

MAGNESIUM AND ITS ESSENTIAL ROLE IN HEALTH

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INTRODUCTION

Magnesium has a very important role and function in life. It is one of the familiar metals that, in minute amounts, is necessary for body's proper metabolism to occur. It normally occurs at low concentrations and is known as a trace metal. Its bioavailability may change due to aging. A number of surveys show magnesium intake by old persons to be lower than the corresponding reference nutrient intakes, however, its deficiency among the elderly is also well documented, especially among the institutionalised and people with pathologies¹.

The absorption of minerals is dependent on many different factors, not the least of which is age, as well as adequacy of stomach acid output, balance of bowel flora, presence or lack of intestinal illness and parasites and amount of dietary fibre intake. Aging increases the risk of gastric atrophy, a condition that commonly is associated with a decreased secretion of hydrochloric acid in the stomach². The problem becomes when level of hydrochloric acid output decreases and the body's ability to absorb minerals from the food-bound form diminishes. This inability to adequately absorb minerals contributes to age-associated degeneration. Gastric atrophy or conditions such as achlorhydria (lack of stomach acid) or hypochlorhydria (inadequate stomach acid) can also impair the body's absorption of important minerals. Achlorhydria has been found in children as young as five or six years of age. Hypochlorhydria, however, is more commonly seen after age 35. It is estimated that between 15-35 percent of adults over age of 60 have some degree of gastric atrophy including hypochlorhydria. The absorption and efficient use of minerals in the body can also be affected by excessive levels of non-essential mineral contaminants such as aluminum, arsenic, cadmium, lead and mercury³. These toxic minerals can have an "unbalancing" effect on the body's cells. The body has a need for approximately 70 friendly trace element heavy metals, but there are another 12 poisonous heavy metals such as Lead, Mercury, Aluminum, Arsenic, Cadmium, Nickel etc. that act as poisonous interference to the enzyme systems and metabolism of the body. In general, heavy metals (HM) are systemic toxins with specific neurotoxic, nephrotoxic, fetotoxic and teratogenic effects. Heavy metals can directly influence behaviour by impairing mental and neurological function, influencing neurotransmitter production and utilization and altering numerous metabolic body processes.

Systems in which toxic metal elements can induce impairment and dysfunction include the blood and cardiovascular, eliminative pathways (colon, liver, kidneys, skin), endocrine (hormonal), energy production pathways, enzymatic, gastrointestinal, immune, nervous (central and peripheral), reproductive, and urinary. Chronic symptoms frequently associated with excessive accumulation of heavy metals include fatigue, musculoskeletal pain, neurological disorders, depression, failing memory and allergic hypersensitivity⁴. Heavy metals disrupt a vast array of metabolic processes. Heavy metals alter pro-oxidant/antioxidant balance and bind to free sulfhydryl groups, resulting in inhibition of glutathione metabolism, numerous enzymes and hormone function. Nutritionally, HM are directly antagonistic to essential trace elements and compete with nutrient elements for binding sites on transport and storage proteins, metalloenzymes and receptors. Disruption of the metabolism and balance of nutrient elements result in marked aberrations in the metabolism of carbohydrate, protein/amino acids, lipids, neurotransmitters and hormones. Lead and mercury are well known for their direct, destructive effects on neuronal function while cadmium and lead have direct adverse effects on cells in the arterial wall⁵⁻⁶. In this commentary, the role of Magnesium in health and diseases is discussed.

IMPORTANCE OF MAGNESIUM IN HEALTH AND DISEASES

Magnesium (Mg) is one of the most abundant ions present in living cells and its plasma concentration is remarkably constant in healthy subjects. Magnesium plays important roles in the structure and the function of the human body. The adult human body contains about 25 grams of magnesium. Over 60% of all the magnesium in the body is found in the skeleton, about 27% in muscle, while 6 to 7% is found in other cells and less than 1% is found outside cells. Magnesium is involved in more than 300 essential metabolic reactions⁷. In cellular systems, magnesium is the second most abundant element and is involved in basically all metabolic pathways. At physiologically relevant concentrations, magnesium itself is not genotoxic, but is highly required to maintain genomic stability. Besides its stabilizing effect on DNA and chromatin structure, magnesium is an essential cofactor in almost all enzymatic systems involved in DNA processing. Most obvious in studies on DNA replication, its function is not only charge-related, but

very specific with respect to the high fidelity of DNA synthesis. Furthermore, as essential cofactor in nucleotide excision repair, base excision repair and mismatch repair magnesium is required for the removal of DNA damage generated by environmental mutagens, endogenous processes and DNA replication. Intracellular magnesium concentrations are highly regulated and magnesium acts as an intracellular regulator of cell cycle control and apoptosis⁸.

The metabolism of carbohydrates and fats to produce energy requires numerous magnesium-dependent chemical reactions. Magnesium is required by the adenosine triphosphate (ATP) synthesizing protein in mitochondria. ATP, the molecule that provides energy for almost all metabolic processes exists primarily as a complex with magnesium (MgATP). Magnesium is required at a number of steps during the synthesis of nucleic acids (DNA and RNA) and proteins. A number of enzymes participating in the synthesis of carbohydrates and lipids require magnesium for their activity. Glutathione, an important antioxidant requires magnesium for its synthesis. Magnesium plays a structural role in bone, cell membranes and chromosomes⁹. Magnesium is also required for the active transport of ions like potassium and calcium across cell membranes. Through its role in ion transport systems, magnesium affects the conduction of nerve impulses, muscle contraction and the normal rhythm of the heart. Cell signaling requires MgATP for the phosphorylation of proteins and the formation of the cell signaling molecule, cyclic adenosine monophosphate (cAMP). cAMP is involved in many processes including the secretion of parathyroid hormone (PTH). Calcium and magnesium levels in the fluid surrounding cells affect the migration of a number of different cell types. Such effects on cell migration may be important in wound healing¹⁰. Plasma and intracellular Mg concentrations are tightly regulated by several factors. Among them, insulin seems to be one of the most important. *In vitro* and *in vivo* studies have demonstrated that insulin may modulate the shift of Mg from extracellular to intracellular space. Intracellular Mg concentration has also been shown to be effective in modulating insulin action (mainly oxidative glucose metabolism), offset calcium-related excitation-contraction coupling and decrease smooth cell responsiveness to depolarizing stimuli. A poor intracellular Mg concentration, as found in noninsulin-dependent diabetes mellitus (NIDDM) and in hypertensive patients may result in a defective tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration. Both events are responsible for the impairment in insulin action and a worsening of insulin resistance in noninsulin-dependent diabetic and hypertensive patients. By contrast, in NIDDM patients daily Mg administration, restoring a more

appropriate intracellular Mg concentration contributes to improve insulin-mediated glucose uptake. The benefits deriving from daily Mg supplementation in NIDDM patients are further supported by epidemiological studies showing that high daily Mg intake is predictive of a lower incidence of NIDDM. A growing body of studies suggest that intracellular Mg may play a key role in modulating insulin-mediated glucose uptake and vascular tone¹¹.

NUTRIENT INTERACTIONS

High doses of zinc in supplement form appear to interfere with the absorption of magnesium. Large increases in the intake of dietary fiber have been found to decrease magnesium utilization in experimental studies¹². However, the extent to which dietary fiber affects magnesium nutritional status in individuals with a varied diet outside the laboratory is not clear. Dietary protein may affect magnesium absorption. The active form of vitamin D (calcitriol) may increase the intestinal absorption of magnesium to a small extent. However, magnesium absorption does not seem to be calcitriol-dependent as is the absorption of calcium and phosphate. High calcium intake has not been found to affect magnesium balance in most studies. Inadequate blood magnesium levels are known to result in low blood calcium levels, resistance to PTH and resistance to some of the effects of vitamin D¹³.

DEFICIENCY AND TOXICITY

Magnesium deficiency in healthy individuals who are consuming a balanced diet is quite rare because magnesium is abundant in both plant and animal foods and because the kidneys are able to limit urinary excretion of magnesium when intake is low. Prolonged diarrhea, Crohn's disease, malabsorption syndromes, surgical removal of a portion of the intestine and intestinal inflammation due to radiation may all lead to magnesium depletion. Diabetes mellitus and long-term use of certain diuretics may result in increased urinary loss of magnesium¹⁴. Poor dietary intake, gastrointestinal problems and increased urinary loss of magnesium may all contribute to magnesium depletion, which is frequently encountered in alcoholics. Several studies have found that elderly people have relatively low dietary intakes of magnesium¹⁵. Because intestinal magnesium absorption tends to decrease and urinary magnesium excretion tends to increase in older individuals, suboptimal dietary magnesium intake may increase the risk of magnesium depletion in the elderly. Magnesium deficiency causes renal complications¹⁶. The appearance of several diseases is related to its depletion in the human body. In radiotherapy as well as in chemotherapy, especially in treatment of cancers with Cis-platinum, hypomagnesaemia is observed. The site effects of

chemotherapy that are due to hypomagnesaemia are decreased using Mg supplements. The role of magnesium in DNA stabilization is concentration dependent. At high concentrations there is an accumulation of Mg binding which induces conformational changes leading to Z-DNA, while at low concentration, there is deficiency and destabilization of DNA. The biological and clinical consequences of abnormal concentrations are DNA cleavage leading to diseases and cancer. Carcinogenesis and cell growth are also magnesium-concentration dependent. Several reports point out that the interaction of magnesium in the presence of other metal ions shows synergism with Li and Mn, but there is magnesium antagonism in DNA binding with the essential metal ions in the order: Zn>Mg>Ca. In the case of toxic metals such as Cd, Ga and Ni there is also antagonism for DNA binding¹⁷.

As evident from animal experiments and epidemiological studies, magnesium deficiency may decrease membrane integrity and membrane function and increase the susceptibility to oxidative stress, cardiovascular heart diseases as well as accelerated aging. The relationship to tumor formation is more complex; magnesium appears to be protective at early stages but promotes the growth of existing tumors. With respect to the magnesium status in humans, the daily intake in most industrialized countries does not reach the current recommended daily dietary allowances (RDA) values, and thus marginal magnesium deficiencies are very common. Mg deficiency has been shown to lead to increased oxidative stress. These results show that the lower antioxidant capacity found in moderate Mg deficiency was not due to a deficit in Mg dietary intakes and was not accompanied by increased lipid susceptibility to in vitro peroxidation¹⁸.

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