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Magnesium Deficiency Results in Oxidation and Fragmentation of DNA, Down Regulation of Telomerase Activity, and Ceramide Release in Cardiovascular Tissues and Cells: Potential Relationship to Atherogenesis, Cardiovascular Diseases and Aging

Editorial

Altura BM[1,2,3,4,5*], Shah NC[1,5], Gatha J. Shah[1], Pérez-Abela JL[6], Altura BT[1,3,4,5]

[1] Department of Physiology and Pharmacology, SUNY Downstate Medical Center, Brooklyn, NY, USA.
[2] Department of Medicine, SUNY Downstate Medical Center, Brooklyn, NY, USA.
[3] Center for Cardiovascular and Muscle Research, SUNY Downstate Medical Center, Brooklyn, NY, USA.
[4] The School of Graduate Studies in Molecular and Cellular Science, State University of New York Downstate Medical Center, Brooklyn, NY, USA.
[5] Bio-Defense Systems, Inc, Rockville Centre, NY, USA.
[6] Instituto Bien de Salud, Lima, Peru.

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Introduction

Aging is clearly agreed to be critical in the etiology of metabolic decline in most human subjects as they near their 65th birthday. A great many human subjects at 65 years of age demonstrate clear signs of metabolic and physiological decline, atherosclerosis in most major arteries, high blood pressure, high serum cholesterol levels, diverse cardiovascular diseases, and often type 2 diabetes mellitus, which contribute in major ways to congestive heart failure by their 75th-85th years. It must be pointed out, here, that all of these aberrations have been shown (or to be associated with) both experimentally and clinically, with the presence of magnesium deficiency (MgD) when they are carefully looked for [1-10].

Magnesium deficiency and cardiovascular diseases

Disturbances in diet are known to promote lipid deposition and accelerate the growth and transformation of smooth muscle cells in the vascular walls and to promote cardiac dysfunction [3, 9-11]. Several epidemiologic studies in North America and Europe have shown that people consuming Western-type diets are low in magnesium (Mg) content (i.e., 30-65% of the RDA for Mg [8-10, 12, 13]; most such diets in the U.S.A. show that 60-80% of Americans are consuming 185-235 mg/day of Mg [8, 13]. In 1900, in contrast, Americans were consuming 450-550 mg/day of Mg [5, 8]. Low Mg content of drinking water, found in areas of soft-water and Mg-poor soil, is associated with high incidences of atherosclerosis, ischemic heart disease (IHD), coronary vasospasm, hypertension, and sudden-cardiac death (SCD) [2, 5, 8, 14-18]. Both animal and human studies have shown an inverse relationship between dietary intake of Mg and atherosclerosis [5, 6, 8, 9, 19-21]. The myocardial level of Mg has consistently been observed to be lower in subjects dying from IHD and SCD in soft-water areas than those in hard-water areas [2, 4-6, 8, 9, 19-21]. Mg plays essential roles in more than 500 enzymatic reactions in the body and is required for all energy-generating reactions and oxidative phosphorylation [22]. More than 45 years ago, two of us demonstrated that Mg^{2+} behaves as a natural calcium channel blocker in both cardiac and vascular smooth muscle (VSM) cells [2, 23-26]. We also showed in experimental animals that Mg behaves as a natural statin in that it can lower blood cholesterol and triglyceride levels as well as act as a powerful vasodilator in the microcirculation and cardiac muscle relaxant [4, 6-8, 19, 27-30]. Hypermagnesemic diets have been shown to ameliorate hypertension and atherogenesis [1-6, 8-10, 19-22, 32-34]. Using sensitive and newly designed specific Mg^{2+}-ion selective electrodes, our laboratories demonstrated that patients with hypertension,

***Corresponding Author**:
Burton M. Altura,
Professor, Department of Physiology and Pharmacology, SUNY Downstate Medical Center, Brooklyn, NY 11203, USA.
Tel: 718-270-2194
E-mail: baltura@downstate.edu

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IHD, cardiac failure, strokes, diabetes types 1 and 2, gestational diabetes, renal-induced vascular changes (associated with elevated serum cholesterol), preeclampsia, hemorrhage, sickle cell anemia in children (and adults), and atherosclerosis exhibit significant reductions in serum/plasma/whole blood levels of ionized, but not total blood levels of Mg [5, 6, 8, 34-56]. Our group has also shown that dietary deficiency in rabbits and rats causes vascular remodeling concomitant with atherogenesis (i.e., arteriolar wall hypertrophy and alterations in the matrices of the vascular walls) and hypertension [4-6, 8, 19, 57-59]. These exciting results have been confirmed, essentially, by other investigators [20, 21, 32, 33]. Some of these results have recently been observed to result in an acceleration of the aging process [60, 61]. A number of the pathophysiological and molecular-biochemical alterations typically noted in tissues and cells in the aging process have been noted in MgD tissues and cells recently by our group and some other investigators [4, 6-8, 19, 61-72].

Magnesium deficiency associated with pathophysiological and biochemical alterations characteristic of aging tissues and cells: relationship to telomerases, ceramide, NF-kB and proto-oncogenes

It is well-known that the aging process is associated with elevations in blood/serum/tissue/cell levels of many of the same proinflammatory cytokines and chemokines found in MgD animals, eg., IL-1, IL-2, IL-6, TNF-alpha, among others [for recent reviews, see [61]]. Reduced levels of telomerases are known to be associated with elevated levels of several cytokines (e.g., TNF-alpha) in a number of aged cell types as well as in serum and cardiovascular tissues and VSM cells of MgD animals [for recent review, see [61]]; these phenomena being associated with (and correlated to ionized Mg levels; ceramide generation; and activation of NF-kB and proto-oncogene pathways) [61, 67, 68, 74-76]. It should be pointed out, here, that normal amounts of telomerases in all cell types are required to promote efficient cell cycle kinetics and normal cell growth [77, 78]. MgD is well-known to promote disturbances in cell cycle kinetics [79-81] via reactive oxygen and nitrogen species, most likely acting to downregulate telomerases [61]. Several studies have demonstrated that MgD, both *in situ* and *in vitro*, cause formation of reactive oxygen (ROS) and nitrogen species (NOS) [5, 6, 8, 61, 63-69]. Interestingly, the increased levels of cellular ROS and NOS were found to be associated with oxidation of DNA and increased levels of the tumor suppressor gene, increased levels of p53 and ceramide, in cardiovascular tissues and cells of MgD animals [61, 67, 68, 74-76].

Magnesium deficiency causes oxidation of DNA and increased levels of ceramide and p53: possible relation to cellular mutations and epigenetics

Recently, our laboratories have shown in animals, subjected to 21 days of MgD, that telomerase levels are downregulated and coupled to fragmentation and oxidation of DNA and increased levels of the tumor suppressor gene, p53 [61, 74]. We believe such data supports the idea that MgD could lead to multiple mutations in the genomes of multiple cell types found in the initiation of atherogenesis and congestive heart failure. Previous studies from our group [8, 61-64, 67, 68, 74-76, 82, 83], when viewed in the light of these findings, would lend additional support to the hypothesis that mutations and transformations of VSM cells, endothelial cells, and cardiac myocytes caused by MgD, fragmentation of DNA, and oxidation of DNA(all seen in atherogenesis, hypertension, strokes, and congestive heart failure) may play major roles in the aging process, thus leading to multiple cardiovascular changes, including inflammations of the vascular walls, high blood presure (due to formed elemental changes, release of ceramides, release of cytokines, excess wall lipid deposition and peroxidation, etc), cardiac dysfunctions, and eventual cardiac failure.

Several years ago, we suggested that MgD, by itself, probably acts as a genotoxic agent [74, 76]. As is known, one of ceramide's major pathophysiological actions is its ability to induce cell differentiation and transformation [83-87]. Abnormal cell differentiation, transformation, and growth are pivotal events of atherogenesis, hypertension, and cardiac failure. Hyperplasia and cardiovascular hypertrophy are common events in aging, atherosclerosis, hypertension, and cardiac failure. However, the precise mechanism(s) regulating alterations in tissue mass are not completely understood [11, 87]. The tumor suppressor protein p53, ceramide, and telomerases are now known to play key roles in cell transformation, apoptotic events, and the aging process [11, 61, 73, 77, 78]. Both ceramide and p53 can induce cell cycle arrest (and senescence), induce programmed cell death, and are associated with oxidation and fragmentation of DNA (i.e., genotoxic events) [84-86, 88-91]. MgD can produce all of these alterations in multiple cell types, including cardiac and VSM cell types [4-6, 8, 59-64, 67, 68, 74-76]. In view of all of these events noted in MgD animals and cells we would be remiss if some discussion regarding the potential role of epigenetics to magnesium deficiency's long-term effects on the aging process was not pointed out here. All organisms begin as a single cell, which divides through a process of stem cells creating a mass, via a series of carefully-designed changes in gene expression, which is required to form the tissues and cells of the fetal organism. The process of epigenetics orchestrates which genes have to be turned-on in each cell type, and then maintains the particular type of gene expression, or in other words, the particular cell's molecular identity via how DNA encodes the gene. Anything that produces modifications in the chromatin structure can affect a particular gene expression via transcription [92, 93]. Thus, if MgD-states are, indeed, genotoxic as we have suggested [74, 76], then the chromatin structure of one or more cell types (e.g., cardiac, endothelial, or vascular) could be modified and affect one or more genes and cell phenotype, as is found in atherogenesis. DNA methylation, histone modification, and microRNA alterations are known epigenetic pathways. We, thus, believe that prolonged MgD-states should be categorized as another epigenetic mechanism. But, how could all of these irreversible MgD-induced changes be avoided with ease?

Importance of Mg supplemented drinking water and beverages

Over the past two-plus decades, our laboratories have been investigating the utility of Mg-supplemented or naturally-occurring spring waters to avoid the pitfalls of dietary-induced MgD-states [4-6, 8, 19, 37, 47, 61-68, 74-76]. Our results, so far, bolster the idea that water intake (e.g., from tap waters, well waters, bottled waters, beverages using tap/well/spring waters, or desalinated waters) in humans should contain at least 25-40 mg/liter/day of Mg^{2+} [61, 68, 74-76]. A number of experiments done in our labs indicate that most, if not all the cardiovascular

manifestations observed in experimental animals found to be MgD, can be avoided by supplementing drinking waters with appropriate amounts of Mg^{2+}. The latter inclusion in our diets should go a long-way towards the prevention of cardiovascular diseases and ameliorate the aging process of bodily tissues and cells in humans worldwide. Interestingly, on the basis of our work, the World Health Organization has taken our recommendations seriously, for the first time [94].

Conclusions

There is a growing awareness that dietary deficiency of magnesium is becoming a serious problem, particularly in the Western World. Disturbances in diet are known to promote lipid deposition in the arterial walls and accelerate growth and transformation of smooth muscle cells in vascular walls which are linked to dietary deficiency of magnesium. The myocardial level of Mg has consistently been observed to be lowered in humans dying from IHD and sudden-cardiac death in soft-water areas than in those people living in hard-water areas. Use of specific Mg^{2+} ion-selective electrodes has been useful, clinically, to reveal serious underlying Mg- deficient states in patients presenting with various cardiovascular diseases (CVD). Mg deficiency (MgD) is associated with pathophysiological and biochemical alterations characteristic of aging cells and tissues which are related to upregulation of enzymes in the sphingolipid pathway and release of cytokines, ROS, NOS, activation of NF-kB and proto-oncogenes, resulting in cellular production of free ceramide, p53, and disturbances in cell cycle kinetics of vascular smooth muscle and cardiac muscle cells. The consequences of MgD lead to oxidation and fragmentation of DNA and inflammation in cells of the cardiovascular system, phenomena characteristic of atherosclerosis, aging, and CVD. We suggest that MgD states are genotoxic and, thus, one or more cell types (e.g., cardiac, endothelial and/or vascular) could be modified and affect one or more genes and cell phenotype, as is found in atherogenesis, representing epigenetic cell-induced changes. Supplementation of drinking waters (including beverages) is recommended in order to prevent and reduce CVD.

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