutamic acid back to glutamine. Where the liver is not functioning properly, the muscle tissue helps out with the detoxification of ammonia. If this also proves insufficient, then toxic concentrations of ammonia can occur in the body.

Sport
Due to its sizeable mass, muscle tissue is the most significant producer of glutamine in the body. L-glutamine is also the driving force behind the process of muscle tissue formation. Glutamine is the most abundant, most used amino acid in muscle tissue. If sufficient glutamine is not present, then protein synthesis stagnates. If strenuous exertion is subsequently undertaken, then this will give rise to a paradoxical situation in which glutamine levels will fall dramatically right at the time when the body needs glutamine most. A period of a few hours is required following strenuous exertion (e.g. during sport) in order to restore levels of glutamine. Under healthy training conditions, a gentle day of training will improve recovery from a hard day of training, because some use of the muscles (as opposed to complete physical inactivity) boosts glutamine synthesis. Reduced availability of glutamine subsequent to training may already be a sign of overtraining. If adequate recovery is not possible, as is the case during periods of heavy training or competition, a cumulative effect can arise. Practitioners of sport who overtrain can have low levels of glutamine in the plasma for months, even years. A glutamine deficiency reduces the quality and function of the intestinal epithelium, increases the risk of infection and allergies, and slows down wound healing. Endurance athletes (e.g. marathon runners) are particularly at risk. In their case, glutamine supplements support the intestinal epithelium and boost the immune system, thereby reducing the chances of infection and allowing the body to use its energy for the benefit of their performance.

Medical relevance
Although healthy people are themselves quite capable of producing sufficient glutamine, in many cases glutamine nevertheless turns out to be an essential nutrient. During stress (e.g. due to infection or injury), the need for L-glutamine is exceedingly high (3-4 times the normal need). The muscles respond to this need by releasing their stored L-glutamine for use elsewhere in the body. Where the stress is short-lived, glutamine levels in the muscles are quickly restored. In cases of protracted metabolic stress (e.g. chronic infection) the need for L-glutamine is very high. This may lead to the availability of L-glutamine being inadequate, resulting in such things as muscle damage and diminished immunity. In addition, there is a drastic fall in glutamine absorption in the small intestine in cases of stress and malnourishment. If this leads to dysbiosis in or adverse effects on the gut flora, then the glutamine deficiency can become serious. In the event of hospitalization or operations, for instance, it could result in an increased risk of serious complications.

Glutamine can be used for the following indications (for example):

- Glutamine is extremely important for proper wound healing. Patients with serious injuries (such as burns or following operations) have a markedly increased need for glutamine, because the healing process entails increased cell division and synthesis of DNA and proteins. Fibroblasts, macrophages and lymphocytes have a high need for glutamine.
- In patients with immunodeficiencies, glutamine is required for optimum immune cell function (monocytes, lymphocytes and neutrophils). Furthermore, glutamine improves the barrier function of the intestines, reducing the risk of secondary infections from the gut. In the case of patients in intensive care units, the addition of glutamine to parenteral nutrition virtually always turns out to have a beneficial effect on a variety of clinical parameters. Glutamine supplements prove to be a beneficial intervention to prevent or treat sepsis and multiple organ failure. Glutamine decreases the duration of hospitalization and lowers the chances of death due to postoperative infectious complications. In neonatology, glutamine-enriched parenteral nutrition administered to babies with a very low birth rate proves to radically reduce the chances of gastrointestinal infections and atopic dermatitis. Research covering the first six years of life suggests a lasting benefit, which in turn goes to show just how important a good start in life is.
- Increased intestinal permeability and inflammatory intestinal diseases. The gut needs to be able to absorb nutrients yet also defend against a great many harmful substances and microbes. Glutamine plays an important role in this regard as it reinforces the intestinal lining. Glutamine is important for continuous regeneration of the rapidly dividing cells of the intestinal epithelium, particularly in the small intestine. These cells are completely regenerated every 3-4 days. The importance of glutamine for the intestinal epithelium is appositely illustrated by the fact that not less than forty percent of overall glutamine consumption occurs in the gut.

In cases of glutamine deficiency, the intestinal epithelial cells can atrophy, which results not only in decreased absorption of nutrients but also in the possibility of increased permeability of the intestinal epithelium. The intestinal epithelial cells use glutamine as a source of energy for a very specific reason. After all, the breakdown of glutamine as a source of energy releases nitrogen and carbon. Nitrogen and carbon are used in cell division to form exact copies of the DNA. It is precisely the rapidly dividing cells that are susceptible to incorrect
copying of DNA. As such, it should be evident that intake of extra glutamine has an important preventive function in the development of diseases such as Crohn’s and ulcerative colitis. Fairly recent research on laboratory animals with colitis shows that glutamine supplements completely avert the formation of scar tissue. Scar tissue is an irreversible effect of the intestinal inflammation and can result in stenosis (narrowing) of, and loss of function in, the intestinal tract.

In patients receiving enteral or parenteral nutrition, glutamine speeds up the healing process, which is almost certainly attributable to its nourishing effect on the intestinal mucosa, its reduction of the permeability of the intestinal epithelium and/or its countering s-IgA depletion.

**Safety**

In general it holds that use of L-glutamine is safe. One-off doses ranging from 20 to 30 grams have been tolerated without side effects by healthy adults, and research shows that athletes who took a daily dose of 28 grams of glutamine over a period of 14 days experienced no negative effects whatsoever. Daily doses of up to 0.65 g/kg of body weight have been well tolerated by patients and did not result in abnormal ammonia levels. In view of the effect of glutamine supplements on insulin secretion, caution is advised in the case of people using diabetes medication.

Experience has shown that some people are apparently oversensitive to monosodium glutamate (MSG, E621), the sodium salt of glutamic acid that is used as a flavour enhancer in many ready-made soups and sauces and ready meals. Scientific research has not provided any clarity on this presumed sensitivity. MSG is used unsparring in some restaurants under the name Ye-tsin. Consequently, those who are oversensitive to this flavour enhancer are prone to developing so-called ‘Chinese restaurant syndrome’, also known as ‘monosodium glutamate symptom complex’. Headache, nausea, dizziness, palpitations, cold sweat, stomach pain, erythema and other symptoms may occur. It is possible that people with MSG sensitivity could respond to L-glutamine supplements as well.

**INDICATIONS**

- chronic infections
- intensive practice of sport
- glutathione synthesis
- immunodeficiency (amongst others, AIDS)
- withdrawal symptoms of alcoholism and addictions in general
- gastritis
- ulcers in the stomach and duodenum (including ulcerative colitis)
- motor and sensory overstimulation
- complementary therapy during chemotherapy and radiotherapy
- leaky gut syndrome
- metabolic reprogramming

**CONTRA-INDICATIONS**

Contraindications: none known at the indicated dose of L-glutamine.

**SIDE EFFECTS**

As far as is known, L-glutamine causes no adverse effects at the indicated dose.

**INTERACTIONS**

Interactions with mainstream or natural remedies are possible. Consult an expert about this.

**DOSEDODE**

A commonly used daily dose of L-glutamine is 5-10 grams. Intake of the amount should preferably be divided into several small portions spread throughout the day.

In order to combat competition with other amino acids, it would be advisable to take glutamine at least half an hour before a meal. The dosage can be adjusted according to one's needs or the clinical picture. For example, it is estimated that an AIDS patient will already require 10 grams of glutamine per day from as early as the initial stages of the disease. In cases of severe immunodeficiency or in patients undergoing a bone marrow transplant, doses of up to 40 grams per day are occasionally used. Glutamine is heat-sensitive; for that reason it should not be mixed with hot drinks.

**REFERENCES**


