THE ROLE OF MAGNESIUM GLYCYL GLUTAMINE CHELATE IN MUSCLE REGENERATION

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Physical movement involves not only the intricate neuromuscular coordination of body movements, but there are also many very complex adjustments relating to metabolism, respiration and circulation. The energy required for muscular work is derived from the oxidation of fuels. This occurs primarily in the muscles. These fuels consist chiefly of carbohydrates and fat and, to a lesser extent, amino acids. When amino acids have been sourced from body protein there can be significant consequences on the health and overall well-being of the individual.

During strenuous physical activity, the maximum rate of aerobic energy release from the tissues is attained in the second or third minute of the exhausting activity. It is at this point that oxygen consumption is at its highest level. After the strenuous physical activity period has concluded, the oxygen consumption does not immediately return to its pre-activity level. It declines logarithmically, as a function of time, with more oxygen being consumed than is required to sustain the body during the resting period. Some of this excess oxygen is stored in the venous blood and muscle hemoglobins. Another part of that oxygen is involved in the rapid re-synthesis of high-energy phosphate molecules such as ATP and phosphocreatine which were metabolized during the physical activity. And finally, part of that oxygen is used to facilitate the slow removal of lactic acid which accumulated in the muscles as a by-product of the pyruvate that was formed during the anaerobic breakdown of muscle glycogen for energy in the working muscles.[1]

Glycogen, of course, is the chief carbohydrate storage material in man. It is formed in the liver and also largely stored in the liver, although smaller amounts can be found in other tissues, especially the muscles. During strenuous physical activity, the glycogen is depolymerized to glucose and liberated for energy as needed. As blood sugar and liver/muscle glycogen are metabolized through oxidation, steroids such as cortisol and glucocortroids are secreted by the adrenal cortex to stimulate glucogenesis to replenish the store of glycogen.

For glucogenesis to occur as a result of strenuous physical activity, muscle proteins are broken down into their component amino acids. One of the chief adrenal cortex hormones associated with this process, as noted above, is the glucocortroids. They facilitate protein catabolism of the muscles and extraheptic tissue, thus producing an increased amount of plasma amino acids. These amino acids, which are delivered to the blood, are subsequently taken up by the liver and synthesized into additional glucose. Besides promoting muscle catabolism, glucocortroids also increase the trapping of these amino acids by the liver prior to glucogenesis.[2]

In addition to their involvement in muscle protein catabolism during strenuous physical activity, glucocortroids are also secreted and stimulate muscle catabolism during periods of caloric malnutrition and/or fasting. Where there is insufficient caloric intake during a state of fasting, glucogenesis is stimulated which initially inhibits the general use of glucose by the tissues and redirecting it to the brain to maintain the proper functioning of that organ. The lack of glucose to support muscle activity consequently stimulates the catabolism of the muscle

protein resulting in increased plasma amino acids and increased heptic glucogenesis for the muscles.

Because hypoglycemia usually accompanies individuals who are subjected to stress resulting from disease, surgery, or other physical injuries, there is also an increased release of the corticosteroids by the adrenals for protective purposes during these states. With the rise in glucocortroids, there is a corresponding rise in blood sugar levels which is accompanied by catabolism of muscle protein.[2] The sequence of these nutritional responses is summarized in Figure 1. During the course of the illness, there are several major nutritional problems that result from the concomitant acceleration of protein catabolism. Thus alterations in the patterns of the body's protein metabolism become one of the most important general nutritional consequences of the illness.[2a] The same could be said for the other causes of physical stress, sever physical activity and/or malnutrition.

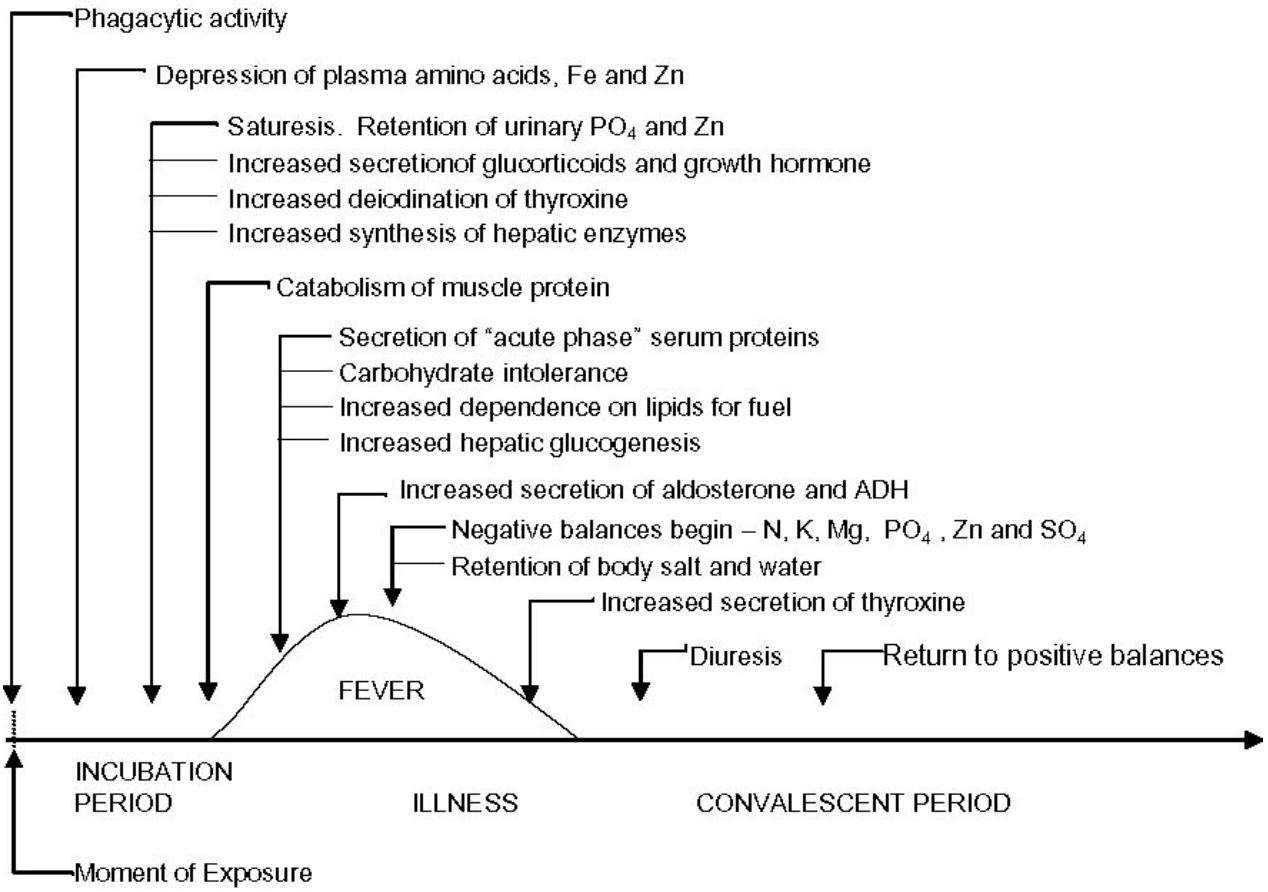

Figure 1. A schematic sequential representation of the body's nutritional responses which evolve during the course of a "typical" infectious illness.[3]

The muscle protein contains certain amino acids that are more directly involved in the building or synthesis of skeletal muscular protein than some of the other amino acids. These include glutamine, glycine, and arginine. Each of these amino acids has a well defined metabolic role relating to muscle development. For example, in the case of glutamine, it has been

demonstrated that there is a direct correlation between the rate of muscle protein synthesis and extramuscular glutamine concentration. Glutamine has an anabolic effect on muscle development; that is, it promotes the synthesis of muscle protein.[3, 4] Furthermore, not only does glutamine or L-glutamine have an anabolic effect on muscle development, but it also stimulates the accumulation of muscle glycogen for use as energy.[3] In the cells of the muscles there are significant quantities of glutamine that are not linked to any other amino acids. As such, they are "free floating" and readily available to the body for anabolism in the transanimation process and for energy in times of need.[5]

During times of strenuous physical activity, stress, or fasting and after first removing glutamine from the plasma for glucogenesis, cortisol stimulates the increased efflux of glutamine from the intracellular glutamine pool in the muscles. As the intracellular glutamine is released into the blood to maintain blood levels of glutamine, it creates a threat to glutamine homeostasis in the muscles. The intracellular glutamine pool has to be replenished from either increased catabolism of muscle protein or from dietary sources.[6]

As the cortisol mobilizes the protein and amino acids, including glutamine, from skeletal muscle it funnels them into the liver where they are broken down and rebuilt as glucose and glycogen. The higher cortisol level also stimulates the increased production of a number of enzymes which are involved in heptic glucogenesis. As this occurs, blood sugar tends to elevate, liver glycogen is increased, and there is greater resistance to insulin by preventing glucose entry into muscle and adipose tissue. As these naturally occurring metabolic processes take place, and the net rates of glutamine utilization exceed the net rates of production, glutamine depletion from the muscles results. While there may be an insufficiency of other amino acids as well as glutamine, it is the loss of the glutamine that first initiates other metabolic problems within the body.

Muscle wasting, which is associated with a drop in glutamine levels is seen as the direct result of increased cortical production, as noted above. Cognitive functioning is also affected by lower glutamine levels. Glutamine is a precursor to the neurotransmitter π-aminobutyric acid and rapidly can cross the blood-brain barrier. As such, 75% of the total free amino acids in the brain are in the form of aspartic and glutamic acids, including glutamine.[7] As seen in the following formula, glutamate is the product of glutamine metabolism.[7a]

Glutamate from glutamine functions as a neurotransmitter.

$$_{L}-"Gluta\min e"+HCO_3^- + 2ATP + H_2O \xrightarrow{\frac{Mg2+}{K+}} H_2N-CO-OPO_3H_2 + 2ADP + P_i +_{L}-glutamate$$

When there is a negative glutamine balance in the body due to heptic demands for glucogenesis, it will affect the proper functioning of the central nervous system. Some types of depression appear to be one manifestation of a glutamine deficiency.[8]

When glutamine is supplemented in the diet, researchers have noted that the extra glutamine reduces or eliminates muscle breakdown.[8] It also reduces depression.[9] But glutamine cannot fulfill its metabolic role in muscle anabolism without the involvement of magnesium. Referring back to Figure 1, magnesium depletion occurs in times of physical stress resulting from illness. Magnesium is the activator of numerous enzyme systems and as such approximately half of the magnesium in the body is found in the liver and muscle tissues. As in the case with glutamine, strenuous physical activity, stress from disease, injury or surgery and malabsorption all cause depletion of magnesium tissue levels.[10,11] Casoni et al., have reported that magnesium status will change with exercise.[12] For example, a decline in magnesium tissue levels can be the result of hypermetabolic compensation and the increased elaboration of catecholamines, glucagons, and mineral corticoids. Others have reported that physical performance will also change with magnesium supplementation.[13]

Not only is magnesium necessary for the generation of energy within the body as an enzymatic co-factor in the ATP molecule, it is also essential for the synthesis of carbamoyl phosphate synthesis which is directly involved with glutamine in protein synthesis. Carbamoyl phosphate synthesis is present in the cytoplasm of the cells that compose rapidly growing tissue, such as muscle. The activity of this enzyme appears to parallel the growth rate of the muscle.[14] Carbumoyl phosphate synthesis is essential for the utilization of NH_3 from glutamine for arginine and pyrimidine synthesis as well as several other amino acids. This process, known as transanimation, is the major mechanism of moving the amino group from the glutamine to other carbon chains to form other amino acids.[14a] Thus, magnesium is essential to catalyze the enzymatic reaction which is involved in amino acid synthesis within the muscles.

Magnesium is also involved in protein synthesis by contributing to the bonding of messenger RNA to the specific ribsomes as seen in Figure 2. The magnesium bonds messenger RNA to the amino acids for protein synthesis. When magnesium is deficient, there is an ungluing and diminution of protein synthesis.[15] Thus, a magnesium insufficiency, like a glutamine deficiency, can ultimately reduce with anabolism of muscle protein tissue.

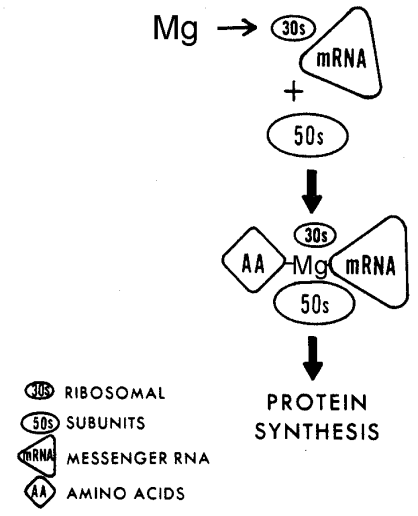

Figure 2. Effect of magnesium on protein synthesis.[15]

Since both magnesium and glutamine are both interdependent and essential for muscle anabolism and, in particular, for increasing muscle mass in times of strenuous exercise, stress from disease, injury or surgery, or fasting/malnutrition, it is nutritionally reasonable to supplement these two nutrients together. Unfortunately from a practical point of view, this approach presents some problems. Free form glutamine is not stable in solution and will rapidly decompose into pyroglutamic acid and ammonia. The substitution of the more stable glutamate (a glutamine derivative) for glutamine does not provide the extra nitrogen that is found in the glutamine. That extra nitrogen is essential for protein synthesis during the transanimation process. On the other hand, oral administration of free inorganic magnesium salts can also cause serious side effects, including intestinal irritability, loose stools, or diarrhea.

For glutamine supplementation to be effective, the glutamine molecule must be stabilized without its essential components being altered, i.e, the loss of the NH_3 molecule. The key to stabilizing the glutamine is to bind it to a bioavailable magnesium amino acid chelate molecule. For magnesium supplementation to be effective, it must be both bioavailable and at the same time not cause gastric upset. When magnesium is ingested in the amino acid chelated form, its bioavailability is enhanced and gastric upsets are reduced.[16] In order to stabilize the glutamine and prevent the potential gastric upset of the magnesium, magnesium ions are chelated to both glycine and glutamine in a patented process.[17] This creates a molecule which is depicted in Figure 3.[17] The resulting chelate contains one magnesium cation which is covalently bonded to one mole of glycine and one mole of glutamine. The molecule contains 10% magnesium, 60% glutamine, and 30% glycine. In this form, the glutamine becomes stabilized and the magnesium remains bioavailable but not toxic.

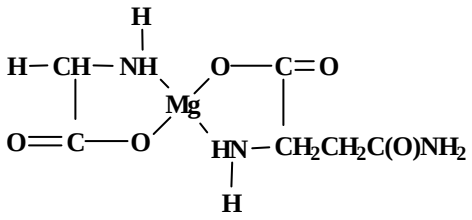

Figure 3. The molecular structure of magnesium glycyl glutamine chelate. [17]

To demonstrate the effectiveness of this molecule, two clinical studies were designed. The purpose of the first study was to show that the glutamine in the magnesium glycyl glutamine chelate remained stable in solution. If glutamine were to decompose prior to or during oral administration, then there would be no measurable increase in plasma glutamine levels. If, on the other hand, the glutamine in the chelate molecule remained stable, this would be clinically manifested as elevated glutamine levels in the plasma immediately following administration of the chelate molecule.[17,18]

The study involved seven males between the ages of 39 and 59 years. All were working in an office environment and did not engage in any strenuous physical activity during the study period. Immediately after taking a venous blood sample from each volunteer by venipuncture,

each participant consumed a previously prepared solution which contained 400 mg of magnesium glycyl glutamine chelate (40 mg Mg, 240 mg glutamine, and 120 mg glycine). Besides the initial blood sample, three additional venous blood samples were obtained from each study participant at thirty minute intervals. All of the blood samples were assayed for glutamine concentrations by high pressure liquid chromatography (HPLC). Figure 4 shows the mean changes in the plasma glutamine levels at the commencement and at 30 minutes, 60 minutes, and 90 minutes post administration of the magnesium glycyl glutamine chelate.

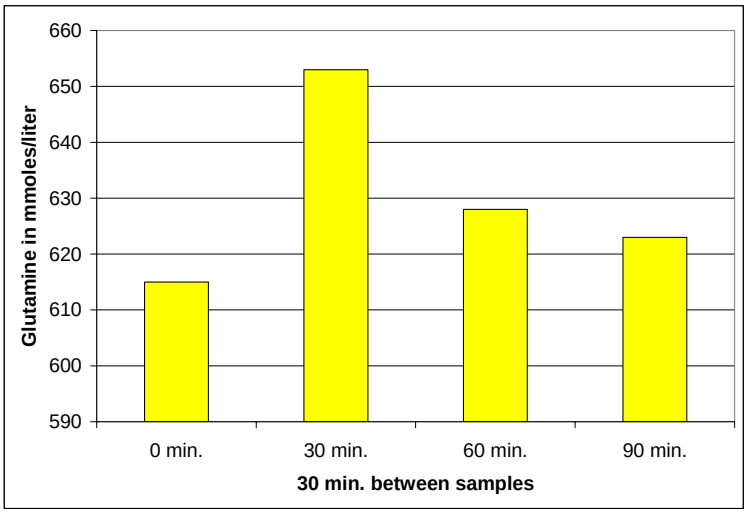

Figure 4. Mean plasma glutamine levels in adult males following the administration of 400 mg of magnesium glycyl glutamine chelate in solution.[18]

Absorption of the magnesium glycyl glutamine chelate into the blood from the gut was very rapid following its ingestion. The mean plasma level of glutamine peaked at about 30 minutes post treatment and then declined, presumably as the glutamine was removed from the plasma and taken up by the liver and muscle tissue. These findings seem to support the observation that even a small amount of stable glutamine (240mg), when administered orally as part of a magnesium amino acid chelate molecule, is capable of raising the plasma glutamine level.

The fact that the supplementation of this molecule results in elevated plasma glutamine levels has little metabolic significance unless the higher amount of glutamine in the blood translates into increased muscle mass during activity that will potentially lead to muscle catabolism. The second study in this two part series addressed this aspect of supplementation.[17]

Twenty three adult male body builders volunteered to participate in this second study. One group, the chelate group, contained eleven volunteers. The other group, which was labeled the steroid group, contained twelve volunteers. All of the participants, who frequented the same gym, were about the same weight and at about the same training level in their body building activities. During the study, all of the volunteers maintained similar exercise schedules and activities.

At the commencement of the study, lean body mass (muscle mass) was determined in each individual by a trained physiologist. Following these determinations, each day the participants in the chelate group received a supplement containing 400 mg of the magnesium glycyl glutamine chelate. The steroid group received a daily supplement containing 2,000 mcg of an anabolic steroid, testosterone. Each of the participants was made fully aware of what he was ingesting and the potential negative consequences of taking the supplements, and each signed a release agreeing to his participation in the study. The administration of the non-steroid anabolic supplement and the anabolic steroid continued on a daily basis for 8 weeks (56 days). At the conclusion of the test period, the lean muscle mass in each individual was again determined and the changes calculated. Additionally, blood pressure, total cholesterol, HDL cholesterol, and triglycerides were measured in each volunteer at the commencement and conclusion of the study and changes, if any, were noted.

The participants in the chelate group who were taking the non-steroid anabolic formulation (the magnesium glycyl glutamine chelate) had a mean increase in lean body mass (muscle) of 7.04 pounds (3.2 kg). During that same period, the anabolic steroid group that consumed the testosterone had a mean increase in its lean body mass of 6.6 pounds (3.0 kg). These increases are seen in Figure 5. Additionally the chelate group did not manifest any changes in blood pressure, cholesterol, HDL cholesterol or triglycerides whereas the cholesterol level and triglycerides were elevated in the steroid group on a mean basis.

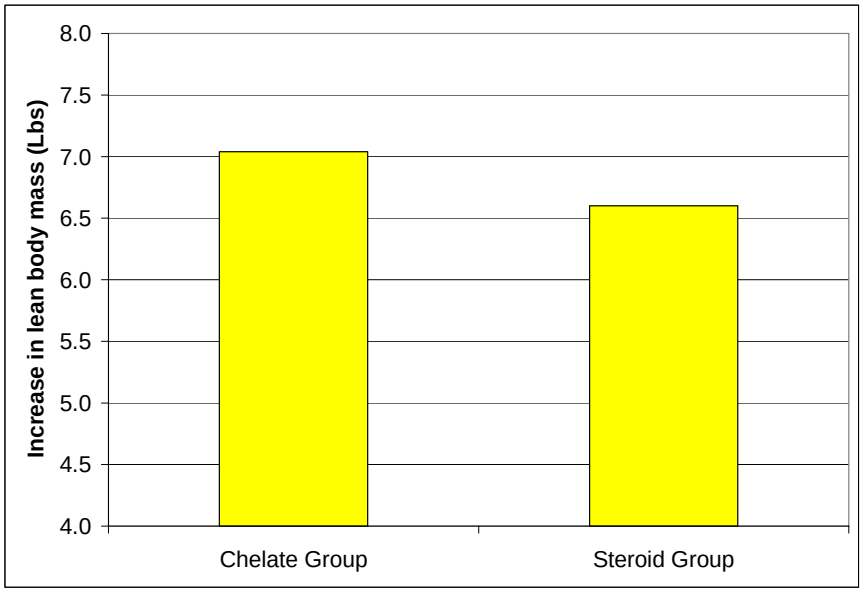

Figure 5. The 56 day increase in lean muscle mass in individuals consuming either 400 mg of magnesium glycyl glutamine chelate or 2000 mcg of testosterone.

This second study suggested that the daily ingestion of a small amount of stabilized glutamine (240 mg) when covalently bonded to a bioavailable magnesium amino acid chelate can synergistically increase lean muscle mass at least as effectively and perhaps more effectively than daily supplementation of 2,000 mcg of the anabolic steroid, testosterone, without the usual immediate side effects associated with the steroid, not to mention the long term side effects.

The need for supplemental glutamine to assist in restoring low plasma glutamine levels which in turn improves glutamine tissue stores and helps in conserving or promoting lean muscle mass during periods of potential muscle catabolism is obvious. Glutamine supplementation, by itself, is ineffective, however, due to glutamine's low stability and the additional metabolic requirement of needing magnesium to activate some of the anabolic enzymes associated with the glutamine. The same factors that cause glutamine depletion from the body – intense physical activity, stress from disease, physical injury, or disease, and fasting/malnutrition – also cause magnesium depletion. Thus if a need for glutamine is indicated in order to restore or prevent muscle catabolism, so is magnesium. They function synergistically in restoring or building lean muscle mass.

When the glutamine is chelated to the magnesium and becomes part of a magnesium amino acid chelate molecule, not only is the glutamine stabilized and thus remains active, but it also becomes an essential part of a totally functional molecule that has been demonstrated in clinical tests to be superior to supplemented anabolic steroids without the side effects of the steroids.

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