Orthomolecular Medicine and Heart Health: Unmasking the Magnesium Link to Multiple Risk Factors for Cardiovascular Disease

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Abstract *There is a substantial literature on the role of magnesium deficiency in the development of many of the chronic diseases of aging. In particular magnesium deficiency has a major impact on the development and progression of cardiovascular disease. Magnesium deficits are induced by western-style diets and genetic differences in magnesium needs, as well as the continuous depletion of magnesium by chronic stress and many commonly used drugs. This article outlines our current understanding of magnesium physiology and its effect on heart health, including its requirement for blood pressure and cholesterol control, and prevention of arrhythmias and tissue calcification. Problems with identifying magnesium deficiency from blood tests alone, functional biomarkers for detecting inadequate magnesium tissue stores, and the effective use of magnesium supplements to improve heart health are discussed.*

Introduction

Cardiovascular disease (CVD) is a major cause of mortality and morbidity in industrialized countries, and an increasing concern in developing countries. Independent risk factors frequently co-exist in the same individuals, and include hypertension, arterial calcification, hypercholesterolemia, and heart rhythm abnormalities. Drug treatments for primary and secondary prevention target each risk factor separately. A growing problem, therefore, is the use of polypharmacy in individuals with cardiovascular disease, and the major challenge this creates for adverse reactions due to drug-drug interactions.[1]

In orthomolecular medicine the focus is different, and aims to identify and correct potential nutritional deficiencies that may underlie multiple system dysfunctions. The various roles of vitamin D, omega-3 fats, antioxidants and the B-vitamins in heart health are all currently under investigation. A relationship between magnesium and risk of CVD has long been proposed.[2] Variations in CVD risk between different countries, and also between different areas of the same country have been shown roughly to correlate with regional variations in the magnesium content of soil and water.[3] Diets rich in vegetables and fruit, nuts, seeds and whole grains, currently recommended to reduce the prevalence of CVD, are also coincidentally high in magnesium.[4]

Magnesium is a required co-factor for over 300 regulatory enzymes. Virtually all hormonal reactions are magnesium dependent. Besides being directly required for specific enzymes, magnesium is indirectly involved in all enzymatic processes, since adenosine triphosphate must be complexed to Mg^{2+} to be metabolically available. Magnesium status affects cholesterol levels, blood pressure and arterial calcification, and defi-

ciency is a known risk factor for atrial fibrillation. A unifying hypothesis, therefore, as to why hypertension, hypercholesterolemia and other CVD risk factors so often occur in the same individual may be inadequate intakes of this critically important mineral.

Magnesium and Cardiovascular Disease

Magnesium acts as a calcium antagonist, competing for calcium absorption and reabsorption in the kidneys,[5] as well as calcium influx into cells. Because of this function magnesium has been dubbed "nature's physiological calcium channel blocker".[6] At least in animal models, adequate magnesium will prevent and even reduce calcification of arterial tissue and decrease vascular injury.[7] Through its association with sodium, potassium, and calcium, magnesium is closely involved in maintaining cellular electrolyte balance and adequate amounts of magnesium are needed to maintain normal levels of potassium.[8]

Magnesium plays a pivotal role in the regulation of skeletal, cardiac and smooth muscle relaxation following contraction.[9] Calcium needs to rise in muscle cells for contraction to occur. However before relaxation can follow, calcium must be shifted either outside the cell or back into storage sites within the cell (sarcoplasmic reticulum). This process depends on the availability of magnesium.[10] Inadequate magnesium intake will therefore impede relaxation of smooth and cardiac muscle and increase the risk of atrial fibrillation and hypertension as well as coronary and cerebral vasospasm.[11]

Magnesium deficiency induces endothelial dysfunction in animal models and in cultured endothelial cells. The functional and structural integrity of the endothelium is critical in preventing atherosclerosis. Correcting magnesium homoeostasis has therefore been suggested as a useful and inexpensive intervention to prevent and treat endothelial dysfunction, and in turn, atherosclerosis.[12]

Magnesium and Cholesterol Regulation

Magnesium is required for the appropriate regulation of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase), the enzyme that controls cholesterol production, switching HMG-CoA activity on and off as needed. In this respect magnesium overlaps in function with the widely used statin drugs, which work through inhibiting HMG-CoA.[13] However, continuous inhibition of cholesterol production would limit its availability for cell membrane synthesis and repair, as a precursor for sex and stress hormones, and for vitamin D. Lower circulating testosterone, which protects against cardiovascular disease risk in both men and women[14,15] has been reported in statin users.[16] On the other hand, supplementing with magnesium has been shown to increase both free and total testosterone.[17]

Magnesium has anti-inflammatory properties, and magnesium deficiency magnifies both immune system and oxidative stress, with a consequent increase in systemic inflammation.[18] Inflammation is an initiating factor that stimulates a cascade of events resulting in endothelial dysfunction, thrombosis and pro-atherogenic changes in lipoprotein metabolism. One study examined the effect of restricting 14 post-menopausal women to a magnesium intake of 33% of the RDA, a level of intake not uncommon in those consuming western-style diets. Magnesium restriction over a period of 78 days induced heart arrhythmias, increased serum glucose, urinary excretion of potassium and sodium, altered cholesterol homeostasis and decreased levels of the endogenous antioxidant, superoxide dismutase.[19]

Magnesium Deficiency

Magnesium deficiency may be due to the genetic inability to absorb magnesium, inherited renal magnesium wasting, excretion of excessive amounts of magnesium due to stress, or low nutritional intake.[20] Serum magnesium is maintained within a narrow range by the small intestine and kidneys. In response to high dietary intake, kidney excretion increases. When intake falls, the small intestine and kidney both increase their fractional magnesium absorption. If magnesium depletion continues, bone stores help to maintain serum magnesium by exchang-

ing part of their content with extracellular fluid.[21] Ongoing magnesium status therefore depends on the health of both organs: magnesium deficiency is a known complication of inflammatory bowel disease,[22] while serious kidney disease (creatinine clearance <30 mL/min) may result in hypermagnesemia.[23]

In many western nations dietary intake of magnesium is sub-optimal. In Canada, for example, the estimated daily intake of magnesium in those consuming an average diet is between 200 and 300 mg daily,[24] whereas the Recommended Daily Allowance (RDA), which varies depending on age and sex is 320 mg for females over 30 years of age, 400 mg in pregnancy and 360 mg during lactation, and the RDA for men over 30 is 420 mg. However, it has been suggested that the RDA underestimates daily needs and that 500-750 mg/day is more realistic.[25] In the United States, the 1999–2000 National Health and Nutrition Examination Survey found 79% of adults had magnesium intakes below the RDA.[26]

Apart from chocolate, foods richest in magnesium are not prominent in Western Diets (see **Table 1**, below). Interestingly, consumption of dark chocolate has several beneficial effects on heart health, including a reduction in blood pressure, improvement of vascular function and glucose metabolism, and reduction of platelet aggregation and adhesion.[27] Researchers usually assume that the benefits of chocolate are due solely to its antioxidant properties, and its contribution to enhancing magnesium intake is rarely considered.

Apart from diet, several medical conditions may influence magnesium status. Chronic diarrhea and vomiting results in magnesium deficiency,[28] and polyuria associated with poorly controlled diabetes depletes magnesium stores.[29] Because of increased demand for magnesium by skeletal muscle under conditions of sustained exertion, intense or prolonged exercise will negatively affect magnesium status.[30] Excess alcohol intake[31] and commonly prescribed drugs, including many targeted at heart disease such as loop and thiazide diuretics, deplete magnesium.

A recent drug safety communiqué from the United States Food and Drug Administration (FDA) warned of magnesium depletion by proton pump inhibitors – some of the most commonly prescribed drugs in North America. The alert listed warning signs of magnesium depletion, including leg cramps, muscle twitching and weakness, tremors, tetany, seizures, atrial fibrillation, supraventricular tachycardia, and abnormal QT interval.[32] The FDA further stressed that this magnesium depletion might be exacerbated in those taking other drugs known to deplete magnesium, such as digoxin and diuretics, both commonly used in CVD patients.

Table 1. Some Food Sources of Magnesium

Pumpkin seeds	½ cup	350 mg
Chocolate (baking)	3 ½ oz	295 mg
Mixed nuts	½ cup	150 mg
Black beans	1 cup	120 mg
Halibut	3 oz	70 mg
Oatmeal	1 cup cooked	56 mg
Spinach	1 cup fresh	44 mg
Shrimp	3 oz	31 mg
Beef steak	4 oz	22 mg
Whole-wheat bread	1 slice	18 mg

Calcium/Magnesium Balance, Stress and Calcium Supplements

The shortfall between actual and recommended magnesium intake is further complicated by the widespread tissue depletion of magnesium by stress.[33] Effector hormones of the hypothalamic-pituitary-adrenal axis trigger a fall in intracellular magnesium levels, which results in an influx of calcium into neurons causing hyperexcitability. This in turn produces hypertonicity in all types of muscle. Cardiac muscle and vascular smooth muscle are particularly reactive, since they must respond rapidly to sudden acute stress.[34] This reaction is a necessary preparation for the "fight or flight" response and under normal physiological conditions cells will return to their relaxed state once the emergency is past. However, under conditions of chronic stress, deficiency of magnesium relative to calcium will result in sustained contraction of skeletal, cardiac and vascular smooth muscle.[35]

A dramatic shift in calcium to magnesium balance can be seen in modern diets. Unlike our hunter-gatherer forebears, modern diets are low in magnesium, and because of the ready availability and consumption of dairy products, much higher in calcium. The combination of modern dietary changes compared to our ancient ancestors, the common use of magnesium depleting drugs, high levels of stress in urban lifestyles, and the increased intakes of calcium supplements to prevent osteoporosis would favour an elevation of intracellular free calcium and a deficit of free magnesium, thus increasing the threshold for skeletal, cardiac and vascular smooth muscle contractility. In large cohort studies, consuming calcium supplements without reference to magnesium intakes has been shown to be associated with increased risks of heart disease in both men and women.[36,37]

Both simple magnesium deficiency and changes in the calcium/magnesium balance may therefore increase vulnerability to cardiovascular disease.

Testing for Magnesium Deficiency

Laboratory assessment of magnesium status is notoriously difficult.[38] Magnesium is not a static ion, but moves between compartments and across membranes. A drop in serum magnesium is quickly normalized from bone or intracellular stores. Nor is magnesium fixed in red blood cells, which means that measuring magnesium by conventional standards (i.e., in the serum, plasma or red blood cells) cannot reliably indicate an individual's magnesium status.

Estimation of intracellular ionized magnesium may more accurately reflect magnesium status. Buccal epithelial cells are easy to access and believed to approximate tissue stores because of their rapid turnover time (<3 days). In one study of cardiac patients undergoing bypass surgery, magnesium was lower in such cells compared to healthy controls, whereas there was no difference in serum measurements. Magnesium levels in buccal cells correlated well with atrial biopsy specimens taken from the same patients during surgery.[39] However, the test is not routinely available, and so far there is no published data to support the reliability of the test in less seriously ill patients.

The magnesium loading test is used by some clinics, and it is considered reliable. However, it is cumbersome and usually requires a 24-hour baseline urine collection to estimate basal urinary excretion, followed by another 24-hour collection after an oral or intravenous magnesium challenge.

Functional Biomarkers of Magnesium Deficiency

An alternative approach that requires no laboratory tests uses functional evidence of calcium/magnesium imbalance as a biomarker of magnesium status. Theoretically, inadequate tissue stores of magnesium should manifest as malfunctions of skeletal muscle, such as leg cramps or spasms (Charley Horse), muscle twitching (fasciculations), restless leg syndrome and hypertonicity or "tight" muscles. Imbalances will also be obvious in smooth muscle, resulting in physical signs of dysregulated lung function such as shortness of breath, wheezing or asthma, and perhaps frequent sighing.

The tone of the bladder is dependent on the calcium to magnesium balance and hyperactive bladders, especially at night when

magnesium needs are highest, frequently respond well to magnesium supplementation. Magnesium's role in relaxing gastrointestinal smooth muscle has long been exploited in the treatment of functional constipation, especially in children.[40] Although there are a myriad of functional symptoms of magnesium deficiency, a simple inventory which can be used to quickly identify magnesium shortfalls in individual patients is shown in **Table 2** (below).

Magnesium Supplementation

Except in the case of overt renal failure, where they are contraindicated, the most effective way to improve magnesium status is with oral supplementation. A standard dose of 5mg/kg/day has been proposed.[41] However, individual needs for magnesium are hard to predict and vary from time to time even in the same individual, depending on stress levels, diet and concurrent medications. A standard dose may therefore not achieve optimal outcomes in all individuals.

Titrating Magnesium to Bowel Tolerance

A tried and tested method for optimizing magnesium intake is to increase intake to bowel tolerance, thus creating a positive magnesium balance. As noted above, a shortfall in magnesium will inhibit normal gastrointestinal peristalsis and result in sluggish bowel function. When increasing magnesium it is important that the potential cathartic action does not overwhelm gastrointestinal capacity to absorb magnesium. A very gradual increase in magnesium (every 3-4 days), in small incremental doses (approximately 50 mg elemental magnesium every three days) to generate 1-2 soft bowel movements daily achieves the best outcomes, as evidenced by the gradual disappearance of symptoms listed in Table 2. Coincidentally, the central nervous system symptoms associated with magnesium deficits such as anxiety, fatigue, headaches, insomnia and hyper-emotionality should also be somewhat relieved.

While not all symptoms in Table 2 will be present in all individuals, those that are present should resolve using this method. Especially in those with long-standing constipation, the amount of magnesium required to achieve bowel tolerance will vary from one individual to another. Where constipation is a prominent complaint, it is important first to rule out other medical causes of constipation, such as a bowel obstruction, malignancy, or hypothyroidism. Even those with apparently normal bowel function can increase magnesium using this approach, although their optimal dose will be lower than that needed for individuals with chronic

Table 2. Identifying Magnesium Deficiency: Questions to Ask Patients*

1. Do you get leg or foot cramps?
2. Are your shoulders frequently tight or tense at the end of the day?
3. Does your back ever go into spasm?
4. Do you ever experience muscle twitching, especially around the eye?
5. Do you suffer from wheezing or asthma, especially after exercise?
6. Do you experience any shortness of breath, for example, climbing stairs?
7. Do you sigh frequently?
8. Do you ever get palpitations or suffer from an irregular heart beat??
9. Do you need to urinate frequently, especially at night?
10. Are you ever constipated?

*Note that patients are unlikely to suffer from all of these symptoms. However, all the symptoms that are present should resolve after appropriate magnesium supplementation.

constipation. Benefits may include improved mood, sleep and energy levels.

The form of magnesium used is very important. Magnesium hydroxide has been used to treat constipation in geriatric patients with good results, not only improving bowel function but also markers of lipid and carbohydrate metabolism, suggesting a systemic as well as laxative effect.[42] Magnesium oxide has the highest concentration of elemental magnesium by weight, but compared with the citrate salts of magnesium is not well absorbed.[43] A major downside to magnesium citrate is that although well absorbed, it is rapidly eliminated by the kidneys,[43] and in the opinion of the author not the best form to use when tissue deficits need to be repleted.

Protein bound forms of magnesium have been shown to be well absorbed and highly bioavailable.[44] Clinical experience suggests that amino acid chelates of magnesium (glycinate, aspartate, taurate) give the best overall therapeutic effect, although currently doses per capsule are too high in many of the formulations on the market to be useful for the purposes of titrating to bowel tolerance, which requires a low dose product. Because of the impact of day-to-day stress and the continuous drain on magnesium stores by certain medications, dividing the dose between morning and evening achieves the best outcomes. In the event that time-released forms of magnesium become widely available, these would be the supplements of choice.

Improving the calcium to magnesium balance requires dietary adjustments, including an assessment of calcium intake from food and the maintenance of a steady intake of approximately 1,000 mg of calcium from diet and supplements together. A simple dietary calcium calculator is available for purchase from the Dairy Foundation of BC (see: www.bcdairyfoundation.ca).

Conclusion

Magnesium deficits are induced by modern diets and several chronic health conditions, and are difficult to detect using standard laboratory testing. And because of continuous depletion by chronic stress and many commonly used medications, are not simple to rectify. Poor magnesium status has profound implications for health in general but has particular relevance to cardiovascular disease, since it influences the manifestation of all the major risk factors. As knowledge of widespread magnesium under-nutrition emerges from national surveys, and the considerable variations in magnesium needs across populations becomes clear, the need for magnesium replacement therapy in the prevention and treatment of CVD should be a priority.

At a population level encouraging consumption of a diet that is unprocessed and in which approximately two-thirds of the energy is obtained from plant foods and one-third from animal products has been suggested for improving heart health.[45] This is similar in composition to the Dietary Approaches to Stop Hypertension (DASH) diet which is high in fruits, vegetables, whole grains and low-fat dairy products, and has been proven to lower blood pressure and cholesterol, and risk of heart failure and stroke. Assuming an energy intake of 2,100 calories such a diet would contain approximately 1,100 mg of calcium and 800 mg of magnesium.[45]

While dietary reforms could increase magnesium intake and shift the calcium to magnesium balance to being more favourable upon heart health, individual variations in magnesium needs due to stress, individual genetics or the concurrent use of magnesium depleting drugs require a more rigorous approach. The method of magnesium repletion described in this paper is one approach to customizing magnesium supplementation, and is in line with our understanding of biochemical individuality, a concept enshrined within the principles of orthomolecular medicine. In this respect it is also consistent with the emerging medical model of personalized medicine, which uses genetic or other information about individual patients to guide clinical decision making and customize care for optimal health outcomes.

Competing Interests

The author declares that she has no competing interests.

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