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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

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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 and death by their 75th-85th years. It must be pointed out, here, that people consuming Western-type diets are low in magnesium (Mg) content (i.e., 30-65% of the RDA for 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 Mg deficiency (MgD) when they are carefully looked for [1-6, 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 Mg deficiency (MgD) when they are carefully looked for [1-6, 8-10, 12-13]. Most such diets in the U.S.A. show that 60-80%

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., 30-63% 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 Mg deficiency (MgD) when they are carefully looked for [1-6, 8-10, 12-13]. Most such diets in the U.S.A. show that 60-80%

Keywords: Ceramide; Nuclear Factor kB; Proto-Oncogenes; Sphingolipids; Cytokines; p53.
Magnesium deficiency results in oxidation and fragmentation of DNA, down-regulation of genes, cellular mutations and epigenetics typically noted in tissues and cells in the aging process. These alterations in multiple cell types, including cardiac and VSM cells, are associated with oxidation and fragmentation of DNA (i.e., atherogenesis, oxidation, and fragmentation of DNA), which is known to promote disturbances in cell cycle kinetics. Reduced levels of telomerases are known to be associated with elevated levels of several cytokines (e.g., TNF-alpha) that produce modifications in the chromatin structure can affect a particular gene expression via transcription. Thus, if MgD-states are, indeed, genotoxic as we have suggested, 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. 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. 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-stages [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++ [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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