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Commentary

Can Hypomagnesemia Put the Squeeze on Coronary Arteries: An Unappreciated Factor in Myocardial Ischemia, Heart Attacks and Sudden Cardiac Death

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Does hypomagnesemia frequently contribute to myocardial ischemia and myocardial infarction? Will increased dietary intake of magnesium lower the risk of ischemic heart disease (IHD) and acute myocardial infarction (AMI)? Does magnesium (Mg) have a therapeutic value in preventing IHD and AMIs?

These are very important questions to raise at a time when so much attention and monies are being expended on non-occlusive causes of ischemia and infarction. Our work, dating back to 1970 [1-7] has provided insights into these questions. These initial experimental studies have stimulated numerous clinical trials around the globe that support roles for increased dietary Mg intake in both the prevention/amelioration of IHD and AMI as well as the use of Mg therapeutically [8-16]. Experimental studies on numerous mammalian species demonstrate that hypomagnesemia can produce coronary arterial vasoconstriction, decreased blood flows, inflammations, atherogenesis, and increased vascular reactivity, resulting in continuous coronary arterial vasospasm, and over a period of time, IHD, AMIs, or sudden cardiac death (SCD) [3,4,17-31]. This evidence shows that Mg supplements reduce ischemia, and that an increase in dietary Mg intake would reduce the incidence of atherosclerosis, coronary arterial diseases and improve the quality of life.

Examination of the sera of approximately 35 cardiac patients in our hospitals, diagnosed with Prinzmetal angina, and using specifically-designed electrodes for measurement of ionized Mg levels revealed that, on average, there was a 35-40% decrease in ionized Mg levels [46-50]. Measurement of interleukin 1a, TNF-alpha, and c-reactive protein indicated a strong inverse correlation to the serum ionized Mg level [unpublished findings].

In 1768, Dr. William Heberden was the first person to note an occurrence of chest pain attacks (i.e. angina pectoris) that seemed to be pathologically –related to occluded coronary arteries. These episodes are triggered by exercise, as well as other forms of exertion, and usually relieved by rest and nitroglycerin tablets. Prinzmetal angina is not to be confused with classic cases of angina that occur in the

absence of exercise or exertion. It is now agreed that Prinzmetal angina is caused by coronary vasospasm. It has been our contention for almost 40 years that a major cause of Prinzmetal angina are low levels of ionized Mg in the sera and coronary vascular smooth muscle cells [5,6], as patients given supplemental amounts daily of Mg exhibit markedly reduced Prinzmetal angina attacks when subjected to exercise [10,11].

Evidence from hard-water vs. soft-water studies and autopsy studies support role of Mg deficiency

Evidence which has been accumulating for almost 40 years, since our initial discoveries, consists of data from hard- and soft-water studies, autopsy studies, serum measurements of both ionized and total Mg levels following AMIs and IHD attacks, treatment series involving Mg, and extensive studies of magnesium's effects on vascular tone, vascular reactivity and single coronary vascular smooth muscle cells [1-50]. There have been a substantial number of both experimental and clinical studies, in various parts of the world, to determine whether the mineral content of drinking waters correlate with incidence of cardiovascular diseases (CVDs). The results strongly suggest that such a correlation does exist [8,9,14,28,29,51- 59]. As early as 1962, a study in Glasgow, Scotland showed that there were 855 cardiac deaths per 100,000 men, ages 45 - 64, who drank soft-waters, but in London where the men , of similar ages, drank hard-waters, there were only 581 deaths per 100,00, a very significant difference [51,52,56]. In 1966, an American study showed that in Lincoln, Nebraska, where the men drank hard-waters, the cardiac death rate was 300 per 100,00 while in Savannah, Georgia, where the men drank soft-waters, the cardiac death rate was 800 per 100, 000, thus almost triple the cardiac death-rate in the men that imbibed hard-drinking waters in Nebraska [60]. Finland, the country with one of the highest cardiac death- rates in the world, is also a country with very soft-drinking waters, particularly, in the eastern –half [61]. Similar types of studies have been observed in Canada, Scandinavia, France, Germany, Italy, and several eastern European nations [8,27,28,54-59].

Although these soft-versus hard-water studies have been criticized, and are still in some circles, controversial, in our opinion, the overwhelming data with thousands of human subjects, can no longer be ignored. A clear correlation, using meta-analyses, between Mg levels in the drinking waters and IHD as well as sudden-cardiac death seems to emerge [60- 62]. This correlation is evident from autopsy studies. One well-done study done in the UK, among others, revealed that the coronary arteries obtained from subjects living in hard-water areas, had significantly higher levels of Mg in cardiac muscle than cardiac muscle obtained from cardiac deaths in subjects living in soft-water drinking regions [8,28,62-65]. A Canadian study showed similar results [66,67].

Many scientists and physicians have taken issue with these latter associations of Mg levels in drinking waters and the incidence of death-rates from IHD and AMIs. In the early 1980's, an editorial in JAMA suggested that the proposed link between soft-waters and heart disease is an unsubstantiated idea [68]. These authors attempted to posit that only an inconsequential proportion of mineral intake comes from the water supply. Unfortunately, "they did not do their homework". Depending upon which geographic region one lives in, the intake of Mg ranges from 1 - 2 mg/l to as much as almost 600 mg/l [8,67].

Despite these skeptics, there is a clear, overwhelming amount of evidence which demonstrates a strong correlation between water intake levels of Mg and the incidence of IHD [51-68]. It must also be pointed out, here, that hard-waters could contain very low levels of Mg but very high levels of calcium (Ca); hard-water by definition is made up of only Mg and Ca, Mg alone, or Ca alone. In Lille, France the hardness of the drinking -waters is one of the highest in the world, i.e. 661. However, it only contains on average about 15 mg/l of Mg [8, 67]. This helps to explain the inconsistency among various drinking –waters and the incidence of IHD and sudden cardiac death-rates in our opinion. Even though the bulk of Mg dietary intake may not come from drinking-waters, it could provide as much as 450 mg/l/day if all beverages imbibed/day is taken into consideration. In regions where water hardness is 400, the drinking water would provide about 75 mg of Mg/day in an average of two liters of water, or about 25% of the RDA. This could spell the difference

between an adequate amount of Mg/day versus inadequate, as the daily intakes of Mg/day in the U.S. and European population have fallen to 136 - 235 mg of Mg/day (between 30 - 65% of what is needed to sustain multiple bodily functions [28,34,65].

Clinical evidence linking hypomagnesemia to heart diseases

There is now an overwhelming amount of clinical evidence to show that hypomagnesemia is, indeed, linked to heart diseases. Patients on diuretics, those with digitalis toxicity, alcoholics, those taking proton-pump inhibitors, patients on chemotherapeutic drugs, and cancer patients subjected to x-irradiation all have a high degree of hypomagnesemia, IHD, AMIs, and sudden-cardiac death, many of whom when treated with Mg supplements live longer and have better qualities of life [28,64,69]. In addition, it has been clear for some time that various methods commonly used in food preparation often cause tremendous loss of Mg contents [8,28,65].

We, therefore, must conclude that dietary intake of Mg, food preparation, and various drugs are clearly masking the role of Mg deficiency in Prinzmetal angina, IHD, AMIs, and SCD. Ionized hypomagnesemia should clearly be looked for in all cardiovascular disease states and SCD.

Mechanisms involved in Mg-deficiency-induced vasospasm

Ever since two of us first discovered that low Mg^{2+} environments caused vasospasm of arterial and arteriolar blood vessels, more than 50 years ago [1-6], we have been interested in what mechanism(s) is responsible for the important, powerful contractions of the arteries and arterioles. At first, we found evidence that low Mg^{2+} resulted in opening membrane channels allowing free calcium ions to flow into the vascular smooth muscle cells (both from the extracellular compartment and membrane -bound stores), as well as cause a release of Ca^{2+} from intracellular stores [1-6]. However, on further and deeper investigation, we found a great deal of evidence that several signaling pathways, besides Ca^{2+}mobilization, were being activated, as well, by the low Mg^{2+} [70-85]. An array of numerous cellular signaling pathways clearly are now known to be responsible for the arterial vasospasms seen in patients with low Mg levels such as the activation of several protein kinase C isozymes [70,90], activation of phosphoinositol-3-kinases [70,91,92], activation of mitogen-activated protein kinases [91,92], activation of membrane tyrosine kinases [91,92], activation of proto-oncogenes (i.e., c-jun, c-fos) [73,84], inhibition of nitric oxide pathways [34,75,76], inhibition of release of cytokines and chemokines [32,34, 74,83,84,88,90], inhibition of formation of reactive oxygen species (ROS) and nitrogen oxygen species (RNS) [34,72,73,81,82,83,87,89,93], regulation of membrane, transmembrane and intracellular Mg^{2+}/Ca^{2+}ratio [19,21,22,23,26,34,73,94-99], inhibition of homocysteine formation and release [100] and formation of nuclear -factor- kB [70,72-74].

Very recent studies, from our laboratories, indicate that low Mg^{2+} environments induce formation of several sphingolipids (i.e., ceramides, sphingosine, sphingosine-1-phosphate) [34,69,70,74,78-85,90] and induce the formation and release of platelet-activating factor (PAF) [69,77,83,84-86]. If each of these cellular signaling pathways is inhibited, with specific molecular antagonists, the vasospasms are either attenuated or inhibited [84]. Whether some of these molecular antagonists should be given to Prinzmetal, IHD, or AMI human subjects becomes an interesting question which remains to be investigated.

Magnesium deficiency induces different forms of programmed cell death in cardiovascular tissues and cells

In addition to this latter important question, it should be noted, here, that we have found that experimental short-term Mg deficiency in animals causes three different forms of programmed cell death in cardiac atrial, ventricular, and arterial smooth muscle cells, namely apoptosis, necroptosis, and ferroptosis [87-89]. Such findings, if extended to human subjects, could be early biomarkers for future Prinzmetal attacks, early signs of IHD, and/or early signs of an AMI. We believe it will be quite important to investigate these potential scenarios.

The need for adequate daily intake of bioavailable Mg

Last, but not least, our data bolster the idea, we have espoused previously, that daily intake of Mg (from tap waters, well waters, bottled waters, beverages using tap/spring/well waters, or desalinated waters) for ingestion by humans should contain at least 25 - 40 mg Mg^{2+}/l [34,70,74,79-81,84-86]. The latter amount of Mg in our diets should go a long way towards the prevention of Prinzmetal angina, IHD,

AMIs, and SCD and ameliorate the aging process. In 2009, The World Health Organization recommended our guidelines of 25 - 40 mg Mg^{2+}/day to be included in drinking waters for human consumption [101].

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Volume 10 Issue 7 July 2019