Magnesium Deficiency and Cardiovascular Disease

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Abstract

Cardiovascular disease is the number one cause of death and disability in the world. Low magnesium intake and low serum levels of magnesium have been inversely related to cardiovascular diseases and cardiovascular mortality in several epidemiological and meta-analytic studies. However, magnesium status is rarely evaluated in patients with cardiovascular diseases. Dietary evaluation is uncommon and supplementation is rarely advised or prescribed. This brief review scrutinizes the role this 'forgotten electrolyte' plays in cardiovascular health and cardiovascular disease.

Highlights

- Magnesium is the fourth most abundant mineral in the human body.
- Magnesium plays an important role in health and disease.
- Magnesium levels are inversely related to cardiovascular disease and cardiovascular mortality.
- Hypomagnesemia is also associated with an increase in all-cause mortality.
- Hypomagnesemia often goes clinically undetected as symptoms may be mild and nonspecific.
- Health care providers should maintain a high level of suspicion for this deficiency, especially in the critically ill.

INTRODUCTION

Magnesium (Mg) is a ubiquitous mineral. It is the ninth most abundant element in the universe, and the eighth most common element in the crust of our earth (1). It is the fourth most abundant mineral in the body (2). It is estimated that 99% of total body Mg is located in bone, muscles and non-muscular soft tissue (3). The main reservoir in the human body is the bone which contains about 60% if the total body Mg, with the remaining 40% residing in soft tissues (4). Less than 1% of Mg is found in the serum, where it maintains a tight concentrations range between 0.75 and 0.95 millimoles (mmol)/L (3,5). It is the second most common intracellular divalent cation (6).

The recommended daily allowance for Mg in adults is 4.5 mg/Kg/day (7) or around 400 mg/day in men and 300-310 mg/day in women (5). The daily requirement is higher in athletes, during pregnancy and lactation, and following a debilitating illness. Mg intake remains low in the United States. According to the NHANES 2005–2006 survey, almost one half of all American adults have an inadequate nutritional intake (8,9). Mg is plentiful in green leafy vegetables (spinach, avocado, edamame - which are rich in Mg containing chlorophyll) cereal, whole grains, nuts (almonds, cashews and peanuts), legumes and some shellfish and spices (10,11). Several commercial foods, including breakfast cereals are fortified with Mg. Tap water, especially 'hard water' contains up to 30 mg/L of Mg, and is a good nutritional source (12). Boiling of Mg rich foods and cooking may result in a significant loss (13). Processing or refining foods may result in a whopping 85% loss of Mg (14). The body absorbs approximately 30% to 40% of the dietary Mg consumed (15).

Hypomagnesemia is defined as a serum Mg level less than 0.75 mmol/L (16). Causes of Mg deficiency are numerous and include poor dietary intake, alcoholism, diarrhea, hereditary factors and intake of proton pump inhibitors (17,18). It is occasionally seen in the elderly and those with diabetes mellitus (19). Symptoms of hypomagnesemia are usually mild and may be limited to non-specific fatigue, muscle weakness and numbness (20) Symptomatic Mg deficiency is rare in healthy individuals (21). However, asymptomatic deficiency is not uncommon in hospitalized patients, with a prevalence of 10% or higher (22), and prognosticates an increased mortality in the critically ill (23).

Mg plays an important physiological role in the body (24,25). Its role has been implicated in adenosine triphosphate metabolism, RNA and DNA synthesis, protein synthesis and a multitude of crucial enzymatic reactions (26,27). It helps regulate muscular contraction (28,29), blood pressure (30), glucose metabolism/insulin sensitivity (31), cardiac excitability (32), vasomotor tone (33), and nerve transmission and neuromuscular conduction (34).

The role of Mg in human diseases has been increasingly recognized over the last two decades. Low levels of Mg have been associated with a number of chronic and inflammatory diseases, such as Alzheimer's disease, asthma, attention deficit hyperactivity disorder, eclampsia, insulin resistance, type-2 diabetes mellitus, migraine headaches, depression, kidney stones and osteoporosis (7,35). Hypomagnesemia has been linked to an increase in all-cause mortality (36). Its deficiency has also been implicated in several cardiovascular diseases (37-40). Low serum Mg concentrations also predict an increased cardiovascular mortality (36).

This brief review investigates our present understanding of the role played by this mineral in the prevention, pathogenesis and prognosis of cardiovascular diseases.

METHODS

A comprehensive literature search was carried out using the PubMed and PMC database of the US National Library of Medicine, National Institutes of Health, on Mg and cardiovascular risk factors and cardiovascular diseases. Additional studies were identified by searching bibliographies of reviews and were consulted, if relevant. Available scientific grey material was also reviewed.

RESULTS

There were 6712 citations listed in PubMed under 'Mg and cardiovascular diseases', with the earliest one being listed in 1946. Expanded search on magnesium and cardiovascular risk factors and specific diseases was also done; Mg and: hypertension (2385 citations dating back to 1934); diabetes mellitus (1247 citations dating back to 1947); coronary artery disease/angina (256 citations dating back to 1952); stroke (586 citations dating back to 1974); and cardiac arrhythmias (1561 dating back to 1946). Interrogation of PMC revealed the following number of citations under Mg and: cardiovascular disease (11,419); hypertension (8838); diabetes mellitus (5040); coronary artery disease (3847); stroke (6014) and cardiac arrhythmias (2225).

DISCUSSION

It is estimated that every year over 17.5 million people die from cardiovascular diseases (CVDs) in the world. This represents 31% of all global deaths. Three quarters of these occur in low and middle income countries. CVD's include coronary artery disease, heart failure, stroke and peripheral vascular disease. Heart attacks and strokes are responsible for almost 80% of the cardiovascular deaths (41). In the United States, in 2013, CVD's were responsible for nearly 801,000 deaths – or about one of every three deaths. (42). CVD's are also a leading cause of disability throughout the world, exerting extensive emotional and financial burden on individuals, families, societies and countries (43,44).

Mg plays an important role in the normal functioning of the cardiovascular system. Normal Mg levels appear to provide some degree of safety/benefit in ischemic heart disease, stroke and cardiac arrhythmias. An inverse association has been noted in three other conditions which play an important role in the pathogenesis of cardiovascular diseases, namely, hypertension, diabetes mellitus and the metabolic syndrome.

ISCHEMIC HEART DISEASE

Patients with low Mg levels have a higher risk of coronary artery disease (45,46). High Mg levels are associated with a reduced cardiovascular disease and mortality (36). This inverse association between Mg levels and coronary artery disease has been noted both in women (47) and men (48). Low Mg levels have also been implicated in major adverse events following drug-eluting stent (DES) implantation (49). Mg levels are frequently low after cardiac surgery and may play a role in the development of post-operative arrhythmias (50,51). Hypomagnesemia with Mg < 2 mEq/L or less is also associated with increased mortality in ambulatory heart failure patents (52). The main pathology in ischemic heart disease is atherosclerosis (53), and Mg deficiency may exacerbate this process (37,54-57). Epidemiological studies have found a direct correlation between low Mg levels and atherosclerosis (58,59). Hypomagnesemia also adversely affects lipid metabolism (7) and CRP (60). Both of these abnormalities have deleterious effects on endothelial function (61), accelerating atherosclerosis.

STROKE

Low Mg levels have been implicated in ischemic stroke (62,63) and several neurological disorders (64). Increased levels of serum Mg are inversely associated with the incidence of ischemic stroke (65). Mg levels have also been inversely associated with several risk factors for stroke, such as hypertension (66) and diabetes (67). Plasma Mg has also been inversely associated with atrial fibrillation (68), a major risk factor for embolic stroke (69). Mg supplementation (70) or a diet rich in Mg (71) have resulted in reducing the incidence of ischemic stroke. The use of intravenous Mg has also been suggested during the treatment of acute stroke (72). Mechanisms of benefit of Mg in stroke include antagonism of glutamate release, NMDA receptor blockade, calcium channel antagonism, and maintenance of cerebral blood flow (73).

CARDIAC ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

Low Mg levels are suspected as being arrhythmogenic (74). Recent studies have reported a significantly reduced risk of ventricular arrhythmia (75) and sudden cardiac death (76) with elevated serum Mg concentrations. Several reports have implicated hypomagnesemia in serious ventricular arrhythmias – ventricular tachycardia (77), ventricular fibrillation (78), and polymorphic ventricular tachycardia ‘torsades de pointes’ (79,80). Premature ventricular complexes (PVC’s) are predictive of future cardiac events and sudden cardiac death. (81-85). Hypo-magnesia is associated with increased PVC’s in a diabetic population (86). Mg may also help in the treatment of digitalis toxicity related arrhythmias (87). Intravenous Mg has also been used to treat ventricular tachycardia (88) and is recommended as a first line therapy for tosades de pointes associated with long QT interval (89) Low Mg intake has also been linked to increased supraventricular arrhythmias (90), including atrial fibrillation (91).

HYPERTENSION

Patients with hypertension tend to have lower Mg levels (18,92) Epidemiological studies suggest that increased Mg intake is associated with less hypertension (30). Further, Mg supplementation reduces blood pressure (93-96) This has also been confirmed in ambulatory BP monitoring (97). Mg supplementation can be achieved by using mineral salt substitute (98-100). These reductions in BP are partially attributable to a reduction in sodium intake (101). Mechanisms include alterations sodium and potassium activity (102), suppression of the adrenergic activity and possible natriuresis (96). The final result is a reduction in vascular resistance and the blood pressure (103).

DIABETES MELLITUS

Epidemiologic studies show a high prevalence of hypomagnesaemia and lower intracellular Mg concentrations in diabetic subjects (31,104). Hypo-magnesium is associated with a more rapid progression of diabetes and an increased risk for diabetes complications (105). These include retinopathy, nephropathy, and foot ulcers (104). On the other hand, adequate Mg intake is consistently associated with a better control in diabetics (106,107). Mg supplementation may also help in preventing progression to diabetes in patients with normal or impaired glucose tolerance (108-110). Mg supplementation may also help prevent or assuage diabetic complications, especially neuropathy (111.112). Salt replaced with salt substitute (rich in K and mg) has also helped reduce blood pressure in hypertensive type II diabetics (113). Mg is intricately involved in insulin action and development of insulin resistance.

METABOLIC SYNDROME

Metabolic syndrome is associated with an increased risk of cardiovascular (coronary heart disease, stroke, vascular dysfunction) and all-cause mortality (114,115). Hypomagnesemia and metabolic syndrome commonly co-exist and low levels of the former are associated with a higher prevalence of the metabolic syndrome. (31,116-119). Higher dietary Mg intake is associated with a lower risk of developing a metabolic syndrome (120).

CONCLUSIONS

Mg plays an important role in human health and disease. Mg deficiency plays an important pathogenic role in the precipitation, progression and prognosis of many diseases and is associated with an increase in all-cause mortality. Its levels also appear to be inversely linked to cardiovascular disease and mortality. It behooves healthcare providers to be cognizant of the role of Mg, the ‘unappreciated electrolyte’, in cardiovascular diseases and to keep a vigilant lookout for hypomagnesemia, especially in cardiac patients with a severe presentation, poor response to treatment or an accelerated progression to complications. Ensuring adequate nutritional intake is extremely important in cardiovascular patients. Supplementation may be required if nutrition consisting of foods rich in magnesium do not meet the requirements.

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