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Editorial Open Access

Regulated RIPK3 Necroptosis is Produced in Cardiovascular Tissues and Cells in Dietary Magnesium Deficiency: Roles of Cytokines and Their Potential Importance in Inflammation and Atherogenesis

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Editorial

An earlier report from our research group, suggested a progressive dietary and/or a metabolite-induced loss of magnesium (Mg) during early developmental stages of life, particularly in coronary arteries could lead to coronary arterial spasm (CAS), ischemic heart disease (IHD), and sudden cardiac death (SCD) [1]. After our first report, a number of clinical studies have been reported, in support of our hypothesis, at least in adults [2-7]. Autopsies driven results from children who died due to accidental causes have been reported to which show early signs of atherogenesis (i.e., fatty streaks on the walls of the aorta and carotid arteries in young children as early as six years of age) [8]. Intriguingly, atherosclerosis is the prime cause of premature death in developing countries and even in United States, which further has been assumed to play a major role in the etiology of hypertension and strokes.

Irregularities in daily-diets are known to induce inflammatory lesions, which are believed to mediate the initiation process of atherogenesis. Further, the same diet disturbances have been reported to promote lipid deposition and accelerate the growth and transformation of the smooth muscle cells in the vascular walls [9-14]. Lack of dietary Mg accumulation has been experimentally demonstrated to cause hypertension [11-13], atherogenesis [11,15-20], and strokes [11,19,21-23]. On the other hand, hypermagnesemic diets have been reported to ameliorate hypertension, atherogenesis, stroke, and normalize the levels of certain inflammatory responses [11-15,19-32]. As per Western diet concerns, subnormal dietary intake of Mg is reported among the majority of the American population and the Mg shortfall level ranges from between 65 to 275 mg of Mg/d in different demographic regimes [11,14,24,26,33-36]. In recent years, the statistical data of USA NHANES indicates that, near about 65% of the American population is suffering from Mg deficiency [37]. Moreover, several epidemiologic studies from North America and Europe have shown that, both children and adults were low in the Mg content, while they were consuming Western-type diets and surprisingly a large portion of the low Mg individuals were in the gestation period (<30-50% of the RDA for these populations) [11,37-42].

Improvisation in the specific Mg^{2+}-ion selective electrodes, by our research group demonstrated for the first time that, patients suffering from hypertension, IHD, cardiac failure, renal-induced vascular diseases, diabetic vascular disease, and strokes as well as atherogenesis exhibit significant reductions in serum/plasma/whole blood levels of ionized, but not necessarily total, blood levels of Mg [11,18,19,22-24,41-62]. Even in rabbit and rat model systems our group has shown that, dietary deficiencies of Mg results in vascular remodelling (i.e., arteriolar wall hypertrophy and alterations in the matrices of the vascular walls), which was concomitant with atherogenesis, high blood pressure, and microvascular vasospasm [11-13,16,18,19,22,24,34,42,57-61]. Similar study outcomes also have been reported by others supporting the contention of our findings [17,20,27,28,62].

During the process of atherosclerosis, it has been shown that, the lipid-rich plaques on the blood vessel intimas are complexed with macrophages, lipids, T lymphocytes, and cholesterol crystals [63]. Large necrotic cores are the major characteristic feature of such lesions, which strengthen the plaques and make it rigid [64]. In our studies, we have recapitulated the phenomenology of atherosclerotic characteristic lesions in rabbits with dietary low Mg intake (with increased cholesterol intake) ([16,65] unpublished findings). Though, the underlying molecular mechanism behind the initiation of such inflammatory fatty lesions (with transformed vascular smooth muscle cells) is still not eloquently understood. Employing transmission electron microscopy (TEM), in our Mg-deficient rabbit experimentation suggested to us that, both the vascular smooth muscle cells and macrophages of the lipid-laden arterial vessels exhibited necrosis and apoptosis [16,65,66, unpublished findings of Stempak, BT Altura, M Brust and BM Altura]. Further, investigation using TEM on cardiac and arterial muscle cells of Mg-deficient rats also showed clear signs of necrosis as well as apoptosis [66-78; N Shah, BT Altura and BM Altura, unpublished findings]. Experimentation with high-power TEM revealed that, these Mg-deficient muscle cells exhibited what is now termed "necroptosis".

Necroptosis is a specific type of cell death, which morphologically is characterized by increases in cell volume and swelling of organelles (e.g., of mitochondria, Golgi, ER, etc). As a consequence, rupture of plasma membranes was evident from our studies, which ultimately results into significant losses of intracellular contents [67-69]. Moreover, similar experimentation in a rodent model system showed very similar characteristics in arterial and cardiac muscles, under high power TEM. With the help of progressive research and studies now it is

clear that, "necroptosis" occurs in a very controlled and regulated fashion [67-69] and requires the involvement of two serine/threonine kinase, receptor-interacting proteins namely, RIPK1 and RIPK3 [67-71]. It has been shown that, release of the cytokine TNF-alpha (TNF-α) initiates the activation of RIPK1 and RIPK3 [70,71]. Though, several lines of evidence have been reported that, RIPK1 and RIPK3 can be regulated by the activation and release of other cytokines (e.g., IL-1beta, Interferon-gamma) also [68-71].

The RIPK1 and RIPK3 cell-signaling pathway has recently been shown to be associated in the formation of inflammasomes in many types of cells and tissues. Our studies have clearly shown that, rat cardiac and vascular smooth muscle cells exposed to short-term Mg deficiency, exhibit an early and profound elevation in cellular and plasma lelels of TNF-alpha (i.e., 5-10 fold), IL-beta and interferon-gamma as well [11,18,42,58-60,72-78]. Interestingly, our experimentation with necrostatin-1, an inhibitor of RIPK1 and RIPK3 activation, reduces activation and formation of NF-kB in Mg-deficient peripheral and cerebral vascular smooth muscle cells [78]. Earlier reports indicate that, NF-kB inhibition is known to reduce necroptosis and formation of inflammasomes [68-71]. It is notable in this regard that, Karunkaran et al. state, i.e., "necroptic cell death is activated in human advanced atherosclerotic plaques" [79], fits in well with our findings. Their studies have shown that, macrophages residing within the plaques were increased in RIPK3 concentration. Hence, there is a likely possibility that, a major pathway in Mg-deficiency-induced inflammation and atherogenesis warrants the activation of RIPK1 and RIPK3. In support of the above contention, our research group has experimentally shown that there is a 5-8 fold upregulation of RIPK3 in cardiac and vascular muscle cells obtained from rats exposed to short-term Mg-deficiency [78].

Taken together, our on-going findings provide new potential insights into the underestimated role of Mg deficiency in the USA and Western World, which results into atherogenesis, inflammations and presents high risks for coronary artery disease, IHD, and SCD.

For the last 25-30 years, our research group has been investigating the efficacy of Mg-supplemented or naturally-occurring spring waters and has suggested their role to prevent the disease risks due to dietary- and/or metabolically-induced magnesium deficiency [11,41,42,57-61,65,72-79-83]. Our results, also encourages the idea that, water intake (e.g., from tap waters, well waters, bottled waters, beverages using tap/well/spring waters, or desalinated waters) should contain at least 25-40 mg/liter/day of Mg^{2+} [58-60,76,77,81]. In this context, our group has performed several conclusive experiments and highlighted most of the detrimental pathophysiological implications of Mg deficiency, which includes decreased cardiac output, decreased myocardial contractility, decreased coronary blood flows, mitochondrial release of cytochrome C, lipid peroxidation of cardiac and vascular muscle membranes, increased cellular levels of NO and p53, release of cytokines and chemokines, increased cellular entry of calcium ions and overload, increases in membrane permeability, myocardial acidification, loss of cellular ATP, DNA damage, shortening of telomeres, apoptosis, and necroptosis [11,41,42,57-61,72-79-83]. Our results have shown that, the said anomalies can be either prevented or ameliorated with the administration of adequate Mg^{2+} mixed with drinking water.

The outcome of our studies could influence the vast long-term clinical trials in the patients administered with adequate amounts Mg^{2+}-supplemented waters (i.e., 25-40 mg/liter/day), which could further validate our hypothesis and justify the need for Mg^{2+}-supplements.

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