Why is there an Association between Retinal Vein Occlusion, Vision Loss, Myocardial Infarction, Stroke and Mortality: Potential Roles of Hypomagnesaemia, Release of Sphingolipids, and Platelet-Activating Factor

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Abstract

Although numerous hypotheses (and potential risk factors), have been offered to explain the origins and potential mechanism(s) for central retinal vein occlusion (RVO) in patients of diverse ages, there is no agreement. Recently, considerable epidemiological evidence has been brought forth which indicates a strong association between RVO, myocardial infarctions, heart failure, and stroke. Magnesium (Mg) deficiency (mgD) has long-been associated with glaucoma and diabetic retinopathy. Over the past three decades, our laboratories have found strong associations of mgD linked to morbidity/ mortality in cardiovascular diseases such as myocardial infarctions, cardiac failure, atherogenesis, and strokes, both experimentally and clinically. More recently, we have reported direct links of mgD in these disease syndromes with generation and release of ceramides and platelet-activating factor (PAF). In this report, we present a novel hypothesis for a probable underlying mgD and release of ceramides and PAF as causal factors in development and progression of RVO. We believe this hypothesis could prove useful in the diagnosis and treatment of RVO

Keywords: Glaucoma; Diabetic retinopathy; Ceramides; PAF; Microcirculation; Eye diseases;

Introduction

A number of epidemiologic studies from around the world suggest a growing relationship between retinal vein occlusion (RVO), myocardial infarction, and mortality which is unexplained [for recent review, see 1]. Depending upon geographic region, age, and race the incidence varies between 2.8 per 1000(white Caucasians) and 6.9 per 1000 (Hispanics) with blacks in between (i.e., 3.9 per 1000) [see 2, for recent review]. Gender does not

appear to be a factor. However, the incidence of RVO clearly is dependent upon age with prevalence ranging from 0.3(40-49 years old) to 5.6 (80-100 years) [2]. Why there are these differences with race and age is, again, not known.

Although the pathogenesis of RVO remains to be nebulous, it has been hypothesized that its origin is probably related to hemodynamic changes (e.g., venous stasis), degenerative changes of the vascular walls, and blood hyper coagulability [3,4,5]. Risk factors for RVO include hypertension, arteriosclerosis, diabetes mellitus (DM), hyperlipidemia, stroke, blood viscosity, and thrombophilia [3]. Cigarette smoking also enhances the risk of RVO as do systemic inflammatory conditions, and glaucoma [3, 6]. In addition, preeclampsia in women also appears to pose an increased risk for development of RVO [7]. Browning in his compendium has stated that "the patho physiology of retinal vein occlusion consists of three components of Virchow's triad- abnormalities of the vessel wall, alterations in the blood (e.g., abnormalities of viscosity and coagulation), and alterations in blood flow" [8]. Is there a common factor(s) underlying all of these diverse risk factors?

Over the past 35 years, a considerable body of evidence has been brought forth which clearly indicates that all of the above risk factors for development of RVO including age, race, vascular changes, blood coagulability , arteriosclerosis, DM, stroke, systemic inflammatory conditions , hypertension, glaucoma, macular edema, vitreous hemorrhage, retinitis pigmentosa, and preeclampsia have been associated with deficient (mgD) states, both experimentally in animals and in human subjects [e.g., see 9- 19].

Magnesium Deficiency and Glaucoma

Glaucoma is an eye condition characterized by a chronic neuropathy causing vision loss. Elevated intraocular pressure (IOP) is known to be a major risk factor for development of glaucoma. But, this risk factor, in itself, does not appear to adequately explain the course of the disease [20]. Most of the individuals showing increased IOP do not develop glaucoma; interestingly approximately one-half of the patients with glaucomatous optic neuropathy show IOP's in the normal range [21]. Thus, it has become obvious that factors (unknown) ,other than elevated IOP, must perforce be important factors in development of glaucoma. Alterations in ocular blood flows and oxidative stresses have been suggested as causal factors [20,21]. Mg has been shown to increase ocular blood flow in patients with glaucoma and appears to have protective attributes against oxidative stresses and apoptosis [15]. Using rats, it has been demonstrated that dietary Mg deficiency can result in necrosis of the retinal pigment epithelium [10]. Multifocal necrosis and myelination disturbances have been noted in the optic nerve [16]. Moreover, using dietary Mg deficiency, in rats, it has been reported that the numbers of microvilli in the corneal epithelial and endothelial cells were decreased in number [17]. Interestingly, Mg taurate has been found to alter the progression of cataracts in some patients [22]. In addition, it has long been known that patients with diabetes (types 1 and 2), have often low serum total Mg levels [23,24,25]. We have shown that the physiologically, important ionized level of Mg^{2+} is clearly reduced in both blood and red blood cells in diabetes [24-28]. Our laboratories, almost 35 years ago, first demonstrated that low extracellular $Mg^{2=}$ levels result in decreased cerebral blood flows. Subsequently, we found that low $[Mg^{2+}]_0$ resulted in reductions in cellular free Mg and vasospasm of cerebral blood vessels as well as oxidative stress, DNA damage, induction of nuclear factor-KB, induction of proto-oncogenes c-fos and c-jun, down regulation of telomerase activity, and apoptosis of cerebral vascular smooth muscles in primary cultures [30-41]. Working with aged glaucoma patients (65-82 years old), and ^{31}P-NMR spectroscopy and ion-selective electrodes, we found the serum ionized Mg level as well as the red blood cell Mg^{2+} level to be significantly reduced (e.g., serum : 0.55 vs. 0.66 mm in aged-matched controls; p<0.001) [Resnick, Altura, Altura, 1995, unpublished data] . The significance of our findings are discussed in detail, below, in the remaining sections of this report.

Magnesium, Mg Deficiency, Diet, Vasospasm, and Cardiovascular Pathobiology

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 [33,35,39,42-46]. Major risk factors in development of RVO are atherosclerotic changes , endothelial damage ,hypertension, and thrombus formation (as stated above) as well as increased growth of microscopic blood vessels in the retina; all of these can be inhibited/ameliorated by adequate Mg levels [15,22,24-28,33,34, 40-47]. Several epidemiologic studies in North America and Europe have shown that people consuming Western-type diets are low in Mg content(i.e., 30-65% of the RDA for Mg [40,44-46, 48-50]); most such diets in the U.S.A. show that 60-80% of Americans are consuming185-235 mg/day of Mg [40,44-46,48-50]. The elderly(who demonstrate the highest risk for RVO) exhibit the lowest levels of magnesium intake worldwide. In 1900, Americans were consuming about 450-550 mg/day [35,40]. Low Mg content of drinking water, found in areas of soft-water and Mg-poor soil, is associated with high incidences of atherosclerosis, hypertension, thrombosis, ischemic heart disease (IHD), coronary vasospasm, and sudden cardiac death (SCD) [33,40,51-55]. Both animal and human studies have shown an inverse relationship between dietary intake of Mg and atherosclerosis [33,35,40, 56,57]. 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 living in hard-water areas [33,35,40,43-45,51-55]. 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 [31,33,35,40,58-67]. We also showed that Mg behaves as a natural statin in that it can lower both cholesterol and triglyceride levels [43] as well as act as a powerful vasodilator in the microcirculation [67-70] , on coronary arteries [33,65,66,71-79], as well as on cerebral blood vessels[29,32-34], and as a cardiac muscle relaxant [33-35,65,75-77]. Hypermagnesemic diets have been shown to ameliorate hypertension, diabetes mellitus, atherosclerosis, thrombosis, hypercoagulability, strokes, myocardial infarctions, and preeclampsia-eclampsia; all conditions associated with RVO [28,33-35,40,42-46,56,57,65,80-88]. Using sensitive and newly-designed, specific Mg^{2+}-ion selective electrodes, our laboratories showed that patients with hypertension, IHD, cardiac failure, strokes, diabetes mellitus types I and 2 ,atherosclerosis, myocardial infarctions, aging, and preeclampsia-eclampsia, and women with diverse cardiovascular disturbances exhibit significant reductions in serum/plasma/ whole blood levels of ionized but not necessarily total, blood levels of Mg[24-28,34-37,40,89-107]. In addition, using ^{31}P-NMR spectroscopy, we demonstrated that a number of patients with these cardiovascular-disease syndromes exhibit lowered Mg^{2+} levels in red blood cells [25-27,106,107]. Our group has also shown that dietary deficiencies of Mg in rats and rabbits causes vascular remodeling (i.e., arteriolar wall hypertrophy, increased capillary growth, and alterations in the matrices of the vascular walls) concomitant with atherogenesis, elevated blood pressure and micro vascular vasospasm [33,35,40,43,47,108-111]; these microvessel changes being in many respects similar to what happens in the retinas of RVO -victims.

Approximately 45 years ago, two of us reported that declining levels of extracellular Mg^{2+} ($[Mg^{2+}]_0$) in isolated arteries and arterioles resulted in concentration-dependent constriction and vasospasm [58,59] . These phenomena were noted, subsequently, in vitro and in vivo, in cerebral, coronary, umbilical -placental, and splanchnic blood vessels [29-37,39,40,60-66,70-74, 76,77,108-112]. These low $[Mg^{2+}]_0$-induced vasospasms could only be attenuated or inhibited with elevated concentrations of Mg^{2+}. In addition, we noted that small venous vessel (i.e., 60-100um o.d.) vasospasm, induced by low $[Mg^{2+}]_0$, would often result in rupture

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of post capillary venules (i.e., 35-55 um o.d.) with extravasations of blood and formed elements into the surrounding brain tissues ,as observed by direct in -situ TV microscopic studies on the intact cerebral microcirculation in the living brains of rats [32-35,47,87,110]; these inflammatory responses are ,thus, very similar to what is observed in patients with RVO. Ever since our early findings on the intact brain and coronary tree were published [58,59], a number of clinical studies on the hearts of diseased patients have been published which support our hypothesis [113-116]. Using intact rats subjected to Mg deficient diets (MDD) , and employing ^{31}P-nuclear magnetic resonance spectroscopy (^{31}P-NMR) , and optical-reflectance spectroscopy [34,35,40,41,77,78,117], we have noted that low levels of dietary Mg intake result in reductions in cerebral blood flows, reduction in cerebral and VSM $[Mg^{2+}]_i$, reduced levels of ATP, increased cellular levels of inorganic phosphate, reduced cellular levels of intracellular pH, generation of powerful reactive oxygen and nitrogen species, $[Ca^{2+}]_i$ overload, and reduction in mitochondrial levels of cytochrome oxidase , thus resulting in hypoxic states . Since the retinal circulation is, physiologically, in many ways, similar to the cerebral circulation [8] , we believe that the characteristic changes seen in the retinas of RVO patients[for review, see 8] may perforce be due , in part, to a Mg deficiency. However, since 1997 we have found dramatic evidence that MDD results in inflammatory-like conditions, activation of multiple enzymatic pathways which result in formation of sphingolipids (e.g., ceramide, sphingosine, spingosine-1-phosphate,etc) , and synthesis and release of platelet-activating factor(PAF) [41,87,88,118-128].

Low Mg^{2+}, Increased Adhesiveness to Venular Endothelial Walls, Increased Post capillary Permeability and Vasoconstriction in the Microcirculation: Relation to Inflammatory Reactions

Inflammation usually is defined as a response of microcirculatory blood vessels and the tissues they perfuse to infections and damaged tissues which bring cells and host-defense factors /molecules directly from the circulation to all the diverse sites where they are required, in order to eliminate/ degrade all the offending agents [129,130]. The mediators of the innate -defense mechanisms include white blood cells, phagocytic leukocytes, monocytes, macrophages, antibodies, and cytokines, chemokines, and complement proteins. The inflammatory process brings these cells and molecules to the damaged or necrotic tissues. Such events are observed in patients with RVO [for review, see 8]. During the normal inflammatory process, leukocytes, macrophages, and monocytes migrate across the venous capillary walls through gaps between the endothelial cells, due to increases in permeability and move to the site(s) of injury via chemotaxis [129,130] . The normal mediators for these processes to take place are: adhesion molecules; and cytokines and chemokines [129,130]. Interestingly, we have found in diverse microcirculatory beds of rats and mice, fed low dietary Mg intake, increased adhesiveness of leukocytes, monocytes, and platelets to the venular walls coupled with vasoconstriction/ spasm and increased postcapillary venular permeability [127,

unpublished findings]; obviously, these phenomena are clear signs of inflammatory responses and have been observed in retinas of patients with RVO [8]. Toll-like receptor-mediated (TLRM) pathways appear to be activated in the MDD animals [15, 22]. We have found that these TLRM pathways are activated through nuclear-factor kappa B (NF-KB) in MDD and seem to take place early in the Mg deficient tissues [unpublished findings]. Whether similar phenomena take place in patients' retinas presenting with RVO remains to be seen.

Mg^{2+}Regulates Sphingolipid Pathways in Cerebral and Coronary Vascular Smooth Muscle Cells: Potential Impact in Patients with RVO

Recent studies from our laboratories, over the past two decades, indicate that Mg^{2+} ions can modulate sphingolipid pathways in a variety of VSM and cardiac cell types, including coronary and cerebral VSM [40,41,87,118-126]. One of these byproducts is ceramide. Ceramides are sphingolipids known to be released as a consequence of sphingomyelinases (smases) acting on sphingomyelin (SM), a component of all cell membranes(external and internal), or as a consequence of activation of serine palmitoyl transferase 1 and 2(SPT 1 and SPPT 2)(a synthetic pathway) [131,132], activation of ceramide synthase, or a "salvage pathway" [126] . Ceramides are now thought to play important roles in fundamental processes such as inflammation, angiogenesis, atherogenesis, membrane-receptor functions, cell proliferation, microcirculatory blood flows, cell adhesion, immunogenic responses, and apoptosis, among others [for recent review, see 133] . Note that all of these functions/ characteristics are not only found in MDD animals, but also in patients with RVO. It is of considerable interest to note, here, that, experimentally, myocardial infarctions have been shown to be associated with rising levels of ceramides [134,135]. In human subjects, it has been reported that stable angina pectoris, unstable angina pectoris, and acute myocardial infarction are also associated with rising levels of ceramides [136,137]. In some of these patients, a clear elevation in smases was observed [136]. Although such studies have not, to our knowledge, been undertaken in patients presenting with RVO, we suspect, when looked for, this will be the case, along with Mg^{2+} deficiency.

Mg^{2+}-Deficient Environments Lead to Formation of PAF: Potential Significance to RVO

PAF is known to play major roles in both inflammatory reactions and atherogenesis [138-140]. A variety of the circulating blood-formed elements (e.g., polymorph nuclear leukocytes, platelets, basophils, and macrophages) as well as endothelial cells can elaborate PAF [139,140]. We have, very recently, demonstrated that cerebral, aortic and coronary VSM cells can also elaborate and release PAF [87,127]. There are some reports that both PAF and ceramides may result in transformation of VSM cells from one phenotype to another, as is typical in the atherosclerotic process [139,140]. In addition, like we have observed in MDD, PAF produces vasoconstriction of blood vessels in a variety of VSM cell types [for recent review, see 127] , as do several of the ceramides [141, unpublished findings

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]. A number of investigators , employing intravital microscopy techniques, similar to those used by our laboratories [142-145], have demonstrated that PAF increased the number of white blood cells in the microvessels concomitant with intense vasoconstriction-spasms with increasing concentrations of the putative lipid mediator (i.e., PAF), less leukocyte rolling on the endothelial cell walls, and increased adherence of the leukocytes to the endothelial surfaces with increases in venular-capillary permeability . Using open and closed chambers implanted in rodent cerebral cortex and skeletal muscles, as mentioned above, we have observed similar phenomena [87,127, unpublished finings]. Furthermore, we have reported that a variety of ceramides produce similar microcirculatory actions in rodent cerebral, cutaneous and skeletal microvascular tissues, including increased permeability of the post capillary walls, the major sites of inflammatory reactions [141, unpublished findings]. Collectively, these in-vivo microcirculatory findings strongly support our hypothesis that both PAF and ceramides induce similar, true inflammatory responses in diverse vascular beds in diverse mammalian species. Added to this are some very recent findings of Moschos et al [146] on diabetic patients with retinopathy who demonstrated increased serum levels of platelet-activating factor acetylhydrolase, the enzyme that produces PAF; the greater the degree of diabetic retinopathy, the more advanced was the disease[146]. We believe similar findings will be found in RVO patients when looked for.

Future Considerations, Challenges, and New Therapeutic Approaches to RVO

Although the exact underlying cause(s) of RVO in patients remains to be determined, a number of magnesium-deficient animal models (e.g., with glaucoma; diabetes mellitus retinopathy) have been utilized to gain insights into possible causes of retinopathy and AMD . Potential use of knock-out and knock-down mice models of these diseases found in Mg-deficient animals could be used to determine changes in the genomes(due to genotoxic effects)[47]. Patients with RVO should be examined for lowered blood and red blood cell levels of ionized Mg using newly-designed Mg^{2+}-ion selective electrodes and ^{31P}NMR spectroscopy. From the above evidence and discussion, it would be judicious to examine RVO-patients for increased levels of ceramides and PAF.

Clinical studies should be undertaken to determine any correlations between the course of RVO development and levels of ionized Mg, ceramides, and PAF. Moreover if such correlations are found, it would probably be prudent to supplement RVO patients with Mg. In addition, it probably would be prudent to determine in double-blind trials whether use of inhibitors of ceramide and PAF generation and release change/benefit the course of the disease along with administration of Mg. Only time will tell whether these animal studies , human studies and clinical trials will prove to validate our hypothesis.

Since we have found in both rats and rabbits, fed low Mg diets, that increased levels of both ceramides and PAF are found , in situ, in all chambers of the heart, and in cerebral, coronary, and

peripheral blood vessels, and these cardiac as well as blood vessel dysfunctions were associated with decreased serum an tissue levels of Mg^{2+}, increased plaques, elevated serum cholesterol, elevated triglycerides, elevated ceramides, and increased generation of PAF [e.g., see 87,127], we believe it is highly unlikely that these in-vivo manifestations are merely epiphenomena. It is more than likely that these alterations underlie some of the causes of RVO and could serve as underpinnings for more precise therapy of RVO in the near future.

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