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Why is Cardiac Morbidity and Mortality Greater Around Christmas, New Year's, Monday Mornings and in the Morning Hours: Potential Roles of Unrecognized Ionized Hypomagnesemia and Release of Ceramides?

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Introduction

There is a growing incidence of lethal cardiac events around Christmas, New Year's and in the morning hours from 4:00 to 10:00 a.m. which is well-established in the USA and in The Southern Hemisphere [1-7]. In addition, many cardiac deaths often occur on Mondays with no satisfactory explanation [2,3]. Many of these deaths are, for the most part, unexplained and listed as "death from "natural causes". Although in the USA, the deaths which occur around Christmas and New Years happen in the cold -winter months, this does not account for many cardiac incidences which occur throughout the year in the early a.m. hours or on Mondays.

A number of explanations have been offered to explain the higher morbidities and mortalities at these special times of the year, morning hours and on Mondays, such as emotional stresses, too much ingestion of alcoholic beverages, improper medical facilities, diet, and/or changes in the physical environments [1-7].

Role of Magnesium in Cardiac Morbidity and Mortality

Ever since our laboratories first reported that magnesium (Mg) deficiency results in vasospasms of small and large coronary arteries, and that these events could be responsible for a great deal of sudden death ischemic heart disease (SDIHD) [8,9], a number of clinical studies have appeared which have confirmed and extended these findings [10-15]. We originally speculated that low dietary Mg intake and /or errors in Mg metabolism could be responsible for a large number of sudden cardiac deaths (SCD) and heart attacks in the Western world [8, 9,16].

In the early 1980's, some clinical studies appeared which suggested that of all electrolytes measured in the blood of hospitalized patients, total serum magnesium (Mg) levels often showed lowered levels, e.g., from 80-50% of normal [17-21]. However, in general, patients admitted to the intensive or coronary care units often demonstrated 60-30% of normal total blood levels of Mg [21-27]. When the blood/sera/plasma from these patients are examined for ionized Mg levels, in addition to the latter measured total Mg levels, these numbers rise to 80-70% in the patients admitted to intensive and coronary care units [26,27]. In addition, the red blood cells obtained from these patients are severely deficient in ionized Mg (e.g., 60-40% of normal; Resnick, Altura, and Altura, unpublished studies). Why is it so important to measure ionized Mg levels, not only total blood Mg levels?

Mg is a co-factor for more than 500 enzyme systems, and is the second most abundant intracellular cation after potassium [28]. It is critical in numerous physiological, cellular and biochemical functions and systems, running the gamut from hormone-receptor binding,

transmembrane fluxes of cations and anions, cellular energy generation, muscle contraction, regulation of DNA and RNA structure, regulation of lipid and carbohydrate metabolism, regulation of plasma lipid levels (i.e., cholesterol, triglycerides, and LDL-cholesterol), regulation of cell and tissue growth, nerve conduction, diverse cardiac functions and cardiac stability, control of vasomotor tone and distribution of blood flows to all organ systems, and cell death (i.e., apoptosis and necroptosis), among many others [28-38]. Mg is depleted in normal methods of food preparation (e.g., boiling, frying, etc.) and processing [39].

The daily intake of Mg has been declining since 1900, from where it was about 500-600 mg/day to about 150-225 mg/day, in many USA and European geographic regions, at the present time [40-42]. Mg is known to exist in three forms; free or ionized, complexed, and protein-bound [26]. These three fractions constitute the total serum and cell Mg [26]. In addition, up until our studies, there were no reliable methods to measure ionized Mg on whole blood, serum, and plasma rapidly (within 1-2 min) in the OR and critical-coronary care units [27].

Of almost 100 patients who were admitted for emergency coronary artery bypass surgery (CABS), at our hospitals (e.g., University Hospital and Kings County Hospitals), 88% of them exhibited significantly lowered levels of serum ionized Mg²⁺, but not necessarily total serum Mg levels [27,43-46]. Of those who were admitted on Holidays, such as Christmas or Thanksgiving, or in the morning hours (i.e., from 2:00 - 7:00 AM), we observed the lowest serum levels of Mg²⁺ (i.e., from 0.40 - 0.52 mM vs. 0.57-0.70 mM-controls, p<0.001). Patients admitted on Monday mornings (i.e., from 2:00 - 9:00 AM) for CABS exhibited, on average 0.48 ± 0.06 mM vs 0.67 ± 0.03 mM (p<0.01). For the most part, many (about 55%) of these CABS patients exhibited near, normal total serum Mg levels.

When we mimicked these, lowered serum Mg²⁺, *in vitro*, using

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isolated, normal canine, baboon, monkey, human or piglet coronary/cerebral arteries, they went into different degrees of vasospasm which could only be relaxed with increased levels of Mg^{2+} , not with calcium channel blockers or a variety of commonly-used vasodilator drugs [8,9,16,47-57]. The artificially-lowered levels of Mg^{2+} also resulted in potentiation of the contractile actions of all types of circulating neurohormonal vasoconstrictor agents (e.g., catecholamines, angiotensin II, serotonin, and a variety of peptides including vasopressin, etc.) [8,9,16,47-58].

From our studies, we believe the data are consistent with the hypothesis that human subjects admitted for emergency CABS on major holidays, in the morning hours, or on Monday mornings not only demonstrate abnormally low Mg^{2+} levels but most likely are predisposed to vasospasm of the coronary and cerebral arterial vessels which would result in increased morbidity and mortality. So, it makes eminent sense that human subjects, worldwide, would be predisposed to increased morbidity and mortality on holidays such as Christmas, New Year's Day and Monday mornings. An important factor involved in these predilections, at these various times of the year, are also most likely due to the excess drinking of alcoholic beverages, coffee and sodas (with caffeine), which have been shown to rapidly deplete vascular smooth muscle, cardiac muscle and endothelial cells of intracellular levels of Mg^{2+} [59-74]. In addition, since many people get heart – burn after heavy meals, they have a tendency to ingest proton-pump inhibitors which also can reduce Mg levels [46]. One must also consider the possibility that a number of the subjects dying from SDIHD and SCD may have been on long-term treatment with cardiac glycosides and/or thiazides, certain antifungal agents (i.e., amphotericin B), aminoglycosides (e.g., gentamicin, tobramycin), loop diuretics (e.g., furosemide), immunosuppressants (e.g., cyclosporine, sirolimus), or even certain chemotherapeutic agents (cisplatin, amacrine), all of which deplete the body of Mg; potential interactions with drinking of alcoholic beverages and/or caffeine – beverages would tend to reinforce (and potentiate) the tendency for considerable, rapid Mg depletion [20-22,30-33,36,74]. Unfortunately, such interactions have not been a focus of any epidemiological studies to our knowledge.

The cellular, biochemical, and molecular mechanisms of how lowered cellular levels of Mg^{2+} cause vasospasm and decreased peripheral, coronary, and cerebral blood flows, inflammation, ischemic events, atherogenesis, and diverse forms of cell death have been a long-time focus of our laboratories which are presented and discussed elsewhere [16,29,31,32,34,35,37,38,47-64,75-98]. In this context, using proton – nuclear magnetic spectroscopy (NMR), P^{31} – NMR, and brand-new ELISA assays, we have found that low levels of extracellular Mg^{2+} ($[Mg^{2+}]_o$) rapidly generated ceramides and other sphingolipids [32,34,82-89,91-93,96-98] which, heretofore, were totally unknown as potential causal factors in SDIHD, sudden cardiac death (SCD), congestive heart failure (CHF) and coronary artery disease (CAD). This work led us to hypothesize that dietary deficiency and/or inborn metabolic-induced deficiency of Mg could result in increased morbidity and mortality from coronary and cerebral arterial vasospasms. But, how would generation of ceramides and/or other sphingolipids (e.g., sphingosine; sphingosine-1-phosphate) result in susceptibility to SDIHD, SCD, CHF, and CAD?

Ceramides are sphingolipids known to be released as a consequence of sphingomyelinases (SMase) acting on sphingomyelin (SM), a component of all cell membranes, or as a consequence of the activation of serine palmitoyl transferase 1 and 2 (SPT 1 and SPT 2) (a *de novo* synthetic pathway) [99-101]. Ceramides are now thought to

play important roles in fundamental processes such as inflammation, angiogenesis, membrane-receptor functions, cell proliferation, microcirculatory functions, cell adhesion, immunologic responses, excitation-coupling events in smooth muscles, and cell death (i.e., apoptosis) [99-110]. SPT 1 and SPT 2 are the rate-limiting enzymes in the biosynthesis of *de novo* sphingolipids [99,100]. More than 25 years ago, it was first demonstrated that SPT activity was increased in aortas of rabbits fed a high cholesterol diet [111]. A short time (i.e., 1990) after these latter studies were published, two of us showed that dietary deficiency of Mg, in levels found in Western diets, vastly increased atherosclerotic plaque formations in rabbits fed high-cholesterol diets, whereas high dietary levels of Mg inhibited plaque formations [78]. We also noted that early intervention with oral Mg administration reversed the growth and intensity of the plaque formations. SPT is a heterodimer of 53-kDa SPT-1 and SPT-2 subunits [112,113], both of which are bound to the endoplasmic reticulum [114]. An upregulation of SPT activity has been hypothesized to play a role in apoptosis [115]; cell death events which take place in atherogenesis [116-118].

Recently, several of us have reported that Mg deficient (MgD) diets given to rats for only 21 days results in an upregulation of SMases, sphingomyelin synthase, ceramide synthase, SPT -1 and SPT-2 in a variety of cardiovascular tissues and cells as well as decreased levels of SM and phosphatidylcholine (PC) [34,37,85,86,88,91,93,94,119]. We also noted that MgD diets resulted in fragmentation of DNA [37,94], a release of mitochondrial cytochrome C (a result of leaky membranes) [88], an increased expression of apoptotic protease factor-1, an activation of caspase-3 (needed for apoptosis) [87], and upregulation of p53 [119], release of cytokines [91,120], activation of three different nitric oxide isozymes [89], activation of multiple protein kinase C isozymes [120], activation of mitogen-activated kinases (MAPKs) [63,121], activation of tyrosine kinases [121], activation of P-I-3 kinases [63,64] and upregulation of receptor -interacting kinases (e.g., RIPK1 and RIPK3) [38], all hallmarks of various stages of atherogenesis. When specific inhibitors of SMases and SPT (1 and 2) were utilized in primary cultures of vascular smooth muscle (VSM) cells, exposed to low $[Mg^{2+}]_o$ environments, we noted an inhibition of formation and release of ceramides, inhibition of release of cytochrome C, reduced expression of apoptotic protease factor-1, reduced expression of various PKCs, MAPKs, and NO as well as inhibition of release of cytokines, and inhibition of activation of caspase-3 and p53 [34,37,38, 87-89,91-98,119,120]. We believe, collectively, these new studies lend support to our hypothesis that generation and release of ceramides in MgD are pivotal molecules in the initiation of cellular and molecular events leading to inflammatory events and atherogenesis. The fact that we have found elevated ceramide levels in the sera of CABS patients who presented with CHF and CAD strengthens our hypothesis, particularly as the subjects that died of SDIHD and SCD on the holidays and on Monday mornings had the lowest serum levels of ionized Mg coupled to the highest serum levels of the ceramides.

Since we have demonstrated in both rats and rabbits, fed low Mg diets, that increased levels of ceramides are found in situ, in all chambers of the heart, aortae and coronary arterial blood vessels, and these manifestations were associated with increased plaque formations, elevated serum cholesterol, elevated LDL-cholesterol, and elevated triglycerides [35,37,78,96, 97,106], it is highly unlikely that these *in-vivo* manifestations are merely epiphenomena. Only time will -tell whether our hypothesis is correct. But, how could the risk of susceptibility, on holidays, morning hours, and Monday mornings, to SDIHD, SCD, and CAD be avoided or reduced?

Over the past 20 years, our laboratories have been investigating the utility of Mg-supplemented or naturally-occurring spring waters to avoid the potential pitfalls of dietary –induced MgD-states, thus reducing the risks of morbidities and mortality from SDIHD, SCD, and CHF. Our results, so far, bolster the idea that water intake (e.g., from tap waters, well waters, beverages using tap/well/spring, or desalinated waters) in humans should contain at least 25-40 mg/liter/day of Mg²⁺[87-89,91-98, 119,120,122]. A number of studies, done in our labs, indicate that most, if not all the cardiovascular manifestations observed in experimental animals (discussed above) found to be MgD can be avoided by supplementing drinking waters with appropriate amounts of Mg²⁺. Supplementation of diets with adequate amounts of Mg, in our youth, should help to prevent the beginning of atherosclerotic plaques seen in growing children. The inclusion of adequate amounts of Mg in our diets, drinking waters, and beverages should cut-down, tremendously, the risks of SDIHD, SCD, CHF, and CADs, and, in the process, should greatly reduce the current 350 billion dollars/ year spent in the USA, alone, to treat cardiovascular diseases.

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