

MAGNESIUM AND EHLERS-DANLOS SYNDROME

PART ONE: *WHY* PERSONS WITH EDS NEED TO KNOW ABOUT MAGNESIUM

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Everybody should know about magnesium. It's just that important.

"Magnesium is needed for more than 300 biochemical reactions in the body. It helps maintain normal muscle and nerve function, keeps heart rhythm steady, supports a healthy immune system, and keeps bones strong. Magnesium also helps regulate blood sugar levels, promotes normal blood pressure, and is known to be involved in energy metabolism and protein synthesis." – From Magnesium Fact Sheet from the National Institutes of Health (PLEASE TAKE THE TIME TO READ): <http://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/> (Notice also the links provided at the bottom of the Fact Sheet to many of the 62 references.)

What are some of the symptoms of magnesium deficiency?

"Magnesium deficiency can affect virtually every organ system of the body. With regard to skeletal muscle, one may experience twitches, cramps, muscle tension, muscle soreness, including back aches, neck pain, tension headaches and jaw joint (or TMJ) dysfunction. Also, one may experience chest tightness or a peculiar sensation that he can't take a deep breath. Sometimes a person may sigh a lot. ... Symptoms involving impaired contraction of smooth muscles include constipation; urinary spasms; menstrual cramps; difficulty swallowing or a lump in the throat-especially provoked by eating sugar; photophobia, especially difficulty adjusting to oncoming bright headlights in the absence of eye disease; and loud noise sensitivity from stapedius muscle tension in the ear. ... The central nervous system is markedly affected. Symptoms include insomnia, anxiety, hyperactivity and restlessness with constant movement, panic attacks, agoraphobia, and premenstrual irritability. Magnesium deficiency symptoms involving the peripheral nervous system include numbness, tingling, and other abnormal sensations, such as zips, zaps and vibratory sensations. ... Symptoms or signs of the cardiovascular system include palpitations, heart arrhythmias, angina due to spasms of the coronary arteries, high blood pressure and mitral valve prolapse. Be aware that not all of the symptoms need to be present to presume magnesium deficiency; but, many of them often occur together. For example, people with mitral valve prolapse frequently have palpitations, anxiety, panic attacks and premenstrual symptoms. People with magnesium deficiency often seem to be 'uptight.' Other general symptoms include a salt craving, both carbohydrate craving and carbohydrate intolerance, especially of chocolate, and breast tenderness." – From The Importance of Magnesium to Human Nutrition (PLEASE TAKE THE TIME TO READ): http://www.mbschachter.com/importance_of_magnesium_to_human.htm

Two of my personal favorite web-based resources for endless amounts of magnesium-related information are the Journal of Magnesium Research and the Magnesium Online Library.

Magnesium Research: <http://www.magnesiumresearch.com/index.phtml>

Magnesium Online Library: <http://www.mgwater.com/>

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Both the Journal of Magnesium Research and the Magnesium Online Library offer links to many free full text copies and pdf versions of medical journal articles and even the full text versions of books. For example:

Magnesium Deficiency in the Pathogenesis of Disease:

<http://www.mgwater.com/Seelig/Magnesium-Deficiency-in-the-Pathogenesis-of-Disease/>

Magnesium in the Central Nervous System:

<http://www.adelaide.edu.au/press/titles/magnesium/magnesium-ebook.pdf>

Magnesium: The Nutrient That Could Change Your Life:

<http://www.mgwater.com/rodtitle.shtml>

The introduction to the book “Magnesium: The Nutrient That Could Change Your Life” (<http://www.mgwater.com/rodintro.shtml>), first published in 1968, seems as if it was written in today. Although the health impact of magnesium deficiency has been recognized for many years, magnesium has recently become a really hot topic in medicine. Magnesium gets plenty of attention in mainstream media if you tune in. Just take a peek:

Dr Oz: <http://www.doctoroz.com/search?q1=magnesium>

LIVESTRONG: <http://www.livestrong.com/magnesium-deficiency/>

Prevention Magazine: <http://www.prevention.com/magnesium>

While magnesium deficiency is serious for anybody, persons with EDS should take note that magnesium plays a particularly important part in connective tissue and collagen metabolism and tissue maintenance in general. Magnesium deficiency may even accelerate aging. See, for example:

Magnesium and connective tissue.

http://www.jlc.com/en/revues/bio_rech/mrh/e-docs/00/03/FA/53/article.phtml

Regulation of collagen synthesis in human dermal fibroblasts by the sodium and magnesium salts of ascorbyl-2-phosphate.

<http://www.ncbi.nlm.nih.gov/pubmed/8489778>

Correcting magnesium deficiencies may prolong life.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3287408/>

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For persons with EDS, being deficient in magnesium makes many of the unwanted symptoms and conditions related to EDS worse! A few links regarding some of the specific symptoms or conditions often experienced by persons with EDS:

Sleep Disruption

***Magnesium supplementation improves indicators of low magnesium status and inflammatory stress in adults older than 51 years with poor quality sleep.**

<http://www.ncbi.nlm.nih.gov/pubmed/21199787>

***Effects of chronic sleep deprivation on autonomic activity by examining heart rate variability, plasma catecholamine, and intracellular magnesium levels.**

<http://www.ncbi.nlm.nih.gov/pubmed/15754837>

***Effect of chronic stress and sleep deprivation on both flow-mediated dilation in the brachial artery and the intracellular magnesium level in humans.**

<http://www.ncbi.nlm.nih.gov/pubmed/15119699>

***Erythrocyte magnesium and prostaglandin dynamics in chronic sleep deprivation.**

<http://www.ncbi.nlm.nih.gov/pubmed/9068914>

***Changes of cardiopulmonary function and magnesium metabolism in the state of deprivation.**

<http://www.ncbi.nlm.nih.gov/pubmed/7699744>

***Electrolyte content of brain and blood after deprivation of paradoxical sleep.**

<http://www.ncbi.nlm.nih.gov/pubmed/5637725>

Anxiety/Stress

***Latent tetany and anxiety, marginal magnesium deficit, and normocalcemia.**

<http://www.ncbi.nlm.nih.gov/pubmed/1164868>

***Magnesium, stress and neuropsychiatric disorders.**

<http://www.ncbi.nlm.nih.gov/pubmed/1844561>

***Mechanisms of antistress and antidepressive effects of magnesium and pyridoxine.**

<http://www.ncbi.nlm.nih.gov/pubmed/20120072>

***Consequences of magnesium deficiency on the enhancement of stress reactions; preventive and therapeutic implications (a review).**

<http://www.ncbi.nlm.nih.gov/pubmed/7836621>

ADD/ADHD

*** Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. I. Attention deficit hyperactivity disorders.**

http://www.jle.com/e-docs/00/04/18/F1/vers_alt/VersionPDF.pdf

***Magnesium, hyperactivity and autism in children**

Chapter 21 of <http://www.adelaide.edu.au/press/titles/magnesium/magnesium-ebook.pdf>

(See many references at end of chapter, too.)

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Neurologic Conditions

*Central nervous system magnesium deficiency.

<http://www.ncbi.nlm.nih.gov/pubmed/2001142>

*Neurotic, neuromuscular and autonomic nervous form of magnesium imbalance:

<http://www.ncbi.nlm.nih.gov/pubmed/9368238>

*Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. II. Pervasive developmental disorder-autism.

http://www.jle.com/e-docs/00/04/18/F2/vers_alt/VersionPDF.pdf

*Magnesium in the Central Nervous System:

<http://www.adelaide.edu.au/press/titles/magnesium/magnesium-ebook.pdf>

Mitral Valve Prolapse

*The importance of magnesium status in the pathophysiology of mitral valve prolapse.

http://www.jle.com/en/revues/bio_rech/mrh/e-docs/00/04/0C/97/article.phtml

*Therapeutic effect of a magnesium salt in patients suffering from mitral valvular prolapse and latent tetany.

<http://www.ncbi.nlm.nih.gov/pubmed/3914582>

*Clinical symptoms of mitral valve prolapse are related to hypomagnesemia and attenuated by magnesium supplementation.

<http://www.ncbi.nlm.nih.gov/pubmed/9070556>

*Fifteen years experience of the use of magnesium preparations in patients with mitral valve prolapse.

<http://www.ncbi.nlm.nih.gov/pubmed/21878073>

*Magnesium deficiency in the pathogenesis of mitral valve prolapse.

<http://www.ncbi.nlm.nih.gov/pubmed/3014234>

*Recent data on mitral valve prolapse and magnesium deficit.

<http://www.ncbi.nlm.nih.gov/pubmed/3079420>

Malabsorption / Gluten Intolerance, Constipation, Gut Flora Imbalance (Miscellaneous Gastrointestinal Issues)

*Hypomagnesaemia due to malabsorption is not always responsive to oral magnesium oxide supplementation alone.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1773248/pdf/gut05000897.pdf>

*Nutritional Aspects of Magnesium Metabolism

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1272307/pdf/westjmed00230-0028.pdf>

*Incidence of Hypomagnesaemia in Intestinal Malabsorption

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1872271/pdf/brmedj02507-0033.pdf>

*Magnesium deficiency: possible role in osteoporosis associated with gluten-sensitive enteropathy.

<http://www.ncbi.nlm.nih.gov/pubmed/9116391>

*Therapeutic uses of magnesium.

<http://www.aafp.org/afp/2009/0715/p157.pdf>

*Prebiotics, probiotics, and synbiotics affect mineral absorption, bone mineral content, and bone structure.

<http://www.ncbi.nlm.nih.gov/pubmed/17311984>

PreMenstrual Syndrome

* Evaluating the effect of magnesium and magnesium plus vitamin B6 supplement on the severity of premenstrual syndrome.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3208934/>

*Interrelationship of magnesium and estrogen in cardiovascular and bone disorders, eclampsia, migraine and premenstrual syndrome.

<http://www.ncbi.nlm.nih.gov/pubmed/8409107>

Headaches / Migraines

* Blood Magnesium levels in migraineurs within and between the headache attacks: a case control study.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3343674/>

*The effects of magnesium prophylaxis in migraine without aura.

http://www.jle.com/e-docs/00/04/3E/1E/vers_alt/VersionPDF.pdf

*Headache due to photosensitive magnesium depletion.

http://www.jle.com/en/revues/bio_rech/mrh/e-docs/00/04/0F/78/article.phtml

*Magnesium in headache

Chapter 8 of <http://www.adelaide.edu.au/press/titles/magnesium/magnesium-ebook.pdf>

(See numerous references at end of chapter, too.)

Temporomandibular Joint Dysfunction

*Serum nutrient deficiencies in the patient with complex temporomandibular joint problems

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2446412/pdf/bumc0021-0243.pdf>

Pain

*Magnesium involvement in pain

http://www.jle.com/e-docs/00/04/71/35/vers_alt/VersionPDF.pdf

*The role of magnesium in pain

Chapter 11 of <http://www.adelaide.edu.au/press/titles/magnesium/magnesium-ebook.pdf>

(See numerous references at end of chapter, too.)

Addiction

*Magnesium in drug abuse and addiction

Chapter 24 of <http://www.adelaide.edu.au/press/titles/magnesium/magnesium-ebook.pdf>

(See numerous references at end of chapter, too.)

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A few general links in addition to what has already been mentioned above

Magnesium metabolism and its disorders.

<http://www.ncbi.nlm.nih.gov/pubmed/18568054>

Magnesium homeostasis and clinical disorders of magnesium deficiency.

<http://www.ncbi.nlm.nih.gov/pubmed/8173141>

TAKE HOME MESSAGE: Persons with EDS and EDS-related problems very often prove to have significant magnesium deficiency, so they need to **EDUCATE THEMSELVES** regarding the impact of magnesium deficiency on their health and do something about it.

COMING SOON:

PART TWO: *WHAT* PERSONS WITH EDS NEED TO KNOW TO ABOUT MAGNESIUM

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Persons with EDS should recognize signs and symptoms of magnesium deficiency and learn how they can prevent and address magnesium deficiency to ensure positive magnesium balance.

Magnesium is a vital mineral component of the human body. In biochemical terms, magnesium is fourth most abundant cation in the body and the second most abundant intracellular cation, after potassium. Magnesium is the most abundant divalent mineral cation in cells. A normal, healthy adult has about 25 grams of magnesium in their body, with about 1% (about 250mg) present in their blood. It is important to realize that, because magnesium is mainly inside cells and the vast majority is stored deep in body tissues including bone and the nervous system, it has proven very difficult to study in detail from a scientific perspective, and magnesium physiology is relatively poorly understood in comparison with many other aspects of human physiology.

Magnesium is mandatory for over 350 known biochemical processes in the human body. At least 3751 magnesium binding sites have been detected on human proteins. In specific biochemical terms, magnesium is crucial to ATP utilization, glycolysis, the citric acid cycle, gluconeogenesis of noncarbohydrate sources, lipid metabolism, amino acid activation via DNA and RNA polymerase, certain protein degradation pathways, intracellular signaling, intracellular antioxidant synthesis, regulation of second messenger systems, stabilization of compounds critical for DNA maintenance, replication, and transcription, stabilization of cell membranes, regulation of ion channels controlling cellular potassium, and sodium and calcium balance, to name a few. Magnesium is known as a “natural” calcium channel blocker.

A complex interrelationship exists between magnesium, vitamin D, and calcium. For example, moderate to severe deficiency of magnesium will lead to calcium deficiency with symptomatic hypocalcemia. Interestingly, supplementation with calcium and / or cholecalciferol (vitamin D3) without magnesium will not correct the calcium deficit; however, supplementation of magnesium alone will correct the calcium deficit within a few days. Additionally, patients with hypoparathyroidism, malabsorption syndromes, rickets or osteomalacia, or combined magnesium deficiency and hypocalcemia have proven resistant to therapeutic doses of vitamin D unless magnesium was also given. Although the exact nature of altered vitamin D metabolism and/or action in the setting of magnesium deficiency is unclear, the dependence of vitamin D metabolism and vitamin D activity upon healthy magnesium balance is obvious.

Why is magnesium balance particularly relevant for persons with EDS? EDS is a connective tissue disorder. The key molecules of connective tissue fibers are collagen and elastin, proteins which make the thick collagenous fibers, thin reticular fibers, and stretchy elastic fibers that “glue” cells together. Collagen and elastin allow tissues to stretch and contract, bear loads and store mechanical energy. Glycosaminoglycans and proteoglycans are the key molecular components of the fluid portion of connective tissue known as ground substance bathing fibers and cells. Glycosaminoglycans are involved in connective tissue healing. Proteoglycans are involved in allowing connective tissues to tolerate compression. Connective tissue is very

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abundant in the body. Collagen, the most abundant protein in mammals, accounts for about a third of total body protein in humans.

Magnesium is mandatory for regulation of synthesis and degradation of collagen and elastin, proteoglycans, and glycoproteins. Thus, since connective tissue is already the issue at hand in EDS, it is easy to understand how a deficiency of magnesium further negatively affects connective tissue health!

Symptoms of magnesium deficiency include those distinct from the symptoms of EDS as well as those which overlap with known symptoms of EDS and EDS-associated problems. Symptoms of magnesium deficiency are generally acknowledged to occur mainly in the central or peripheral nervous system, musculoskeletal system, digestive tract, and cardiovascular system, but symptoms can occur for every system in the body given magnesium's ubiquitous role in human physiology.

No two persons with magnesium deficiency present in the same fashion. There is no "Master List" of a finite set of specific symptoms or accompanying conditions "Classic" for magnesium deficiency, nor is there a subset of symptoms that every person deficient in magnesium will have. Severe magnesium deficiency can present in a fairly typical fashion, referred to as "Latent Tetany" or "Spasmophilia".

Observed and reported symptoms and associated conditions in persons with varying degrees of magnesium deficiency include:

Central and Peripheral Nervous System Symptoms

- seizures
- epilepsy
- headaches, including migraines
- vertigo
- ataxia
- photophobia
- blurred vision
- vision changes, including changes from day to day
- difficulty adjusting to bright headlights
- blepharospasm (twitching of the eyelid)
- nystagmus (rapid uncontrolled eye movements)
- hyperacusis or noise sensitivity
- hearing loss
- insomnia
- poor REM sleep quality
- unrefreshed sleep
- unusual tiredness or drowsiness
- clouded thinking
- mental fatigue

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- confusion
- inattention
- disorientation
- delirium
- psychosis
- hallucinations
- nervousness
- anxiety
- depression
- apprehension
- belligerence
- “tantrums”
- panic attacks
- agoraphobia
- “uptight” personality
- “high-strung” personality
- general irritability
- premenstrual irritability
- hyperactivity
- restlessness or constant movement
- choreiform movement
- athetoid movement
- fidgeting
- exaggerated startle response
- tics
- twitches
- tremors
- fasciculation
- “jitters”
- hyperreflexia
- positive Chvostek and Trousseau signs
- spontaneous carpal-pedal spasm
- numbness
- tingling
- “zips”
- “zaps”
- pins and needles sensations
- burning sensations
- vibratory sensations
- other abnormal sensations

Musculoskeletal Symptoms

- twitches

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- cramps
- muscle spasm
- muscle “tension”
- pain
- weakness
- muscle atrophy
- “jerkiness”
- neck pain
- back pain
- pain in a “coathanger” distribution
- TMJ dysfunction
- tooth decay
- poor bone development
- bone pain
- osteoporosis
- slow bone healing

Digestive Tract Symptoms

- difficulty swallowing
- lump in the throat
- poor digestion
- constipation

Cardiovascular Symptoms

- palpitations
- arrhythmias
- angina due to coronary artery spasm
- hypertension
- mitral valve prolapse

Other System/Miscellaneous/Multi-system Symptoms

- fatigue
- chest wall tightness
- sighing
- salt craving
- carbohydrate craving
- carbohydrate intolerance
- insulin resistance
- renal and skeletal resistance to parathyroid hormone
- resistance to vitamin D
- electrolyte imbalances (hypocalcemia, hypokalemia, etc.)
- extreme thirst
- extreme hunger

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- unexplained weight loss
- recurring skin, gum, bladder or vaginal yeast infections
- mouth ulcers
- dry, itchy skin
- sores or bruises that heal slowly
- breast tenderness
- premenstrual fluid retention
- menstrual cramps
- preeclampsia
- kidney stones
- urinary spasms
- frequent urination
- incontinence

Persons with EDS need to be especially vigilant for signs of magnesium deficiency when they have additional risk factors affecting magnesium balance, such as diabetes, parathyroid or adrenal disorders, chronic renal disease, lactation, malnutrition or malabsorption, prolonged vomiting, acute or chronic diarrhea, pancreatitis, bowel resection or bypass, excessive diuresis, alcohol use or abuse, use of medications interfering with magnesium absorption or retention, or excessive vitamin D intake, to name a few.

More and more, recent research has focused on the idea that inadequate magnesium intake and, specifically, negative magnesium balance causes or aggravates diseases and conditions, as opposed to the idea that the disease processes are generally to blame for abnormal magnesium handling with resultant magnesium deficiency. The reason studies tend to focus more on intake may be that intake is more readily controllable than renal, abdominal or other losses.

In order to understand how to address magnesium deficiency, a basic understanding of magnesium homeostasis is helpful. The majority of magnesium is typically absorbed from the gut, but magnesium is also absorbable through the skin. The body secretes a small amount of magnesium into the gut to aid in digestion. The amount of magnesium ultimately absorbed through the gut and skin is distributed into tissues throughout the body, with the major portion stored in bone. Magnesium is eliminated from body tissues mainly through urine, and whatever is not absorbed through the gut is eliminated in stool. Magnesium losses also occur with sweat and lactation, with sweating losses typically negligible overall and losses due to lactation usually insignificant, as long as dietary intake is appropriately increased during lactation or lactation is not excessive. The basic approach for addressing magnesium deficiency involves addressing inadequate oral intake for specific needs, improving abdominal absorption, and / or improving renal retention.

Magnesium deficiency is rampant.

The World Health Organization estimates that 75% of persons in the United States have dietary magnesium intake that falls below the recommended intake (RDA) of approximately 420 mg for

males and 320 mg for females, and the average American's intake is only slightly more than half the minimum amount of magnesium required to function effectively.

Magnesium secretion and absorption in the gut is a complex process, and biochemical factors (such as hormones) primarily responsible for regulation of intestinal magnesium transport are as yet unidentified, with the process incompletely understood. Studies estimate in general that we absorb less than a third of the magnesium entering our gut, with the rest eliminated in stool. On average, intestinal absorption is already a fractional process, with over two thirds of what enters the gut remaining in stool. So persons with relatively diminished absorption need either to take in more to absorb an adequate quantity or to find a way to improve absorption in order to shift homeostasis toward a positive balance.

As with intestinal absorption, renal excretion and net retention of magnesium is complex and incompletely understood. Conditions such as hypercalcemia, vigorous exercise, metabolic acidosis, long term IV fluid therapy, osmotic diuretic agents like glucose or urea, magnesium wasting in the setting of taurine insufficiency, alcohol metabolism, caffeine-related diuresis, high intake of oxalate, certain prescription medications, and aging-related changes in the kidney are known to cause renal magnesium retention to decrease, thereby increasing magnesium losses and shifting magnesium homeostasis to a negative balance.

Adequate magnesium intake AND absorption AND retention are each necessary to overcome chronically negative magnesium balance.

INTAKE

No adverse effects have been formally associated with the intake of foods rich in magnesium, except for individuals at baseline risk of magnesium excess, for example due to kidney disease or specific medication side effects.

List of Selected Food Sources of Magnesium (From the National Institutes of Health Magnesium Fact Sheet)

Foods yielding about 20% of the RDA of magnesium:

- Wheat Bran, crude, ¼ cup
- Almonds, dry roasted, 1 ounce
- Spinach, frozen, cooked, ½ cup

Foods yielding about 10-20% of the RDA of magnesium:

- Raisin bran cereal, 1 cup
- Cashews, dry roasted, 1 ounce
- Soybeans, mature, cooked, ½ cup
- Wheat germ, crude, ¼ cup
- Nuts, mixed, dry roasted, 1 ounce
- Bran flakes cereal, ¾ cup
- Shredded wheat cereal, 2 rectangular biscuits

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- Oatmeal, instant, fortified, prepared w/ water, 1 cup
 - Peanuts, dry roasted, 1 ounce
 - Peanut butter, smooth, 2 Tablespoons
 - Potato, baked with skin, 1 medium
 - Blackeye peas, cooked, ½ cup
 - Pinto beans, cooked, ½ cup
 - Rice, brown, long-grained, cooked, ½ cup
- Foods yielding about 5-10% of the RDA of magnesium:
- Lentils, mature seeds, cooked, ½ cup
 - Vegetarian baked beans, ½ cup
 - Kidney beans, canned, ½ cup
 - Chocolate milk, lowfat, 1 cup
 - Banana, raw, 1 medium
 - Yogurt, fruit, low fat, 8 fluid ounces
 - Milk chocolate candy bar, 1.5 ounce bar
 - Milk, lowfat or nonfat, 1 cup
 - Raisins, seedless, ½ cup packed
 - Halibut, cooked, 3 ounces
 - Bread, whole-wheat, commercially prepared, 1 slice
 - Avocado, cubes, ½ cup
 - Chocolate pudding, ready-to-eat, 4 ounces

Many persons with magnesium deficiency find it difficult to meet intake demands through foods alone. Most often, in order to ensure adequate magnesium intake, oral supplementation is a must.

While RDA guidelines are well-established and widely accepted, they are not intended as dosing guidelines for the supplementation of magnesium in persons with magnesium deficiency!

Keep in mind, RDA amounts were determined for “normal”, “average” people in order maintain health. Think of the RDA for magnesium as the amount a healthy person starting out in neutral to positive magnesium balance needs to supplement daily if they realize they will be eating a diet relatively empty of magnesium and they hope to maintain positive magnesium balance. For a person with magnesium deficiency, supplementing with the RDA of magnesium is only likely to gradually address the deficiency if the person's diet is also magnesium rich; if the magnesium deficient person's diet is magnesium poor or they have absorption or retention difficulties, the RDA of magnesium is unlikely to effectively address their deficiency.

A person who has chronic severe magnesium deficiency likely needs considerably more than the RDA of magnesium. Persons with severe magnesium deficiency may need to restore a large portion of the 25 or so grams they should have in total in their body. Oral repletion would be especially challenging in severely magnesium deficient persons with malabsorption. Such persons are likely best served initially by consideration of intravenous supplementation under the supervision of a physician for more rapid and effective results, with subsequent oral and/or topical magnesium.

No consistent evidence-based published guidelines exist regarding recommended dosing of oral magnesium supplements to address magnesium deficiency. When using oral magnesium supplements, dosing typically should not exceed twice the RDA as indicated on the bottle. Severely magnesium deficient patients may tolerate as much as three times the RDA without apparent issue; however, ideally they should be under the supervision of a physician, with monitoring for clinical improvement as well as any signs of magnesium excess. As symptoms improve, dosing may approach the RDA.

Patients who are knowledgeable regarding the signs and symptoms of magnesium deficiency will likely eventually be able to self-titrate according to symptoms.

Oral magnesium supplements are classified as “inorganic” magnesium salts (e.g. magnesium oxide, magnesium sulfate, magnesium hydroxide, magnesium chloride), magnesium acid complexes sometimes referred to as “organic salts” of magnesium (e.g. magnesium citrate, magnesium lactate, magnesium gluconate, magnesium malate, magnesium ascorbate), and amino acid magnesium chelates often referred to as chelated magnesium (e.g. magnesium lysinate, magnesium orotate, magnesium taurate, magnesium glycinate). In this case, the use of the terms “inorganic” and “organic” relates to organicity in the manner defined by a laboratory chemist, not in the manner defined in agriculture, so the notion of “organic” magnesium supplements can be confusing. This means it is possible to use ingredients recognized from an agricultural standpoint as “organic” to manufacture supplements recognized from a laboratory standpoint as “inorganic”, and vice versa. Magnesium salts are fairly simple and inexpensive to produce. Complex processes are required to produce amino acid magnesium chelates, and thus they tend to be the most costly form of oral supplementation.

Considerable debate exists as to the most effective form of oral magnesium supplementation. No specific research exists which has specifically identified any particular supplement as ideal or most effective; however, studies consistently demonstrate that the effectiveness of any particular magnesium supplement depends upon its total magnesium content, its solubility, and its bioavailability.

Typically, the more soluble the form is, the more absorbable it is. Less soluble forms tend to precipitate in the gut, resisting absorption and causing loose stools or gut discomfort. The less soluble forms are in fact often given to constipated patients, regardless of magnesium status, specifically for their cathartic effects. (Think Milk of Magnesia.) Solubility typically correlates directly with absorption and bioavailability.

Bioavailability refers to the proportion of the magnesium contained in the oral supplement that is ultimately absorbable. Bioavailability of commercially available forms of oral magnesium supplements is thought to vary widely. Most experts do not recommend magnesium oxide as the supplement of choice, as it is only about 4% bioavailable due to its poor solubility. Magnesium chloride and amino acid magnesium chelates offer about 80-90% bioavailability. Although magnesium chloride is reported in several studies to offer upwards of 90% bioavailability of magnesium, absorption of the chloride ligand may put the patient at significant risk for chloride

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excess with associated metabolic acidosis. Hyperchloremia can affect oxygen transport and can be accompanied by deep, rapid breathing or shortness of breath, hypertension, weakness, cognitive deficits, agitation, edema, and even coma.

Additionally, magnesium compounds, like many other compounds, depend upon carrier proteins for absorption across the gut wall. In the gut, fierce competition occurs for carrier proteins. The magnesium anion from non-chelated magnesium salts and magnesium acid complexes is typically unbound from its ligand (the anion or the acid) and recombined with other molecules in the chemical soup of the stomach (chyme) to make entirely different non-chelated magnesium compounds, because non-chelated molecular bonds are typically loose and break apart easily. Then, in the intestine, various chemical components of food (such as phosphorous, phytates, lignans, fats, tannins, polyphenols and certain fibers) may bind more readily to carrier proteins or may bind to the non-chelated magnesium compounds, making it more difficult for the non-chelated magnesium compounds to bind to a carrier protein for successful absorption. Amino acid magnesium chelates supply their own carrier protein. The chelated bond is strong, and, in the gut environment, the chelated bond remains intact. The amino acid molecules of amino acid magnesium chelates serve as carrier proteins, thus contributing to the relatively high bioavailability of amino acid magnesium chelate supplements.

It is interesting to note that the chelated form of magnesium supplements is somewhat analogous to chlorophyll, the molecule giving magnesium-rich vegetables their green color. In chelated compounds, a central magnesium ion is bonded to a large organic molecule, a molecule composed of carbon, hydrogen, and other elements such as oxygen and nitrogen. In chelated magnesium supplements, magnesium is chelated to an amino acid molecule. In chlorophyll, magnesium is chelated to a large porphyrin molecule.

While chelated magnesium compounds are found in natural abundance in plants, magnesium salts exist commonly in nature as salts and mineral deposits, and magnesium acid complexes are typically laboratory derived.

Ultimately, many experts recommend the use of an amino acid magnesium chelate as the oral supplement of choice.

Given the complex interrelationships existing between magnesium and other compounds (e.g. calcium, magnesium, zinc, vitamin D, potassium, or other divalent cations), many experts discourage the use of combination preparations of magnesium (e.g. magnesium with calcium, or magnesium with calcium and vitamin D, or magnesium with calcium and zinc) or the arbitrary use of multi-vitamins to address a specific deficiency of magnesium. Experts also encourage a healthy diet rich in magnesium rather than reliance solely on oral supplements as a source of magnesium.

ABSORPTION

Absorption of bioavailable magnesium may be improved by use of prebiotics and probiotics, supplements and foods which are recognized to support and improve gut function and overall health. The human gut is what is known as a microbiome – a microbial biome. (In general terms, a biome is a distinct regional biological community, characterized by typical species and their interactions with their surroundings.) The human body contains over 10 times more microbial cells than human cells, with the majority of microbial cells – hundreds of species – living within the gut. Colonic microbes are known to play an important part in vitamin synthesis and in absorption of nutrients including magnesium, calcium, and iron. Thus, maximization of the health of gut microbiome helps to ensure positive magnesium balance.

Prebiotics such as inulin, fructooligosaccharides, and lactulose are non-digestible food ingredients that nourish and increase the vigor of microbes in the gut microbiome. Prebiotic-rich food examples include soy and tofu, raw, unfiltered apple cider and apple cider vinegar, fruits and vegetables such as bananas, tomatoes, artichokes, garlic, leeks, onions, chard, dandelion root and chicory, and grains such as barley, flax, oats and wheat. Probiotics such as lactobacilli, bifidobacteriae, and certain yeasts are live microbial organisms known to be beneficial to overall gut health. Probiotic-rich food examples include yogurt, kefir, kombucha, sauerkraut, kimchi, and miso. Kefir specifically formulated with FOS or inulin is very high in both prebiotics and probiotics. Prebiotic and probiotic oral supplements are widely available.

Unfortunately, despite sufficient magnesium intake through foods and / or supplements, some persons cannot successfully absorb adequate magnesium to achieve and maintain positive magnesium balance. Diminished absorption (malabsorption) may occur, for example, in the setting of gut inflammation, intestinal mucosal disease, pancreatic insufficiency, candidal overgrowth, inflammatory reactions related to intolerance of proteins such as gluten or casein, vitamin D deficiency, zinc excess, high intake of saturated fats and certain fibers, and surgical bowel resection or bypass.

Persons struggling with chronic magnesium deficiency despite sufficient magnesium intake through foods and / or supplements must consider the use of topical magnesium preparations which are absorbed transdermally such as Epsom salt baths, magnesium chloride baths, or application of magnesium oil. The limit of transdermal absorption from baths or oils is subject to saturation of skin transporters of magnesium. The more body surface exposed to the topical magnesium preparation, the more magnesium absorbed. Once exposed skin transporters are saturated, no further absorption occurs. Research has clearly shown that use of topical magnesium can safely increase plasma magnesium levels, however, individual absorptive rates vary widely, and no generally accepted guidelines exist regarding “dosing” for Epsom salt baths, magnesium chloride baths, or magnesium oils, either in healthy or magnesium deficient individuals. The Epsom Salt Council recommends soaking 3 times weekly for at least 12 minutes in a standard warm water bathtub with 2 cups of Epsom Salt added as a safe level of topical Epsom salt use. It is very likely that patients significantly deficient in magnesium could safely tolerate daily magnesium salt bath soaks or daily application of magnesium oils, however, no specific peer-reviewed research exists on the matter.

When persons with magnesium deficiency prove refractory to correction of the deficiency due to difficulties with intestinal or transdermal absorption of magnesium, or when the deficiency is severe and the clinical presentation is particularly concerning, administration of intravenous magnesium preparations under the supervision of a physician is required in order to achieve positive magnesium balance.

RETENTION

Persons with magnesium deficiency have some ability to affect renal magnesium retention through diet or supplement use. Research has shown that a deficiency of vitamin B6 leads to negative magnesium balance because the lack of vitamin B6 causes increased urinary excretion of magnesium. Thus, addressing vitamin B6 deficiency through diet or supplementation can improve renal magnesium retention. Another deficiency known to increase magnesium wasting is deficiency of taurine, which is known to cause renal wasting of magnesium. Some experts suggest that, because taurine increases renal retention of magnesium, chelated magnesium taurate is ideal for oral supplementation due to its favorable bioavailability for intestinal absorption as well as its positive effect on renal retention of magnesium.

Vigorous exercise should be avoided when a person is severely magnesium deficient, as vigorous exercise increases renal magnesium losses. Other things that are to be avoided when a person is magnesium deficient are alcohol, caffeine, foods high in sugar, and foods high in oxalates.

Renal retention of magnesium can be improved by addressing underlying conditions such as metabolic acidosis or electrolyte imbalances. Additionally, persons with magnesium deficiency may need to avoid medications affecting renal magnesium retention.

Persons with known magnesium deficiency supplementing with magnesium need to be familiar with the documented medication interactions and adverse effects of every prescription medication and every non-prescription medication or supplement they use in order to avoid worsening of magnesium deficiency or dangerous magnesium-medication interactions!

MEDICATIONS WITH KNOWN INTERACTIONS WITH MAGNESIUM (A Partial List)

- Aminoglycosides (e.g. gentamycin, tobramycin): Use with magnesium may cause neuromuscular weakness and paralysis by lowering magnesium levels.
- Antacids (e.g. proton pump inhibitors such as pantoprazole): Use may lower magnesium levels.
- Antibiotics: Magnesium supplements may reduce the absorption of quinolone and fluoroquinolone antibiotics, tetracycline antibiotics, and nitrofurantoin.
- Amphotericin B: Use may cause increased renal magnesium loss.
- Blood Pressure Medications: Magnesium supplements may increase the risk of negative side effects from calcium channel blockers.
- Cisplatin: Use may cause increased renal magnesium loss.
- Corticosteroids (e.g. prednisone): Use may lower magnesium levels.

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- Cyclosporine: Use may cause increased renal magnesium loss.
- Diabetic Medications: Magnesium supplements may increase the absorption of some medications used to control blood sugar levels.
- Digoxin: Low blood levels of magnesium can increase negative effects from digoxin; digoxin can cause more magnesium to be lost in the urine.
- Diuretics (e.g. furosemide, hydrochlorothiazide, bumetanide, and ethacrynic acid): Use may lower magnesium levels.
- Hormone Replacement Therapy: Use may decrease magnesium losses.
- Insulin: Use may lower magnesium levels.
- Labetolol: Use with magnesium can slow heart rate and reduce cardiac output.
- Levothyroxine: Magnesium supplements may possibly reduce effectiveness.
- Mannitol: Use may cause increased renal magnesium loss.
- Metformin: Use may lower magnesium levels.
- Penicillamine: Use may inactivate magnesium.
- Pentamidine: Use may cause increased renal magnesium loss.
- Tacrolimus: Use may cause increased renal magnesium loss.
- Tiludronate and Alendronate: Magnesium supplements may interfere with absorption.

SHOULD I GET A BLOOD TEST?

The most widely practiced method of testing for magnesium deficiency is the serum magnesium test. A normal serum blood level of magnesium can be falsely reassuring against magnesium deficiency. Unfortunately, within the currently established “normal” range for serum blood levels of magnesium used for laboratory interpretation, clinically significant magnesium deficiency may still occur. Studies suggest that as many as half of all cases of true magnesium deficiency are not formally diagnosed and go untreated due to misinterpretation of the significance of “normal” serum blood magnesium levels.

Serum blood measurement of magnesium is directly representative of the concentration of extracellular magnesium in blood that is suspended in serum. A serum blood measurement of magnesium cannot directly indicate anything about the concentration of intracellular magnesium present in red blood cells or, most notably, about the concentration of intracellular magnesium in the tissues of the nervous system or musculoskeletal system. Overall, measurement of serum and red blood cell magnesium concentrations poorly correlate with intracellular magnesium concentration in other tissues.

Often, serum blood magnesium levels do not fall to an abnormally low level until magnesium deficiency is severe to profound. This is because, in apparently healthy persons, the skeleton serves as a storage depot of sorts for about 60% of total body magnesium, and the human body strives to keep blood concentrations of magnesium within a very tight range. It is not unusual for persons with true magnesium deficiency to have a “normal” (or even “high”) serum blood magnesium level, while the amount of magnesium in other tissues is significantly deficient.

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In specific terms, hypomagnesemia is the medical term referring to abnormally low level of magnesium in blood. Hypomagnesemia is NOT synonymous with magnesium deficiency, as magnesium deficiency refers to an abnormally low total level of magnesium throughout the body, not just in the blood. It is of utmost importance to realize that magnesium deficiency can be present without hypomagnesemia!

The bottom line is that it is not possible to “rule out” magnesium deficiency simply by the use of the serum magnesium test.

Although other means of laboratory assessment of magnesium exist (e.g. ionized serum magnesium, intracellular erythrocyte magnesium, direct tissue analysis, renal magnesium excretion, and magnesium load test), they are rarely used by most clinicians, as they are often locally unavailable, relatively inconvenient, or prohibitively expensive.

An algorithm which has proven much more reliable than serum magnesium testing combines the use of serum magnesium level with measurement of renal magnesium excretion and the magnesium load test. Most clinicians do not follow the algorithm in practice. Instead, most clinicians with clinical concern for possible magnesium deficiency recognize the value of empiric treatment of suspected deficiency.

A savvy clinician will rely heavily upon detailed history and physical examination and use serum magnesium testing mainly to establish baseline data prior to initiation of supplementation.

Of course, serum magnesium testing becomes more relevant when monitoring efficacy of supplementation in patients discovered to have hypomagnesemia, as well as to ensure against development of hypermagnesemia in the setting of magnesium excess during supplementation.

WHO SHOULDN'T SUPPLEMENT WITHOUT A HEALTH CARE PROVIDER'S SUPERVISION?

Patients with kidney disease or using prescription medications or supplements known to increase renal retention of magnesium should not use supplemental magnesium without their healthcare provider's supervision. These patients may even need to adhere to a diet low in magnesium.

Additionally, pregnant women, nursing mothers, pediatric patients, and older patients should seek the advice of a healthcare provider or be under a health care provider's supervision when supplementing with magnesium.

TAKE HOME MESSAGE

Persons with EDS and EDS-related problems very often prove to have significant magnesium deficiency, so they need to **EDUCATE THEMSELVES** regarding the impact of magnesium deficiency and how to address it.

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