White Paper: Magnesium

MAGNESIUM OVERVIEW

Magnesium is an essential mineral that serves as an enzyme cofactor for over three hundred biochemical reactions in the body, including those of glycolysis, the first step in harnessing energy from carbohydrates. Magnesium is the fourth most abundant element (after calcium, potassium and sodium), and follows potassium as the second most abundant intracellular cation (positively charged electrolyte) in the body.[12] The adult human body contains approximately 25 grams of magnesium, over 60% of which is found in the skeleton. A third of this skeletal magnesium sits on the surface of the bone, ready to replenish extracellular magnesium concentrations should the need arise, the rest is tightly bound in hydroxyapatite crystals.[8] Muscle tissue contains about 27%, with the bulk of the balance found in other intracellular areas, and less than 1% occurring in the blood.[3]

ABSORPTION

Optimal magnesium absorption requires both parathyroid hormone and vitamin D3.[7,8] Absorption via both paracellular passive and transcellular active transport occurs along the entire length of the gastrointestinal tract with the distal jejunum and ileum being the sites of greatest uptake.[14,39] Absorption by active transport is saturable and takes place at TRPM (transient receptor potential melastin) 6 and 7 ion channels. TRPM6 being the prime intestinal channel, although it is also expressed in the testes, lungs and kidneys. TRPM7 is expressed ubiquitously.[39,62]

Magnesium absorption can be challenging due to a number of factors. Firstly, ingested Magnesium compounds are highly soluble at pH levels found in the stomach, and they can chemically react with hydrochloric acid, forming a magnesium chloride composite. This can further result in the magnesium forming insoluble complexes by binding with substances such as phytates. When this occurs, magnesium is not able to dissociate and be absorbed. The pH of the stomach can be as low as 1.[5,38]

As mentioned above, once the magnesium enters the small intestine, it is absorbed by both passive diffusion and active transport. Active transport occurs via TRPM channels whilst passive diffusion occurs through the small spaces between cells and requires a concentration gradient and small molecular particles in order to be effective. As magnesium is hydrophilic when dissolved, it can become quite a large molecule as it attracts water. The water buffer is referred to as a "hydration shell", the radius of which can increase up to 400 times that of the dehydrated cation, making absorption via passive diffusion almost impossible.[33]

Magnesium has two hydration shells in comparison to calcium which only has one. What's more, magnesium holds water more tightly than calcium, sodium and potassium. This means that the removal of the hydration shell surrounding magnesium takes much more energy than other ions.[2] Claudins are used in the paracellular pathways to reduce the radius of the hydration shell and facilitate absorption.[62]

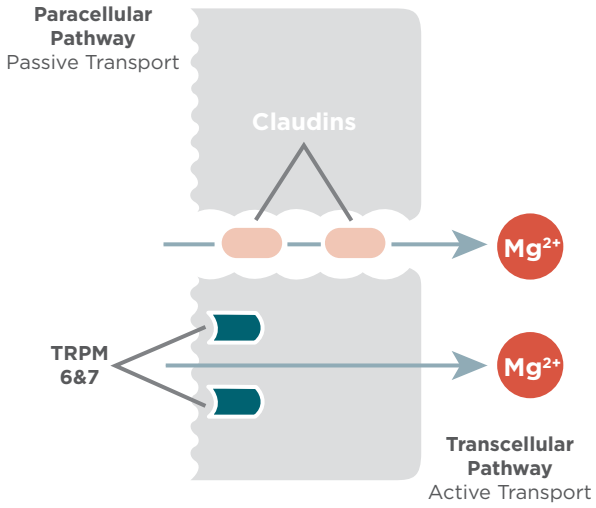


Diagram 1: Magnesium absorption pathways in the intestine.[38]

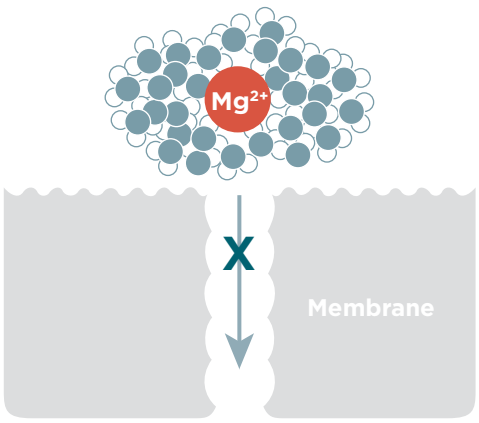


Diagram 2: Hydrated magnesium cation, unable to pass in between the epithelial cells of the small intestine via passive transport due to hydration constraints.[38]

Optimally, magnesium absorption takes place when the compound is resistant to the very low ph. of the stomach (1.5) and is unable to readily dissociate and form a hydration shell. This can be accomplished by the utilisation of a salt or protein that binds to magnesium securely, so it does not dissociate and attract water, and that also has a relatively neutral pH.[38]

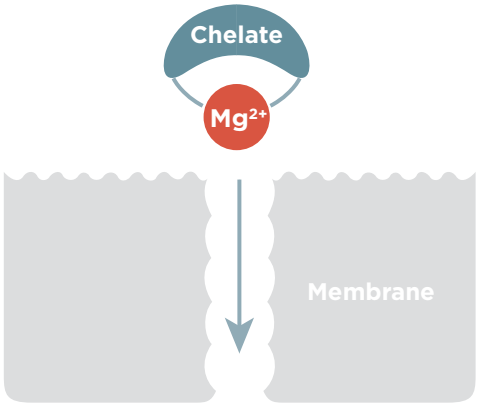


Diagram 3: Chelated magnesium cation: still attached to the chelate and therefore avoiding the hydration shell, well-suited to fit between the epithelial cells.[38]

The amount absorbed is dependent upon magnesium status. Magnesium sufficient (healthy) people absorb between 30 and 50% of ingested magnesium, whilst those who are deficient or who have insufficient intake can absorb up to 70%. Those with high magnesium stores can absorb as little as 11%.[7,8] Magnesium excretion occurs via the kidneys which control magnesium homeostasis. It is estimated that up to 120mg of magnesium is excreted in the urine each day, and excretion is reduced when magnesium status is depleted.[10]

BIOLOGICAL FUNCTIONS

As a structural component of the hydroxyapatite mineral matrix of bone, a natural calcium channel blocker, muscle relaxant, facilitator of calming effects upon the nervous system, and a required element for electrolyte balance and proper functioning of sodium-potassium pumps, magnesium plays a crucial role in supporting physical strength and mobility, muscle contraction, neurological health, cardiac function, and psychological balance. Magnesium's role as an enzyme cofactor for processes that generate ATP underlies its importance in energy production and metabolic processes. Protein synthesis (DNA and RNA), carbohydrate metabolism and neurotransmission are also fundamental metabolic processes that are reliant upon adequate magnesium status.[2,7,9,10]

Enzymatic databases list over 600 enzymes that have magnesium as a cofactor and a further 200 are activated by magnesium. Magnesium is involved in almost every biological and metabolic process that occurs inside the cell.[12]

THE SODIUM-POTASSIUM ATPASE PUMP – THE KEY TO CARDIOVASCULAR, NERVOUS SYSTEM AND MUSCULAR HEALTH AND FUNCTION

Magnesium is a critical regulator of the activity rate of the Sodium-Potassium ATPase pump (Na+, K+- ATPase pump)[17] which is required for removal of sodium from inside the cell in exchange for potassium (i.e., brings potassium back into the cell despite the chemical gradient favouring potassium movement out of the cell).[16] This makes Magnesium critical for maintaining the electrical potential of skeletal and cardiac muscles and nerves, and for neurotransmission across neuromuscular junctions.

Cardiovascular System

Magnesium facilitated calcium efflux is vital for the health and proper functioning of the cardiovascular system. Cardiac and vascular tissues require a tightly balanced relationship between magnesium and calcium to optimise coronary artery blood flow by preventing vascular resistance and for maintaining a normal heart rhythm and blood pressure. An inverse relationship exists between blood pressure and serum magnesium levels.[7] Magnesium has also been shown to be a valuable support nutrient for maintaining healthy endothelial function.[8]

A Magnesium deficiency has not been shown to affect the number of Na+, K+- ATPase pumps, however, it does reduce the activity of the pumps,[17] causing an increase in intracellular sodium, potassium and calcium levels.[8,17] The intracellular increase of these electrolyte ions – particularly calcium, can contribute to calcium-mediated vasoconstriction, whilst also impeding cardiac and smooth muscle relaxation (increasing peripheral resistance and vasospasm),[8] and be a contributing factor in the development of cardiac arrythmia.[17]

Nervous System Health and Function

As detailed in Diagram 4, magnesium in the extracellular space is critical for optimal neurotransmitter binding at the neuronal receptor site and subsequent transmission.[8,19]

Magnesium is a calcium antagonist, inhibiting calcium binding to channel sites and other proteins.[12,26] Magnesium can block N-methyl-D-aspartate (NMDA) glutamate binding/receptor sites preventing their activation. NMDA receptors are ion-channels that arbitrate the movement of calcium across synapses. An increase in calcium influx causes glutamate release and consequent excitatory neurotransmission in the central nervous system.[8,20,25] NMDA receptor activation is associated with numerous biological outcomes such as synaptic plasticity, learning and memory, pain emergence and migraine, sleep[8,20] and mood fluctuations.[21]

The Brain

Magnesium is able to cross the blood brain barrier via active transport facilitated by transport proteins such as Transient Receptor Potential Channel of Melastin 7 (TPRM7) and Magnesium Transporter 1 (MagT1), although

transport has not been shown to alleviate low brain levels of magnesium without a non-protein carrier.[25]

Magnesium can also agonise $GABA_A$ receptors inhibiting neuronal excitation and calming the nervous system.[25]

Low brain levels of magnesium can encourage calcium influx which in turn can cause disruption to the blood brain barrier, inflammation, and oxidative stress.[25]
In summary to the discussion above, Magnesium has a "depressant" action at the synapse level,[26] and low levels of magnesium in the brain and central nervous system can decrease $GABA_A$ receptor activity, leave NMDA receptors open to calcium and glutamate excitation and contribute to nervous system over-excitability.[12,25]

Skeletal Muscle Function

Magnesium is involved in proper skeletal muscle functioning in a number of different ways including oxygen utilisation, the production of energy (ATP and phosphocreatine) and the balance of electrolytes (particularly sodium, calcium and potassium).[13]

Adequate extracellular magnesium is critical for the maintenance of electrical potentials that affect muscle activity.[8]

Diagram 4 shows the role of magnesium in muscle contraction and relaxation. Magnesium is involved in the transport of calcium both into and out of the muscle cell, playing a role in both muscle contraction and relaxation.

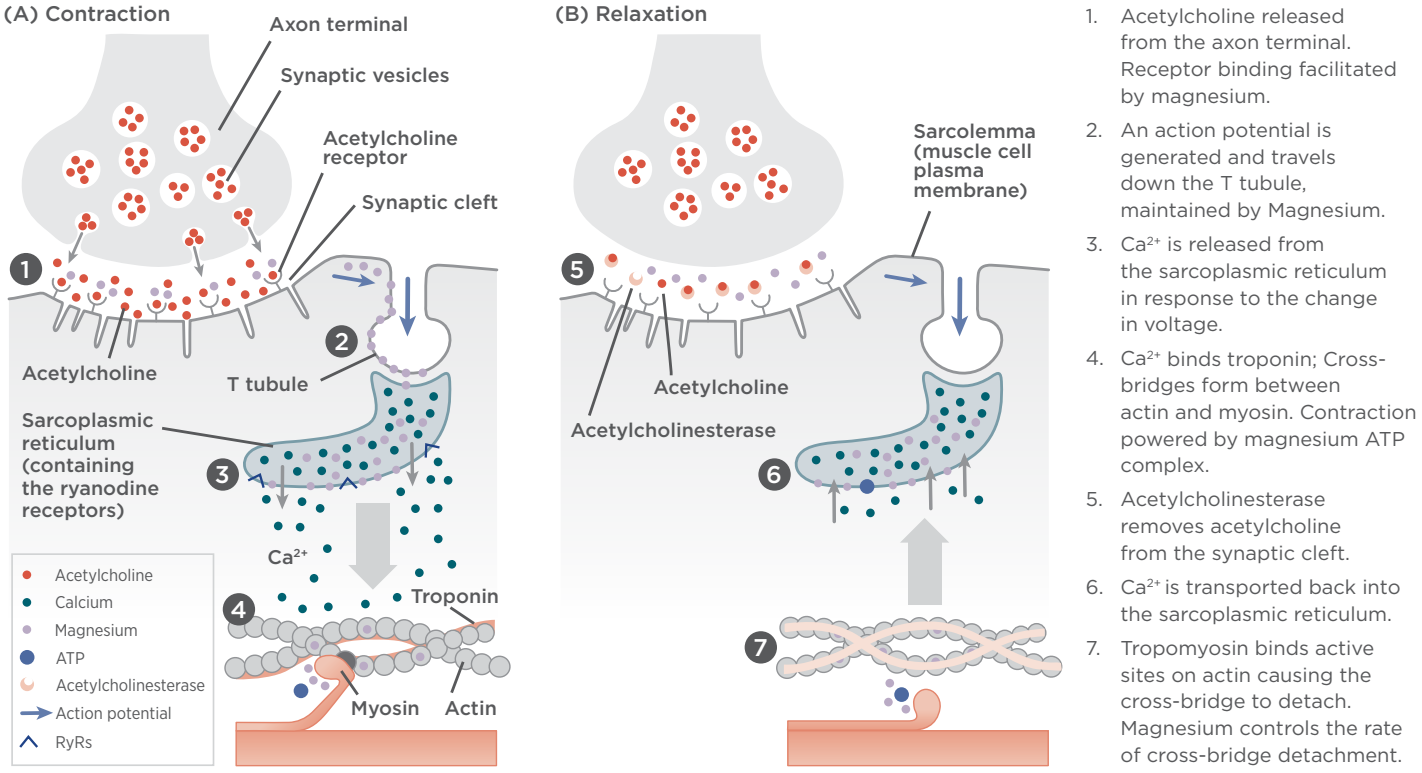
Contraction

At the neuromuscular junction, acetylcholine is released from the neuron. Magnesium then facilitates the binding of acetylcholine to the synaptic receptor, which triggers depolarisation. This action potential then runs along the sarcolemma and into the sarcoplasmic reticulum via the T-Tubule network. It then causes an alteration in Mg 2+ ions which opens the ryanodine receptors (RyRs) in the sarcoplasmic reticulum membrane and channels calcium ions into the sarcoplasm.[19,26] Calcium then binds to troponin, opening a binding site with the myosin head and enabling crossbridge formation. ATP (synthesised by and coupled with Magnesium) then powers the contraction phase.

Also, magnesium regulates troponin expression and stabilises actin by creating an ATP-magnesium-actin bond. Without this bond, the actin protein would deteriorate before the crossbridge was able to form.[19]

Relaxation

Magnesium is involved in muscle relaxation in a couple of different ways. Firstly, it controls the rate of cross bridge disengagement, and secondly, it moderates calcium activity by (i) facilitating calcium removal from the cell by binding with ATP to provide energy for the calcium pumping mechanisms that drive calcium efflux,[19] and (ii) binding competitively to calcium sites, thereby reducing calcium-initiated activity.[49]



1. Acetylcholine released from the axon terminal. Receptor binding facilitated by magnesium.
2. An action potential is generated and travels down the T tubule, maintained by Magnesium.
3. Ca^{2+} is released from the sarcoplasmic reticulum in response to the change in voltage.
4. Ca^{2+} binds troponin; Cross-bridges form between actin and myosin. Contraction powered by magnesium ATP complex.
5. Acetylcholinesterase removes acetylcholine from the synaptic cleft.
6. Ca^{2+} is transported back into the sarcoplasmic reticulum.
7. Tropomyosin binds active sites on actin causing the cross-bridge to detach. Magnesium controls the rate of cross-bridge detachment.

Diagram 4: The physiology of muscle activity; (A) Contraction, (B) Relaxation.

MAGNESIUM, EXERCISE & THE ATHLETE

Extracellular magnesium is temporarily shunted towards myocytes and adipocytes during exercise indicating an enhanced need during high intensity muscle functioning. The amount of magnesium shifted to myocytes and/or adipocytes is determined by the intensity of the exercise and therefore level of oxygen consumption/energy production. This is likely due to Magnesium's role in energy production and resolution of oxidative stress caused by increased oxygen metabolism during muscle contraction.[13]

Furthermore, Magnesium may also have a protective effect, maintaining muscle integrity and limiting muscle damage during both endurance and powder exercise and promote muscle recovery after intense activity.[18] It has been found that systemic inflammation, oxidative stress, myopathy, distorted neuromuscular function and skeletal muscle injuries are all inversely associated with a low magnesium status, highlighting the importance of adequate magnesium intake and status in athletes – possibly over and above the recommended daily intake of the nutrient.[13,18]

Athletes

Strenuous exercise may increase Mg requirements by up to 20%, and intakes less than 260mg/day for active men and 220mg/day for active women may cause Magnesium deficiencies. RDIs for this group may need be higher than the RDIs for the general population.[13,18]

Magnesium losses in this group can be due to:

- Urination (exercise may temporarily increase urinary magnesium excretion)
- Excessive sweating
- Energy production†
- Oxygen uptake†
- Electrolyte balance
- Elevated cortisol levels

† Exercise induces a redistribution of magnesium to accommodate metabolic needs (oxygen utilisation, glycolysis and/or lipolysis)[13]

BONE HEALTH

Magnesium plays a key role in bone metabolism (strength, remodelling and conservation). It makes up about 1% of the mineral content of bone and is a structural component of hydroxyapatite crystals. It is therefore extremely important for normal bone composition and structure.[7,8]

Magnesium is required for the activation of vitamin D which then assists calcium absorption and metabolism.[41] A magnesium deficiency leads to the promotion of substance P and tumor necrosis factor – alpha (TNF-α) in bone tissues which can go on to increase osteoclastic bone resorption, releasing magnesium back into the systemic circulation to replenish the body's magnesium status.[8] Long-term deficiency creates brittle and oversized hydroxyapatite crystals.[7] Deficiency may therefore be a risk factor for the development of osteoporosis through both a reduction in the formation of bone and elevated rates of bone loss.[7,8,12]

Supplementation with magnesium has been shown to decrease the turnover of bone and, when taken with calcium, vitamin D and other minerals, can improve bone density.[8] Bone mineral density has also been shown to be improved with increased dietary magnesium intake in epidemiological studies.[8] In postmenopausal subjects, increases in serum osteocalcin and decreases in serum iPTH and urinary deoxypyridinoline have been found when Magnesium is supplemented in the citrate form,[8,22,23] and the hydroxide form has been associated with improvements in bone mineral density.[7]

CARBOHYDRATE METABOLISM AND BLOOD SUGAR SUPPORT

Magnesium appears to have a regulatory effect on insulin metabolism and deficiency can antagonise insulin resistance by affecting tyrosine kinase activity at the insulin receptor level and increase the risk of the development of type 2 diabetes.[7,8,24] Magnesium plays a role in insulin signalling, insulin receptor kinase phosphorylation and the post receptional activity of insulin.[24] It is involved in glycogen breakdown, affecting the activity of phosphorylase b kinase which in-turn releases glucose-1-phosphate for use. Magnesium also directly influences the activity of the GLUT4 receptor, allowing glucose entrance into the cell,[9,24] and is a co-factor in every enzymatic reaction involved in glycolysis.[24] Magnesium therefore plays a major role in the maintenance of blood glucose and cellular glucose metabolism.

Conversely, insulin and glucose can help to regulate magnesium metabolism, and Type 2 diabetes can drive magnesium deficiency through inadequate intake and increased urinary losses due to both hyperglycaemia and hyperinsulinemia. Decreased cellular magnesium uptake and/or an ATP insufficiency have also been postulated as probable causes.[24] Diabetics have consistently lower intracellular magnesium levels than non-diabetics, and, as a result, insulin resistance and impaired cellular glucose utilisation can worsen, particularly as magnesium deficiency progresses.[24]

MAGNESIUM AND TAURINE

Biological similarity (and potential synergy) exists between magnesium and taurine.

Taurine is a non-essential sulphated amino acid, that is required by a number of biological processes in the cardiovascular and nervous systems.[64] Taurine is essential for the stabilisation of electrically active cell membranes in skeletal and cardiac muscles and the brain, as it regulates excitability by limiting neurotransmitter release and modulating calcium influx and efflux (as does magnesium).

The result being the reduction of over-stimulation in the sympathetic nervous system and cardioprotective effects whereby taurine may influence heartbeat strength, stroke volume and cardiac output.[7,64]

Effects on skeletal muscle may also be shown with taurine supplementation. Taurine is an antioxidant, reducing oxidative stress caused by both carbonyl protein and lipoperoxide. Rises in these oxidant markers have been associated with muscle soreness.[64] Furthermore, there is evidence in both animal and human trials that suggest an improvement in exercise performance after taurine intake.[64,65] This effect has been attributed to the abovementioned antioxidant and calcium modulating activities (in this case in the sarcoplasmic reticulum of skeletal muscle cells), as well as its ability to promote ATP turnover efficiency in the mitochondria,[65] influence energy metabolism in the glycolytic pathway, improve anaerobic capacity and reduce the accumulation of lactic acid in skeletal muscle.[64]

ENERGY METABOLISM

Magnesium is involved in energy production in several different ways. It does this by creating ATP-Mg complexes that link active substances with enzymes catalysing chemical reactions and accelerating metabolic processes.[19] ATP-Mg compounds are the primary energy source for muscle activity and other cellular functions.[9,11]

Magnesium also influences the production of energy in the following ways:

- It is a cofactor in the manufacture of ATP,[7,9,14,19] and then a cofactor in every reaction that involves the transfer and application of ATP[12]
- It supports red blood cell membranes, optimising systemic oxygen transport[19]
- It is required for the phosphorylation of creatine phosphokinase which can regenerate ATP through the formation of phosphocreatine[19]
- It facilitates the oxidation of pyruvate (through pyruvate dehydrogenase) to acetyl CoA – a main player in the metabolism of glucose[19]
- It is required for adequate functioning of mitochondria in the oxidative phosphorylation system, helping to stabilise enzymes throughout the process;[9,15,19] and
- It is involved in glycogen and carbohydrate breakdown and fatty acid oxidation.[9,14]

MAGNESIUM DEFICIENCY

Marginal and secondary magnesium deficiencies are very common, especially among the elderly, those who suffer from gastrointestinal diseases, diabetics, alcoholics, athletes and those taking the medications noted in Table 1.[7,12] Deficiency is often undiagnosed as to date, there isn't a reliable diagnostic tool to assess magnesium status in humans. Deficiency signs can be "vague and idiosyncratic",[1,7] and deficiency is very often asymptomatic.[8]

Most deficiencies are caused by a combination of insufficient dietary intake, poor absorption and elevated excretion/depletion and tissue redistribution.[1,7]

Table 1: Risks Factors for and Causes of Magnesium deficiency[2,7,8,14,39,41]

Dietary	• Excessive intake of alcohol, salt, phosphoric acid (from soft drinks), caffeine • Sodium deficit (via drug administration) • Chronic excessive magnesium intake • Inadequate protein intake combined with inadequate Mg intake (evidence suggests that Mg status can still remain positive if protein intake is greater than 30gm daily whilst Mg intake is inadequate) • Metabolic acidosis (starvation and alcoholism) • Reduced dietary intake
Lifestyle	• Profuse sweating • Intense and prolonged stress • Alcohol consumption

Table 1: Risks Factors for and Causes of Magnesium deficiency continued [2,7,8,14,39,41]

Elevated cortisol levels	• Chronic stress • Sleep deprivation • Athletes and excessive or high frequency exercise
Gastrointestinal disorders * Crohn's patients may require up to 700mg daily	• Malabsorption syndromes • Coeliac and Crohn's* disease • Infections • Inflammatory Bowel Disease and Regional Enteritis • Biliary and intestinal fistulas • Pancreatitis • Partial bowel obstruction • Extensive bowel resection • Vomiting/diarrhoea • Reduced bowel transit time • Acute haemorrhagic pancreatitis
Renal disorders/loss	• Metabolic disorders • Renal failure • Acidosis • Nephrotoxic drugs (e.g. cisplatin, cyclosporin) • Chronic parenteral fluid therapy • Hypercalcaemia • Interstitial nephritis and glomerulonephritis • Chronic pyelonephritis • Nephropathy
Endocrine disorders	• Hyperaldosteronism • Hyperparathyroidism with hypercalcaemia • Hyperthyroidism • Diabetes mellitus ketoacidosis and glycosuria (osmotic diuresis)
Pharmaceutical medications	• Aminoglycoside antibiotics (moderate depletion) • Amphotericin B (major depletion) • Antivirals (ribavirin and foscarvir) (moderate depletion) • Carboplatin, cisplatin • Capecitabine (Xeloda) (moderate depletion) • Cetuximab, panitumumab (moderate depletion) • Corticosteroids (moderate depletion) • Cyclosporin (moderate depletion) • Digoxin (moderate depletion) • Loop and osmotic diuretics (moderate depletion) • Oestrogens (moderate depletion) • Penicillamine (moderate depletion) • Pentamidine (major depletion) • Proton pump inhibitors (major depletion) • Sodium phosphates (moderate depletion) • Tacrolimus (major depletion) • Laxatives (moderate depletion)

Table 2: Signs of deficiency[2,7,12]

- Anorexia, loss of appetite and weight loss
- Nausea and vomiting
- Muscular weakness
- Muscular cramps and spasms/contractions
- Numbness, tingling
- Spontaneous carpal-pedal spasm
- Vertigo, ataxia, athetoid, choreiform movements
- Lethargy & fatigue
- Difficulty remembering things
- Apathy and melancholy
- Confusion
- Dysregulation of biorhythms (sleep etc)
- Depression
- Mental confusion, decreased attention span, poor concentration
- Personality changes
- Hyperirritability and excitability
- Vertigo
- Impaired lung function, bronchial hyperreactivity and wheezing
- Cardiac arrhythmia/coronary spasms
- Tetany and ultimately convulsions if deficiency is prolonged
- Hypocalcaemia and hypokalaemia if deficiency is severe and prolonged

Table 3: Recommended Daily Intakes[15]

Gender	Age (years)	Amount (daily)
All	1-3	80mg
	4-8	130mg
	9-13	240mg
Female	14-18	360mg
	19-30	310mg
	31-70+	320mg
Pregnancy	14-18	400mg
	19-30	350mg
	31-50	360mg
Lactation	14-18	360mg
	19-30	310mg
	31-50	320mg
Male	14-18	410mg
	19-30	400mg
	31-70+	420mg

MAGNESIUM TAKES MANY DIFFERENT FORMS

Magnesium supplements come in both organic and inorganic forms. Numerous trials demonstrate poor bioavailability of inorganic forms compared with organic salts.[27,28,63] Organic salts tend to have a higher water solubility, which tends to create greater absorption capacity.[29] Inorganic compounds tend to form large hydration shells, creating difficulties with absorption via passive processes and lead to an increase in water content in the bowel and subsequent diarrhoea.[38]

Organic salts can include citrate, amino acid chelate, glycinate, aspartate, glycerophosphate and threonate. Inorganic salts include oxide, sulphate, carbonate and hydroxide.[29]

Salts with the highest bioavailability tend to be the most used for magnesium deficiency since absorption is superior.

Magnesium Glycerophosphate

Magnesium glycerophosphate (MgGy) is a chelated source of magnesium, phosphorus, and glycerol. It is formed when a magnesium salt is added to a glycerophosphate anion. The glycerophosphate anion is derived from the joining of a phosphoric acid group with glycerol via esterification. Because the esterified glycerol has two hydroxyl groups, two isomers are created – the α-isomer (glycerol-3-phosphate) and the β-isomer (glycerol-q-phosphate).[40] This salt is one of the most bioavailable and well tolerated compounds.[38,40]

Due to the existence of the phosphorus and glycerol groups, MgGy is also a good source of both phosphorous[5] which contributes to numerous biological processes such as bone health and cellular and tissue repair, phosphorylation, DNA/RNA structure etc; and glycerol which contributes to energy production and phospholipid synthesis.[40]

Furthermore, the entire glycerophosphate molecule is a contributing compound to the glycerophosphate shuttle in the mitochondria. This shuttle is responsible for the transfer of protons and electrons across the mitochondrial membrane, as well as being the site of $FADH_2$ production, the oxidation of which generates 2 ATP molecules via the metabolism of the α-isomer (Glycerol-3-phosphate). Glycerophosphate is also a structural component of phospholipids, thereby contributing to the health and function of cell membranes.[40]

Being an organic form of magnesium, MgGy has a high bioavailability. On top of this, MgGy has a pH of 2-8 enabling it to pass through the stomach with minimal interaction with hydrochloric acid. The chelation strength between magnesium and the glycerophosphate molecule is also strong enough to protect it from becoming overly hydrated, reducing the likelihood of increases to the radius of the molecule and subsequent absorption challenges. Also, the chemical structure of MgGy curls in on itself due

to the opposite charges between oxygen/magnesium and oxygen/hydrogen. This is called a "buckler conformation" and – along with the pH - helps to protect the compound from reacting with stomach acids.[38,40]

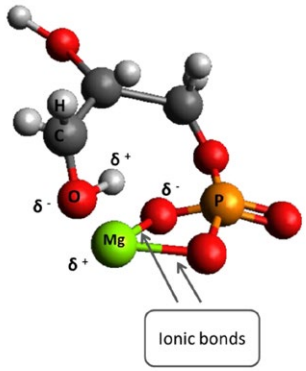


Diagram 5: Chemical structure of Magnesium Glycerophosphate – note the curved "buckler conformation"[40]

Magnesium Orotate

Magnesium Orotate (MO) is a magnesium salt of orotic Acid (OA). It has low solubility in water, making gastric acid binding and hydration shell formation unlikely.[6]

Like other magnesium salts discussed, MO is both a source of magnesium and OA. OA is involved in the synthesis of pyrimidines - one of the two chemical building blocks that cells utilise in the synthesis of both DNA and RNA.[47,48] In animal studies, OA has displayed this action in the myocardium, in a process whereby hepatic release of uridine is directly stimulated to supplement diminished myocardial levels of both pyrimidines and purines.[48] Furthermore, OA has shown to be effective in improving the synthesis of ATP and glycogen in damaged myocardial tissues, thus improving their energy stores,[6,48] minimising ischaemic strain and improving ischaemic tolerance in conditions of cardiovascular stress ranging from high impact exercise (in healthy humans) right through to infarction.[48] On top of the activity attributable to OA in these instances, magnesium's calcium channel blocking activity seems to contribute to an increase in reperfusion and oxygenation of cardiac tissues, resulting in synergistic activity between magnesium and OA. Magnesium may also have antioxidant activity, restricting the formation of free radicals thus reducing oxidant-induced damage.[49]

All of this, combined with the intrinsic relationship between magnesium and ATP, and the fact that OA provides binding sites for the Mg (ATP) complex, shows that OA can be seen as a "Mg-fixing agent", transporting magnesium directly to cells – particularly to those of the myocardium,[6,48] where both magnesium and OA can provide positive outcomes.

Recent focus on MO has brought to light its activity in the gastrointestinal system and its influence over the microbiome-gut-brain axis and GI conditions associated with dysbiosis. It has been found that fluctuating magnesium intake directly influences both the gut microbiota (diversity), and SCFA concentration, and consequently butyrate and propionate levels.[49] Several animal and human studies have been carried out in recent years. These studies have highlighted efficacy in cases where both gastroenterological and psychological symptoms are present together, suggesting that magnesium's effects on NMDA and GABA receptors in the nervous system and its additional effects on the microbiota, may contribute to its activity, and promote magnesium as a potential therapy in conditions affecting the gut-brain-axis.[49]

Magnesium citrate

Magnesium citrate is a magnesium ion bound to citric acid in a ratio of 1:1. It is one of the most bioavailable forms of magnesium due to its very high-water solubility. It is absorbed via passive diffusion similarly to the glycerophosphate compounds.[10,27,28]

As it has such a high bioavailability, it should be considered in cases of deficiency where fast repletion is required, and also for cases where long-term administration is necessary.[57]

Studies using mag citrate (in both citrate and dicitrate forms) have shown efficacy for migraine. Reductions in both frequency and severity of migraines have been shown in subjects suffering from 2-5 migraines per month when doses of 600mg daily have been administered.[32,33]

Citrate forms of magnesium also seem to be effective for nocturnal leg cramps. One randomised, cross-over, placebo-controlled trial supplementing with 300mg magnesium citrate daily found a reduction in nocturnal cramp frequency, but not duration or severity over a 6-week period.[34]

Being a salt that causes fluid secretion and stool bulking, magnesium citrate may also be used as a stool softening laxative. Magnesium citrate has both an osmotic effect (due to its ability to stimulate the activity of Nitric Oxide (NO) in the bowel) and the ability to stimulate cholecystokinin release, resulting in the build-up of fluid and electrolytes in the colonic lumen, and causing an increase in peristalsis and therefore bowel transit. In addition to this, Magnesium citrate may stimulate the production of the proinflammatory mediator platelet aggravating factor (PAF) in the gut which also contributes to fluid accumulation.[35,36,37]

Magnesium Amino Acid Chelate

A highly absorbable form of elemental magnesium chelated to an amino acid. The chelate is tightly bound which prevents the magnesium ion from dissociating, attracting too much water and swelling,[38] however, the bond is not so strong that it prevents cleavage once absorbed. Binding with an amino acid chelate also prevents the magnesium from dissociating and complexing with phytates, phosphates and tannins in the GI tract.[63]

Mineral chelates occur naturally in plants and animals and provide both the mineral and the amino acid for utilisation in the body.[63] Amino acids used for chelation can include glycine, aspartate, phenylalanine, glutamate, leucine etc.

Chelated magnesium is absorbed via an alternative pathway to the active and passive systems described earlier. This third mechanism is a form of active transport that occurs via dipeptide channels which are the primary sites for protein absorption.[63] Ordinarily, proteins in the cell wall chelate cationic minerals just prior to absorption taking place which is time and energy consuming. If pre-chelated supplements are ingested, this endogenous chelating process is not required. Furthermore, dipeptide absorption channels are much more numerous than ionic mineral absorption sites for which magnesium competes with other minerals. Both phenomena result in quicker and more effective absorption.[63]

The amino acid chelated magnesium has applications in dyspepsia, muscle function and energy promotion.[49]

Magnesium glycinate and bisglycinate

Glycinate and bisglycinate magnesium compounds are amino acid chelates (a magnesium bound to the amino acid glycine) and as such are absorbed in the same way as other amino acid chelates – via dipeptide channels.[63] They are also tightly bound to inhibit the formation of a hydration shell.[38]

Again, magnesium glycinate and magnesium bisglycinate contribute both magnesium and glycine to the system upon supplementation, conferring benefits from magnesium to the cardiovascular, nervous and musculoskeletal systems, and from glycine, which may be used to facilitate sleep induction.

Glycine is a non-essential amino acid which influences both excitatory and inhibitory neurotransmission via both glycine receptors and – like magnesium – NMDA receptors.[54] It is thought that glycine may improve sleep quality by supporting the natural circadian correlation between sleep onset and maintenance and core body temperature.[54] Glycine passes passively into the brain where it interacts with NMDA receptors in the suprachiasmatic nucleus in the hypothalamus (the "centre of the circadian rhythm"). This results in vasodilation and a subsequent reduction in core body temperature.[54] In two small human studies, 3g Glycine increased sleep quality and efficacy, reduced latency to sleep onset and slow wave sleep, resulting in a reduction in daytime tiredness and subsequently supported cognitive performance.[54,55]

Glycine also is a component of collagen (helping to support connective tissues and muscle mass) and glutathione. It has activity in the nervous system and immune system and is also involved in energy production.[63]

Chelated magnesium bisglycinate has also been shown to reduce the pain associated with dysmenorrhea and the frequency and severity of leg cramps in pregnant women.[4]

Magnesium aspartate

Magnesium aspartate is a compound that sees magnesium bound to aspartic acid. It has high water solubility and is one of the most bioavailable forms of Magnesium in comparison to other magnesium salts.[8,10,56,62]

L-aspartic acid, like orotic acid, is a precursor in the production of pyrimidines and purines and can be circulated throughout the body including the brain. It is absorbed by active transport in the small intestine then transported to the liver. During both the absorption and transport processes, L-aspartate is broken down into the amino acids alanine, proline, L-arginine and glutamic acid.[29]

Aspartic acid is a non-essential amino acid and a glucogenic Krebs cycle intermediate that is involved in the synthesis of oxaloacetate which enters the citric acid cycle contributing to the production of energy. The two compounds are interconvertible, meaning that oxaloacetate can also be converted back to aspartate[58] where it may to contribute to the essential amino acid pool, or be recycled back into the citric acid cycle. It is also an excitatory neurotransmitter in the brain and spine.[59]

Early research conducted on the value of electrolytes in physical performance in the 1960s looked at the aspartate salts of magnesium and potassium (Spartase). Both animal and human research highlighted the activity of this combination in intermediary metabolism (the citric acid cycle), suggesting improvements in performance endurance and physical fatigue. It was postulated that this occurred due to an extension of the duration of intensity of muscle and nerve activation brought about by an increase in energy production and supply.[60]

Magnesium threonate

One of the newer forms of organic magnesium to be developed is magnesium threonate.

Magnesium Threonate was developed at the Massachusetts Institute of Technology with the aim of producing a unique and highly bioavailable form of magnesium. The compound consists of magnesium and the L-isomer of threonic acid L-Threonate which is a metabolite of ascorbic acid.

Animal studies have so far elucidated benefits upon the brain and central nervous system affecting memory, neuropathic pain and anxiety. As discussed above, this effect is brought about by the ability of magnesium to interact with NMDA receptors preventing excitatory stimulation, and also by inhibiting TNF-α production in the neurons.[25,30,31]

A small human study has been published. In this study, Magnesium threonate was able to effectively improve magnesium status, and influence cognition and brain aging measures in older adults with self-reported cognitive impairment. It was postulated that supplementation with Magnesium threonate was able to affect brain synapse density and plasticity, whilst also contributing to neuronal energy supply.[31]

Table 4: Forms, Bioavailability & Uses[29,41,49,56]

Form	Bioavailability	Use
Oxide	Bioavailability poor	Laxative (constipation), antacid, cardiovascular and neuromuscular health
Hydroxide	Bioavailability poor	Laxative (constipation) and antacid
Chloride	High bioavailability	Electrolyte replenishment, magnesium deficiency
Aspartate	Very high bioavailability	Muscle strength and performance/ endurance; exercise induced lactate production Supports healthy heart rhythm Magnesium deficiency
Citrate	Significantly better absorbed than oxide. Very high bioavailability	Migraines, cramps, constipation Magnesium deficiency
Orotate	High bioavailability and intracellular accumulation	Cardio protection and GIT/microbiome health , magnesium deficiency, antioxidant
Gluconate	Highest oral bioavailability of all salts	Magnesium deficiency
Amino acid chelates	High bioavailability via dipeptide channels	Dyspepsia, energy production, muscle function
Glycinate/bisglycinate	Similar bioavailability to amino aid chelates as absorption takes place via dipeptide channels	Can be useful to support mood, stress, PMS, bone health
Ascorbate	Easy digestion and absorption	Conferring the benefits of both vitamin C and Mg
Phosphate	Insoluble in water therefore bioavailability low	Muscle soreness cardiovascular care, bone health
Sulphate	Low bioavailability and poor ability to replenish intracellular stores of Mg	Sleep, stress, constipation
Threonate	Very high bioavailability	Memory and cognition, brain and central nervous system health

Table 5: Magnesium Supplementation and Clinical Study Outcomes

Form	Dose	Conditions/Cohort	Results
Glycerophosphate	6x95mg daily (570mg)	Heart function concerns	Reduction in ventricular ectopy and heart function support[42]
Citrate	1830mg/daily	Post-Menopausal Osteoporosis	Reduced bone turnover, increased serum osteocalcin, and decreased serum iPTH and urinary deoxypyridinoline [23]
	300mg	Leg cramps	Reduction in frequency of nocturnal leg cramps[34]
	600mg	Migraine without aura	Reduction in frequency and severity of migraines compared to placebo[32]
	600mg (Trimagnesium dicitrate)	Migraine with or without aura	Reduction in migraine frequency[33]
Threonate	1500-2000mg daily (25mg/kg/day)	Self-reported cognitive impairment in older adults	Improvement in body magnesium status; effects on cognition, cognitive fluctuation and clinical measures of brain ageing[31]
Aspartate	Magnesium aspartate (1000mg) & Potassium aspartate (1000mg)	Healthy trained and untrained men	Improvements in energy production and physical endurance[60]
	20mmol daily	Middle-aged & elderly women with untreated mild-moderate hypertension	Healthy blood pressure restored after 6 months of treatment[61]
Orotate	1200mg daily	Postoperative recovery from cardiac surgery	Treatment consisted of Magnesium Orotate (1200mg), CoQ10 (300mg), Alpha Lipoic Acid (300mg), and Omega-3 EFAs (3g) daily for one month prior to surgery. Improvements in post operative recovery and QOL[46]
	6000mg for 1 month, then 3000mg for 11 months	Cardiovascular condition	Improvements in QOL as an adjunct treatment[52]
	MO 1600mg daily SAMe 800mg or 1600mg daily	Psychological conditions (Pilot study) * Hypotheses: (i) High dose SAMe would perform better than low dose; (ii) MO administration to SAMe non-responders would highlight different MOAs to traditional methylation processes	Treatment with MO or SAMe (2-week washout period). MO showed superior results for mood support, suggested reason for difference was MO's effects on microbiome[50]
	1600mg in two divided doses	Psychological conditions	MO and probiotics (with SSRIs) Improvements in energy, well-being and mood as compared with SSRIs alone (as an adjunct treatment)[51]

Table 5: Magnesium Supplementation and Clinical Study Outcomes continued

Oxide	500mg	Insomnia in elderly patients	Improvements in sleep time & sleep efficiency, and reductions in ISI scores, sleep onset latency, serum cortisol and early morning awakening[43]
	12.4 mmol	Periodic Leg Movement related to Insomnia and Restless Legs Syndrome	Reduction in periodic leg movements during sleep (PLMS) associated with and without arousal, and improvements in sleep efficacy and total sleep time[44]
	300mg daily	Healthy elderly women	Improved exercise performance as assessed by the Short Physical Performance Battery (SPPB)[45]
Bisglycinate	300mg daily	Pregnancy-induced leg cramps	Reductions in cramp frequency and intensity compared to placebo[4]
Glycinate	360mg daily in combination with 1000IU D3	Overweight individuals with low 25-hydroxyvitamin D (25OHD) status	Improvements in serum 25OHD levels compared to supplementation with D3 alone or placebo[53]

References supplied on request.