Magnesium is a cofactor in more than 300 enzyme systems that regulate diverse biochemical reactions in the body, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation. Magnesium is required for energy production, oxidative phosphorylation, and glycolysis. Magnesium is a nutrient that the body needs to stay healthy. It is important for many processes in the body, including regulating muscle and nerve function, blood sugar levels, and blood pressure and making protein, bone, and DNA. Magnesium Malate is a compound of magnesium and malic acid, clinically shown to soothe and energize muscle cells. Malic acid is an important component of numerous enzymes key to ATP synthesis and energy production. Therefore, magnesium malate may be helpful in those suffering from fatigue due to fibromyalgia. It is a naturally occurring mineral that is important for many systems in the body, especially the muscles and nerves. Magnesium Malate is used as a laxative to treat occasional constipation. Magnesium is a macro-mineral, which, unlike trace minerals, is needed by the body in large amounts. Calcium, sodium, and potassium are also macro-minerals. The average human body contains about 25 grams of magnesium, one of the six essential minerals that must be supplied in the diet. Additionally, magnesium balances calcium within the body, which is important because overly high doses of calcium, usually from supplements, can cause problems associated with muscle control, including controlling the heart. A test for magnesium is done to: Find a cause for nerve and muscle problems, such as muscle twitches, irritability, and muscle weakness. Find the cause of symptoms such as low blood pressure, nausea, vomiting, diarrhea, dizziness, muscle weakness, and slurred speech. Monitor kidney function.

**Keywords:** Magnesium, electrolytes, Biologic function, Interference, Blood, Analytical methods
The symptoms of magnesium deficiency

Magnesium is an important ingredient to so many of the body’s regulatory and biochemical systems that the impact of low levels spans all areas of health and medical practice. Therefore the symptoms of a magnesium deficit fall into two broad categories – the physical symptoms of overt deficiency and the spectrum of disease states linked to low magnesium levels.

Symptoms include both:

- **Classic “Clinical” Symptoms.** These physical signs of magnesium deficiency are clearly related to both its physiological role and its significant impact on the healthy balance of minerals such as calcium and potassium. Tics, muscle spasms and cramps, seizures, anxiety, and irregular heart rhythms are among the classic signs and symptoms of low magnesium.

- **“Sub-clinical” or “Latent” Symptoms.** These symptoms are present but concealed by an inability to distinguish their signs from other disease states. Caused by low magnesium intake prevalent in nearly all industrialized nations, they can include migraine headaches, insomnia, depression, and chronic fatigue, among others.

The subject of subclinical or chronic latent magnesium deficiency has been one of alarm and increased emphasis in research communities. This growing attention is largely due to epidemiological (population study) links found between ongoing chronic low magnesium and some of the more troubling chronic diseases of our time\(^1\), including hypertension, asthma and osteoporosis\(^1\). Compounding the problem is the knowledge that the body actually strips magnesium and calcium from the bones during periods of “functioning” low magnesium. This effect can cause a doubly difficult scenario: seemingly adequate magnesium levels that mask a true deficiency coupled by ongoing damage to bone structures. Thus experts advise the suspicion of magnesium deficiency whenever risk factors for related conditions are present\(^2\), rather than relying upon tests or overt symptoms alone. The main functions of the human body where magnesium deficiency symptoms may arise are neurological, muscular, and metabolic/cardiovascular. When magnesium is lacking in the body, symptoms are typically seen in these areas\(^2\). The primary symptoms in each functional area of the body are as follows:

**Neurological**

Lethargy, Impaired memory and cognitive function, Nausea and vomiting, Seizures, **Muscular Weakness**, Muscle spasms (tetany), Tics, Muscle cramps, Hyperactive reflexes, Impaired muscle coordination (ataxia), Tremors, Involuntary eye movements and vertigo. There is increased intracellular calcium, Hyperglycemia, Irregular or rapid heartbeats, Coronary spasms.
Importance of magnesium in the human body – treating deficiencies

But the most important are lifestyle and eating habits. Calcification of the Arteries. Though this is not (hopefully) the first symptom of magnesium deficiency, it can be one of the most dangerous, Muscle Spasms and Cramps, Anxiety & Depression, High Blood Pressure/Hypertension.

- Hormone Problems, Pregnancy Complaints, Sleep Problems, Low Energy. The typical diet, which is rich in fat, sugar, salt, synthetic vitamin D, phosphates, protein, and supplemented calcium, not only is deficient in magnesium but actually increases the need for magnesium in the body. Whole and unrefined foods high in magnesium are becoming increasingly rare in the modern diet.

Hypomagnesia is the technical term for dangerously low levels of magnesium in the body. It's typically caused by inadequate intake of dietary magnesium or the body's inability to absorb magnesium. There are 5 Causes of Magnesium Deficiency

1. Muscle Cramps & Spasms

Although the exact cause of muscle cramps and spasms isn’t yet known, many think a lack of minerals is to blame. Specifically, being low in potassium, calcium, or magnesium is thought to cause cramps. Magnesium is important for muscle relaxation. So when you lack magnesium, your muscles can involuntarily contract which can cause painful spasms. This issue is even more common than you may think thanks to our coffee-addicted society. Diuretics (substances that make us pee more) such as coffee, tea, or even blood pressure medications can quickly deplete our mineral stores. When we urinate, minerals leave our body. If you frequently drink coffee or take a diuretic medication, you may want to consider a multi-mineral supplement or take extra care to get more minerals in your diet (especially if you discover you experience many of the symptoms listed here).

2. Chocolate Cravings

DARK chocolate is actually a great source of magnesium. It contains about 24% of your daily requirements in just one square of dark chocolate.

3. Anxiety

Magnesium is the relaxation mineral. Anything that is tight, irritable, crampy, and stiff – whether it is a body part or [even] a mood – is a sign of magnesium deficiency.”

4. Insomnia or Trouble Sleeping

Even a small lack of magnesium is more disturbing. This is because magnesium plays a key role in your central nervous system. Since magnesium is also known to promote relaxation, it is recommended to take a magnesium supplement at night.

5. Constipation

The relaxing effect of magnesium applies for your digestive tract too. When your body is low on magnesium, your intestines tend to contract more. As a result, it’s harder for waste to pass which in turn can lead to constipation. But magnesium isn’t only important for the relaxation of the intestines, it also pulls water

6. High Blood Pressure

Gastrointestinal causes

Magnesium deficiency is frequently observed in conditions causing steatorrhoea or severe chronic diarrhea such as Crohn's disease, ulcerative colitis, celiac disease, Whipple's disease and short bowel syndrome. In general, the degree of magnesium depletion correlates with the severity of diarrhea, stool fat content and fecal magnesium concentration.
An inherited disorder of isolated magnesium malabsorption associated with hypocalcaemia, tetany and seizures has been described in infants as well as in older individuals. Children with this condition usually present at 4–5 weeks of age with generalized convulsions associated with protein losing enteropathy, hypoalbuminaemia and anasarca.

**Renal Causes**

Proximal tubular magnesium reabsorption is proportional to sodium reabsorption, and a reduction in sodium reabsorption during long-term intravenous fluid therapy may result in magnesium deficiency.

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**Classification and characteristics of inherited disorders of renal magnesium wasting**

| Disorders                          | Age at Onset | Serum Mg | Serum Ca | Serum K | Urine Mg | Urine Ca | Nephrocalcinosis | Renal Stones | Pattern of inheritance | Gene | Protein |
|-----------------------------------|--------------|----------|----------|---------|----------|----------|-------------------|--------------|------------------------|------|---------|
| Classical Bartter's syndrome (Type 3) | Infant      | N or ↓  | N        | ↓       | N or ↓   | Variable | Rare              | No           | AR                    | CLCNKB | CLC-Kb chloride channel |
| Gitelman's Syndrome               | Variable     | ↓        | N        | ↓       | ↑        | ↓        | No                | No           | AR                    | SLC12A3 | NCCT Na^+ - K^+ - 2Cl^- co-transporter |
| Familial hypomagnesaemia           | Children    | ↓        | N        | ↑       | ↑        | ↑        | Yes               | Yes          | AR                    | CLDN1 | Paracellin-1 Tight junction protein |
| Hypomagnesaemia with Secondary hypocalcaemia | Infant      | ↓        | ↓        | N       | ↑        | N        | No                | No           | AR                    | TRPM6 | TRPM6 channel |
| Neonatal Bartter's Syndrome (Type 2) | Neonate    | N or ↓  | N        | ↓       | N        | ↑        | Yes               | ?            | AR                    | KCNJ1 | ROMK renal K channel |
| Isolated dominant hypomagnesaemia  | Children    | ↓        | N        | ↑       | ↓        | No      | No                | No           | AD        | FXN    | γ-subunit of the Na^+ - K^+ - ATPase |

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**a) Renal Disease**

Hypomagnesaemia is occasionally observed in chronic renal failure due to an obligatory renal magnesium loss. It is also seen during the diuretic phase of acute renal failure, post-obstructive diuresis and after renal transplantation. Patients on continuous ambulatory peritoneal dialysis develop hypomagnesaemia when low magnesium dialysis fluid is used.

**b) Inherited Disorders**

Classical Bartter's syndrome, which presents in infancy, is associated with hypokalaemia, metabolic alkalosis, hypernatremia and secondary hyperaldosteronism. It is caused by a mutation in CLCNKB gene, which encodes for the chloride channel.
Drugs

It’s, long term administration may produce substantial magnesium depletion due to secondary hyperaldosteronism, increased sodium load and interaction with calcium metabolism. Hypomagnesaemia is a recognized complication of aminoglycoside treatment. It has been associated with a variety of aminoglycosides including gentamicin, tobramycin and amikacin. Symptomatic hypomagnesaemia is seen with high dose treatment especially in the elderly or if there are other associated conditions causing magnesium loss. Aminoglycosides preferentially accumulate in the proximal tubule leading to cell damage and increased excretion of proximal tubular enzymes such as alanine aminopeptidase. Theophylline, especially in toxic doses, is reported to cause hypomagnesaemia. Intravenous administration of theophylline to asthmatic subjects causes increased magnesium excretion, and patients on theophylline have an increased risk of developing hypomagnesaemia. Amphotericin B, a highly nephrotoxic agent, can lead to severe hypokalaemia and hypomagnesaemia during chronic administration, but this can be prevented by amiloride therapy.

Endocrine Causes

Hypomagnesaemia may develop after parathyroidectomy due to the entry of magnesium into cells as part of the ‘hungry bone syndrome’.

Diabetes Mellitus

Magnesium depletion is due to increased magnesium excretion brought about by osmotic diuresis; there may additionally be a specific tubular defect. The decrease in serum magnesium concentration is correlated with fasting blood glucose, glycated hemoglobin, albumin excretion and the duration of diabetes. Magnesium depletion, via its effect on inositol transport, has been suggested to be of pathogenic significance in the development of diabetic complications.

Alcoholism

Hypomagnesaemia is a common finding in acute and chronic alcoholism with an incidence of up to 30%. Mechanisms contributing to magnesium depletion include poor nutritional status, magnesium loss through vomiting and diarrhea, malabsorption resulting from steatorrhoea due to chronic pancreatitis or liver disease, phosphate depletion, vitamin D deficiency, acute alcoholic ketoacidosis, hyperaldosteronism secondary to liver disease and renal tubular dysfunction. Magnesium deficiency in alcoholism may also contribute to complications such as osteoporosis, cardiovascular disease, stroke and hypertension.

Clinical Features of Hypomagnesaemia and magnesium deficiency

| Electrolyte disturbance, Complications of magnesium deficiency, Altered glucose homeostasis, Atherosclerotic vascular disease |
|---|---|---|---|---|---|---|---|---|---|
| Hypokalaemia | Hypertension | Depression, psychosis | Supraventricular arrhythmias | Athetoid movements & choreiform movements | Impaired athletic performance | Asthma | Chronic fatigue syndrome, Neuromuscular and central nervous |
Biochemical manifestations

a) Hypokalaemia

Magnesium and potassium homeostasis are closely related. Potassium depletion cannot be corrected until magnesium depletion is corrected. The exact mechanism for the development of hypokalaemia in magnesium deficiency is not clear, but may be related to the dependence of Na⁺, K⁺-ATPase, Na,K-Cl co-transport.

b) Hypocalcaemia

Hypocalcaemia is a common manifestation in hypomagnesaemia. Up to one third of patients with hypomagnesaemia in intensive care units may have hypocalcaemia. Several factors contribute to the hypocalcaemia of magnesium deficiency. One of the important factors is impaired secretion of PTH. Administration of exogenous PTH to patients with hypocalcaemia, hypomagnesaemia has little effect on serum calcium concentrations or on urinary excretion of cyclic AMP and phosphate. In magnesium deficiency, vitamin D metabolism is altered with a decrease in serum 1,25 dihydroxyvitamin D due to impairment in conversion of 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D.

Neuromuscular and Central Nervous System Manifestations

The earliest manifestations of magnesium deficiency are usually neuromuscular and neuropsychiatric disturbances. The most common clinical manifestations are hyperexcitability, including positive Chvostek's and Trousseau's signs, tremor, fasciculations and tetany. Frank tetany in magnesium deficiency is usually associated with hypocalcaemia. By competitively inhibiting the entry of calcium into pre-synaptic nerve terminals, magnesium influences the release of neurotransmitters at the neuromuscular junction and causes hyper-responsive neuromuscular activity. Magnesium also influences muscle contraction and relaxation by its effect on calcium handling by the muscle cell. In the muscle cell, the sarcoplasmic reticulum regulates the contraction/relaxation cycle by releasing and reactivating calcium. In magnesium deficiency, the release of calcium from the sarcoplasmic reticulum is increased.

The effect of magnesium deficiency on the central nervous system is even more complicated and less well understood. Magnesium deficiency seems to cause an intracellular calcium overload and disturbances in its sub cellular distribution.

Cardiovascular manifestations

Magnesium deficiency can affect cardiac electrical activity, myocardial contractility and vascular tone. It also potentiates digoxin toxicity. Although cardiac arrhythmias are well known to be associated with hypomagnesaemia, the contribution of hypomagnesaemia to its pathogenesis is not fully known due to coexisting hypokalaemia and other electrolyte disturbances.

Magnesium and digoxin toxicity

Hypomagnesaemia and magnesium depletion may contribute to digoxin toxicity even in the presence of apparently therapeutic concentration of serum digoxin. As 16–19% of patients on digitalis have been shown to have hypomagnesaemia, routine monitoring of serum magnesium concentration in digitalized patients may be important. Digoxin is thought to act via its inhibition of Na⁺, K⁺-ATPase, a magnesium dependent enzyme. In low magnesium states intracellular potassium is reduced, enhancing the inhibitory effect of digoxin.

Magnesium and glucose homeostasis

Magnesium affects glucose homeostasis by influencing insulin secretion as well as glucose uptake by cells. Magnesium deficiency inhibits the acute phase of insulin release in response to a glucose challenge. Magnesium also plays a role in glucose disposal and/or insulin sensitivity, and magnesium deficiency is associated with insulin resistance.
Magnesium deficiency and atherosclerosis

Experimental magnesium deficiency is characterized by increased triglycerides, cholesterol, VLDL, LDL, apolipoprotein B and triglyceride-rich lipoproteins and a reduced HDL, apolipoprotein A1 and plasma lecithin-cholesterol acyltransferase activity. Peroxidation of lipoproteins due to free radical production and increased platelet aggregation may also contribute to the development of atherosclerosis.

Magnesium deficiency, hypertension and vascular tone

There is an inverse relationship between magnesium intake and blood pressure and epidemiological studies show an increased incidence of hypertension in areas where the magnesium content of water is low. Insulin resistance caused by magnesium deficiency also increases vascular tone.

Magnesium and bone

Magnesium deficiency has been implicated in osteoporosis. Magnesium content of trabecular bone is significantly lower in subjects with osteoporosis, and magnesium tolerance studies show increased retention of magnesium. Serum and red blood cell magnesium also appear to be lower in these subjects. Recent studies also suggest magnesium supplementation increases bone density or arrests bone loss in 80% of osteoporotic subjects.

Magnesium and renal calculi

Urinary excretion of magnesium was reported to be lower in stone formers in some studies but not in others. Mild asymptomatic hypomagnesaemia can be treated by a diet rich in magnesium. In chronic magnesium loss, oral magnesium supplementation may be required.

Magnesium and asthma

The authors concluded that dietary magnesium intake was independently related to lung function, and low magnesium intake may therefore be involved in the aetiology of asthma. In a recent multicentre trial magnesium sulphate was shown to improve pulmonary function in severe asthma.

Management

It is important to note that the extent of magnesium deficiency is impossible to predict. As oral magnesium is poorly absorbed and, in large doses, causes gastrointestinal side effects, replacement by the oral route is not practicable in symptomatic patients. In critically ill patients with ventricular tachycardia or convulsions, it has been recommended that 8 mmol of magnesium should be given as magnesium sulphate over a minute, followed by 40 mmol of magnesium over the next 5 hours, if necessary; another 40 mmol may be administered over the next 10 hours. In less urgent situations, 0.5 mmol/Kg/24 hr may be given by continuous intravenous infusion or 4 mmol (2 mls of 50% magnesium sulphate) by intramuscular injection every 3 or 4 hours for the first day. Intramuscular injections are painful and intravenous infusion is preferable. Serum magnesium concentration should be monitored frequently. However, restoration of serum magnesium concentration to normal does not necessarily indicate repletion of body magnesium stores and therapy should be continued for approximately 3–7 days. If patients continue to lose magnesium from the intestines or kidneys, therapy may have to be continued for a longer duration. Once repletion has been accomplished, patients can usually maintain a normal magnesium status on a regular diet provided the cause of the magnesium loss has been corrected. If the patient cannot eat, a daily maintenance dose of 4 mmol of magnesium should be given parenterally.

Assessment of renal function before replacement therapy is important, and magnesium therapy in patients with any renal failure should be undertaken cautiously. If there is deterioration in renal function, the dose of magnesium should be halved.
Therapeutic uses of Magnesium

1. Magnesium salts as a cathartic agent was its earliest therapeutic application and is still used for this purpose.
2. Magnesium has been used therapeutically in acute myocardial infarction based on the observation that it causes vasodilatation, improves myocardial contractility, limits infarct size (in animal models of AMI) and modifies coagulation. The second Leicester intravenous magnesium intervention trial (LIMIT.2) was the first large-scale randomised placebo-controlled trial. This study showed a 24% reduction in short-term mortality and a 25% reduction in the incidence of left ventricular failure as well as a reduction in long-term mortality.
3. Magnesium has a well-established role in the management of torsade de pointes (long QT syndrome). However, its role in other arrhythmias is not clear. Nevertheless, magnesium therapy should be considered in those with refractory arrhythmias.
4. Magnesium has been used as a therapeutic agent in the treatment of asthma for many years without any convincing evidence.
5. Magnesium has been used in the treatment of pre-eclampsia and eclampsia. There is now strong evidence that magnesium sulphate is an effective agent in eclampsia. In a large multicentre trial, it was clearly shown that magnesium sulphate was superior to other anticonvulsants in the treatment of eclampsia.

Table 8

| Causes of hypermagnesaemia                   |
|---------------------------------------------|
| **Acute renal failure**, Rhabdomyolysis, Lithium therapy, Familial hypocalciuric hypercalcaemia, Swallowing salt water, Hypothyroidism, Addison's disease, Redistribution, Acidosis, Urethral irrigation, Excessive intake, Cathartics, Rectal, Parenteral |

Causes of hypermagnesaemia

Excessive intake

Magnesium containing medications are commonly used as laxatives, antacids and as rectal enemas. Hypomagnesaemia has often been described with the use of magnesium containing cathartics for treatment of drug overdose, in patients taking magnesium-containing cathartics and antacids for therapeutic purposes and following rectal administration of magnesium, even in the presence of normal renal function. In 75% of these cases hypomagnesaemia was clinically unsuspected, and the total amount of magnesium ingested was not excessive but bowel disorders may have enhanced the absorption.

Renal failure

Hypermagnesaemia is common in patients with end stage renal disease, in those undergoing dialysis and in acute renal failure. In chronic renal failure, serum magnesium concentration is usually maintained until the GFR falls below 30 ml/min. However, severe Hypermagnesaemia may result, especially if magnesium-containing medications are used.

Miscellaneous causes

Lithium therapy causes mild hypermagnesaemia as well as hypercalcaemia. Modest elevations in serum magnesium concentration have been reported in familial hypocalciuric hypercalcaemia. Mild hypermagnesaemia has also been seen in hypothyroidism, Addison's disease and milk alkali syndrome.

Clinical manifestations of hypermagnesaemia

Signs and symptoms of Hypermagnesaemia are not usually apparent until serum magnesium is in excess of 2 mmol/L.
Neuromuscular manifestations

Hypomagnesaemia causes blockage of neuromuscular transmission and depresses the conduction system of the heart and the sympathetic ganglia. The effects of magnesium on the neuromuscular junction are antagonized by calcium and the effects of hypomagnesaemia are therefore exaggerated in the presence of hypocalcaemia.

Cardiovascular manifestations

The negative inotropic effect of Hypermagnesaemia may contribute to the hypotension. Other potential factors contributing to the hypotension include central nervous system effects, skeletal muscle paralysis and depression of the carotid baro-receptor. Magnesium is also cardiotoxic.

Hypocalcaemia

Magnesium intoxication causes a reduction in serum calcium concentration. This has most commonly been reported in patients receiving magnesium therapy for pregnancy-induced hypertension. Serum parathyroid hormone concentration falls rapidly in response to magnesium infusion showing that hypocalcaemia may be partly due to the suppressive effects of acute Hypermagnesaemia on PTH secretion.

Other Effects

Hypomagnesaemia may cause smooth muscle paralysis resulting in paralytic ileus. Hypermagnesaemia may also interfere with blood clotting due to interference with platelet adhesiveness, thrombin generation time and clotting time.

Management of Hypomagnesaemia

The possibility of hypermagnesaemia should be anticipated in any patient receiving magnesium treatment, especially if the patient has reduced renal function, and serum magnesium concentration should be monitored daily.

When hypermagnesaemia is found, magnesium therapy should be withdrawn and this is all that is needed in most patients with mild to moderate hypermagnesaemia. In patients with symptomatic Hypermagnesaemia, serum magnesium should be lowered and the effects of hypermagnesaemia antagonised. Calcium antagonizes the toxic effects of magnesium and therefore patients with severe magnesium intoxication should be given 1 gm of intravenous calcium gluconate. This should be followed by the infusion of 150–100 mg of calcium over 5–10 minutes, which usually causes a dramatic improvement in the patient's clinical condition. Administration of glucose and insulin may also help to promote magnesium entry into cells. If the patient is in renal failure, peritoneal or haemodialysis against a low dialysis magnesium fluid will rapidly and effectively lower the serum magnesium concentration. Occasionally exchange transfusion has been used in severe neonatal Hypermagnesaemia.

7. Headaches and Migraines

Restoring your magnesium levels and adding an adequate source of magnesium in your diet may result in long term relief from migraines or headaches.

8. Irregular Heartbeat

9. Acid Reflux

In cases of constantly suffering from heartburn or acid reflux. Magnesium relaxes both sphincters which relaxes these. But when we lack magnesium in our body, the sphincters or valves at the top and bottom of our stomach cannot properly contain the food. As a result, food & acid can tend to get pushed back up into your esophagus. When the acid hits your esophagus, it causes a painful burning sensation which is the acid reflux or heartburn you feel.

Dietary magnesium

When looking for magnesium supplements, you should either take magnesium glycinate or magnesium citrate. Magnesium glycinate and...
magnesium citrate should not be taken more than the recommendation.

**Conclusion**

Disorders of magnesium metabolism are common in hospital patients and are frequently unrecognized. Low magnesium intake may be a contributor to many diseases including diabetes, cardiovascular disease and osteoporosis. Common complications of hypomagnesaemia include cardiac arrhythmias, and hypocalcaemia. Hypermagnesaemia, though less frequent, can also lead to cardiovascular and neuromuscular manifestations. Early recognition of disordered magnesium metabolism and correction of the electrolyte imbalance is necessary to avoid these complications. Since magnesium helps relax our blood vessels, it does the opposite when we are deficient in magnesium. In other words, a magnesium deficiency can cause high blood pressure by increasing blood vessel constriction.

As you know by now, magnesium is an essential mineral for muscle relaxation. Since heart is also a muscle, it contracts and relaxes. This can cause irregular heartbeats or arrhythmia.

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