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## **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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# 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 consuming 185-235 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 microvascular 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., 60-100  $\mu$ m o.d.) vasospasm, induced by low  $[Mg^{2+}]_0$ , would often result in rupture

of post capillary venules (i.e., 35-55  $\mu\text{m}$  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  $^{31}\text{P}$ -nuclear magnetic resonance spectroscopy ( $^{31}\text{P}$ -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  $[\text{Mg}^{2+}]_i$ , reduced levels of ATP, increased cellular levels of inorganic phosphate, reduced cellular levels of intracellular pH, generation of powerful reactive oxygen and nitrogen species,  $[\text{Ca}^{2+}]_i$  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, sphingosine-1-phosphate, etc), and synthesis and release of platelet-activating factor (PAF) [41,87,88,118-128].

### **Low $\text{Mg}^{2+}$ , 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.

### **$\text{Mg}^{2+}$ 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  $\text{Mg}^{2+}$  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 SPT 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  $\text{Mg}^{2+}$  deficiency.

### **$\text{Mg}^{2+}$ -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]



[]. 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 findings]. 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<sup>2+</sup>-ion selective electrodes and <sup>31</sup>P-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 and tissue levels of Mg<sup>2+</sup>, 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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### **References**

1. Woo SCY, Lip GYH, Lip PL. Associations of retinal artery occlusion and retinal vein occlusion to mortality, stroke, and myocardial infarction: a systematic review. *2016;30(8):1031-1038*. doi: 10.1038/eye.2016.111.
2. Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P et al. The prevalence of retinal vein occlusion: Pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmol.2010;117(2):313-319*. doi: 10.1016/j.ophtha.2009.07.017.
3. Kolar P. Risk factors for central and branch retinal vein occlusion: A meta-analysis of published clinical data. *J Ophthalmol.2014;2014(2014)*: doi: org/10.1155/2014/724780.
4. Yau JWY, Lee P, Wong TY, Best J, Jenkins A. Retinal vein occlusion: an approach to diagnosis, systemic risk factors and management *Int Med J.2008;38(12):904-910*. doi: 10.1111/j.1445-5994.2008.01720.x.
5. Mrad M, Fekih-Mrissa N, Wathek C, Rannen R, Gabsi S, Gritli N. Thrombophilic risk factors in different types of retinal vein occlusion in Tunisian patients. *J Stroke Cerebrovasc Dis.2014;23(6):1592-1598*. doi: 10.1016/j.jstrokecerebrovasdis.2013.12.048.
6. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc.2000;98:133-141*.
7. Rahman I, Saleemi G, Semple D, Stanga P. Pre-eclampsia resulting in central vein occlusion. *2006;20(8):951-955*. DOI:10.1038/sj.eye.6702065
8. Browning D. *Retinal Vein Occlusions*. Springer, London.2012.
9. Goto Y, Furvuta A, Tobimatsu S. Magnesium deficiency differentially affects the retina and visual cortex in intact rats. *J Nutr.2001;131(9):2378-2381*.
10. Gong H, Amemiya T, Takaya K. Retinal changes in magnesium-deficient rats. *Exp Eye Res 72: 23-32*.
11. Liang SY, Lee LR. Retinitis pigmentosa associated with hypomagnesaemia. *Clin Exp Ophthalmol.2010; 38(6):645-647*. DOI: 10.1111/j.1442-9071.2010.02314.x.
12. Gorgels TGMF, Waarsing JH, de Wolf A, ten Brink JB, Loves WJP,

- Bergen AA. Dietary magnesium, but not calcium, prevents vascular calcification in a mouse model for pseudoxanthoma elasticum. *J Mol Med*.2010;88(5):467-475. doi: 10.1007/s00109-010-0596-3.
13. Rahman I, Saleemi G, Semple D, Stanga P. Preeclampsia resulting in central retinal vein occlusion. *2006;20:955-957*. doi:10.1038/sj.eye.6702065.
14. McCoy MA. Hypomagnesemia and new data on vitreous humor magnesium concentration as a post-mortem marker in ruminants. *Magnes Res*.2004;17(2):137-145.
15. Ekici F, Korkmaz S, Karaca EE, Sul S, Tufan HA, et al. The role of magnesium in the pathogenesis and treatment of glaucoma. *Int Scholarly Res Not*.2014;2014(2014): doi.org/10.1155/2014/745439.
16. Gong Y, Takami Y, Amemiya T. Ultrastructure of the optic nerve in magnesium -deficient rats. *Ophthalmic Res* 35(2): 84-92.
17. Gong Y, Takami Y, Kitaoka T, Amemiya T. Corneal changes in magnesium-deficient rats. *Cornea*.2003;22(5):448-456.
18. Hatwai A, Gujral AS, Bhatia rps, Agarwal P, Bajpai HS . Association of hypomagnesemia with diabetic retinopathy. *Acta Ophthalmologica*.1989;67(6):714-716. DOI: 10.1111/j.1755-3768.1989.tb04407.x.
19. Kundu D, Osta M, Mandal T, Bandyopadhyay U, Ray D, Divyendu Gautam. Serum magnesium levels in patients with diabetic reinopathy. *J Nat Sci Biol Med*.2013;4(1):113-116. doi: 10.4103/0976-9668.107270.
20. Mozaffarieh M, Flammer J. New insights in the pathogenesis and treatment of normal tension glaucoma. *Current Opin Pharmacol*.2013;13(1): 43-49. doi: 10.1016/j.coph.2012.10.001.
21. Mozaffarieh M, Flammer J. Is there more to glaucoma treatment than lowering IOP? *Survey Opthamol*.2007; 52(suppl 2): S174-S179. doi. org/10.1016/j.survophthal.2007.08.013.
22. Agarwal R, Iezhitsa L, Agarwal P. Pathogenic role of magnesium deficiency in ophthalmic diseases. *Biometals*.2013; 27(1):5-18.
23. Altura BM, Halevy S, Turlapaty PDMV . Vascular smooth muscle in diabetes and its influence on the reactivity of blood vessels. *Adv Microcirculation*. 1979;8:118-150.
24. Altura BM, Altura BT. Role of magnesium in pathophysiological processes and the clinical utility of magnesium ion-selective electrodes. *Scand J Clin Lab Invest*.1996;224:211-234.
25. Altura BM, Altura BT. Importance of ionized magnesium measurements in physiology and medicine and the need for ion-selective electrodes. *J Clin Case Studies* 2016;1(2):1-4. doi. org/10.16966/2471-4925.111.
26. Resnick LM, Altura BT, Gupta RK, Alderman MH, Altura BM. Intracellular and extracellular magnesium depletion in type 2 diabetes (non-insulin-dependent) diabetes mellitus. *Diabetologia*.1993;36(8):767-770.
27. Bardicef M, Bardicef O, Sorokin Y, Altura BM, Altura BT, et al (1995) Extracellular and intracellular magnesium depletion in pregnancy and gestational diabetes. *Am J Obst Gynecol*.1995;172(3):1009-1013.
28. Djurhuus S, Henriksen E, Kligaard NA, Blaabjerg O, Thyron P, B M Altura et al . Effect of moderate improvement in metabolic control on magnesium and lipid concentrations in type 1 diabetes. *Diabetes Care*.1999;22(4):546-554. doi.org/10.2337/diacare.22.4.546.
29. Altura BT, Altura BM . Withdrawal of magnesium causes vasospasm while elevated magnesium produces relaxation of tone in cerebral arteries. *Neurosci Lett*. 1980;20(3):323-327.
30. Altura BM, Altura BT, Carella A, Turlapaty PDMV. Hypomagnesemia and vasoconstriction: Possible relationship to etiology of sudden death ischemic heart disease and hypertensive vascular disease. *Artery*. 1981;9(3):212-231.
31. Altura BM, Altura BT, Carella A, Turlapaty PDMV. Ca<sup>2+</sup> coupling in vascular smooth muscle: Mg<sup>2+</sup> and buffer effects on contractility and membrane Ca<sup>2+</sup> movements. *Canad J Physiol Pharmacology*.1982;60(4):459-482.
32. Altura BT, Altura BM (1982) The role of magnesium in etiology of strokes and cerebrovasospasm. *Magnes Exp Clin Res*.1982;18(5):277-291. DOI: 10.1111/j.1530-0277.1994.tb00082.x.
33. Altura BM, Altura BT. Magnesium and the cardiovascular system: Experimental and clinical aspects updated. *Metals in Biological Systems* .1990;26:359-416.
34. Altura BM, Altura BT. Role of magnesium in alcohol-induced hypertension and strokes as probed by in vivo television microscopy, digital image microscopy, 31P-NMR spectroscopy and a unique magnesium ion-selective electrode. *Alcohol Clin Exp Res*.1994;18(5):1057-1068.
35. Altura BM, Altura BT. Magnesium and cardiovascular biology: an important link between cardiovascular risk factors and atherogenesis. *Cell Mol Biol Res*.1995;41(5):347-359.
36. Altura BT, Memon ZI, Zhang A, Cracco RQ, Altura BM, Cracco RQ. Low levels of serum ionized magnesium found in patients early after stroke which results in rapid elevation in cytosolic free calcium and spasm in cerebral vascular smooth muscle cells. *Neurosci Lett*.1997;230(1):37-40.
37. Altura BM, Altura BT. Association of alcohol in brain injury, headaches, and stroke with brain tissue and serum levels of ionized magnesium : a review of recent findings and mechanisms of action. *Alcohol*.1999;19(2):119-130.
38. Altura BM, Gebrewold A, Zhang A, Altura BT (2003) Low extracellular magnesium ions induce lipid peroxidation and activation of nuclear factor-kappa B in canine cerebral vascular smooth muscle: possible relation to traumatic brain injury and strokes. *Neurosci Lett* 341: 189-192.
39. Altura BM, Kostellow AB, Zhang A, Li W, Morill GA, Gupta RK et al. Expression of the nuclear factor-kB and proto-oncogenes c-fos and c-jun are induced by low extracellular Mg<sup>2+</sup> in aortic and cerebral vascular smooth muscle cells: possible links to hypertension, atherogenesis , and stroke. *Am J Hypertens*.2003;16(9):701-707.
40. Altura BM, Altura BT. Magnesium: forgotten mineral in cardiovascular biology. *New Perspectives in Magnesium Research*. Springer, New York. 2007;239-260.
41. Shah NC, Shah GJ, Li Z, Jiang XC, Zhang A. Short-term magnesium deficiency downregulates telomerase , upregulates neutral sphingomyelinase and induces oxidative DNA damage in cardiovascular tissues and cells: relevance to atherogenesis, cardiovascular diseases and aging. *Int J Clin Exp Med*.2014;7(3):497-514.
42. Luthringer C, Rayssiguier Y, Gueux E, Berthelot A. Effect of moderate magnesium deficiency on serum lipids, blood pressure and cardiovascular reactivity in normotensive rats. *Br J Nutr*.1988;59(2):243-250.
43. Altura BT, Brust M, Bloom S, Barbour RL, Stempak J, B M Altura. Magnesium dietary intake modulates blood lipid levels and atherogenesis. *Proc Nat Acad Sci USA*.1990;87(5):1840-1844.
44. Seelig MS, Rosanoff A. *The Magnesium Factor*. The Penguin Group, New York.2003.
45. Dean C. *The Magnesium Miracle*. (3rd edn) . Ballantine Books, New

- York.
46. Long S, Romani AM (2014) Role of cellular magnesium in health and disease. *Austin J Nutr Food Sci* 18: 1051.
47. Altura BM, Shah NC, Shah GJ, Perez-Albela JL, Altura BT. Genotoxic effects of magnesium deficiency in the cardiovascular system and their relationships to cardiovascular diseases and atherogenesis. *J Cardiovasc Dis Diagnosis*. 2016. doi:10.4172/2329-9517.100051-008.
48. Ford ES, Mokdad AH. Dietary magnesium intake in a national sample of US adults. *J Nutr*.2003;133(9):2879-2882.
49. Mosfegh A, Goldman Abuja J, Rhodes D, La Comb R. What We Eat in America. NHANES 2005-2006: usual Nutrient Intakes from Food and Water Compared to 1997 Dietary Reference Intakes for Vitamin D, Calcium, Phosphorus, and Magnesium. U.S. Department of Agricultural Research.
50. NHANES 2009-2012. Dietary Reference Intakes for Vitamin D, Calcium, Phosphorus, and Magnesium. U.S. Department of Agricultural Service.
51. Marier JR, Neri LC. Quantifying the role of magnesium in the relationship between mortality/morbidity and water hardness. *Magnesium*.1985;4(2-3):53-59.
52. Leary LP. Content of magnesium in drinking water and deaths from ischaemic heart disease in White South Africans. *Magnesium*.1986;5(3-4):150-153.
53. Chipperfield B, Chipperfield JR. Relation of myocardial metal concentration to water hardness and death-rates from ischaemic heart disease. *Lancet*.1979;2(8145):709-712.
54. Marx A, Neutra RR. Magnesium in drinking water and ischaemic heart disease, *Epidemiol Rev*.1997;19(2):258-272.
55. Rubenowitz E, Molin I, Acelsson G, Rylander R . Magnesium in drinking water in relation to mortality and morbidity from acute myocardial infarction. *Epidemiology*.2000;11(4):416-421.
56. Ouchi Y, Tabata RE, Stegiopolos K, Sato, Hatori A, Orimo H. Effect of dietary magnesium on development of atherosclerosis in cholesterol-fed rabbits. *Arteriosclerosis*.1990;10(5):732-737.
57. King JL, Miller RJ, Blue JP,Jr, O'Brien WD, Jr, Erdman JW,Jr. Inadequate dietary magnesium intake increases atherosclerotic plaque development in rabbits. *Nutr Res*.2009;29(5):343-349. doi: 10.1016/j.nutres.2009.05.001.
58. Altura BM, Altura BT. Influence of magnesium on drug-induced contractions and ion content in rabbit aorta. *Am J Physiol*.1971;220(4):938-944.
59. Altura BM, Altura BT. Magnesium and contraction of arterial smooth muscle. *Microvasc Res*.1974;7(2):145-155.
60. Altura BM, Altura BT (1977) Extracellular magnesium and contraction of vascular smooth muscle. In : Casteels R, Godfraind T, Ruegg JC (eds) *Excitation-Contraction Coupling of Smooth Muscle*. North-Holland Publ Co, Amsterdam, pp. 137-144.
61. Altura BM, Altura BT (1981) General anesthetics and magnesium ions as calcium antagonists. In : *New Perspectives on Calcium Antagonists*. Am Physiol Soc 131-145.
62. Altura BM, Altura BT. Role of magnesium ions in contractility of blood vessels and skeletal muscles. *Magnesium Bulletin* 3: 102-114.
63. Altura BM, Altura BT. Magnesium modulates calcium entry and contractility in vascular smooth muscle. In: *The Mechanism of Gated Calcium Transport across Biological Membranes*. Ohinishi ST, Endo M, eds. Academic Press, New York.1981;137-144.
64. Altura BM, Altura BT, A Carella, P D Turlapaty . Ca<sup>2+</sup> coupling in vascular smooth muscle: Mg<sup>2+</sup> and buffer effects on contractility and membrane Ca<sup>2+</sup> movements. *Canad J Physiol Pharmacol*.1982;60(4):459-482.
65. Altura BT, Altura BM. Magnesium , electrolyte transport, and coronary vascular tone. *Drugs*1984;28(1):120-142.
66. Altura BM, Altura BT, Carella A, Gebrewold A, Murakawa T, Nishio A. Mg<sup>2+</sup>-Ca<sup>2+</sup> interaction in contractility of vascular smooth muscle: Mg<sup>2+</sup> versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. *Canad J Physiol Pharmacol*.1987;65(4):729-745.
67. Nagai I, Gebrewold A, Altura BT, Altura BM. Magnesium salts exert direct vasodilator effects on rat cremaster muscle microcirculation. *Arch Int Pharmacodyn Ther*.1988;294:194-214.
68. Nishio A, Gebrewold A, Altura BT, Altura BM. Comparative effects of magnesium salts on reactivity of arterioles and venules to constrictor agents. An in situ study on microcirculation. *J Pharmacol Exp Ther*.1988;246(3):859-865.
69. Nishio A, Gebrewold A, Altura BT, Altura BM . Comparative vasodilator effects of magnesium salts on rat mesenteric arterioles and venules. *Arch Int Pharmacodyn Ther*.1989;298:139-163.
70. Altura BM, Altura BT. Magnesium and vascular tone and reactivity. *Blood Vessels*.1978;15(1-3):5-16. DOI:10.1159/000158148.
71. Altura BM. Sudden-death ischemic heart disease and dietary magnesium intake: Is the target site coronary vascular smooth muscle? *Med Hypoth*.1979;5(8):843-848.
72. Turlapaty PDMV, Altura BM. Magnesium deficiency produces spasms of coronary arteries: relationship to etiology of sudden death ischemic heart disease. *Science*.1980;208(4440):198-200.
73. Altura BM, Turlapaty PDMV. Withdrawal of magnesium enhances coronary arterial spasms produced by vasoactive agents. *Bt J Pharmacol*.1982;77(4):649-659.
74. Altura BT, Altura BM (1981) Endothelium -dependent relaxation of coronary arteries requires magnesium ions. *Br J Pharmacol* 91: 449-451.
75. Friedman HS, Nguyen TN, Mokraoui AM, Barbour RL, Murakawa T, Altura BM. Effects of magnesium chloride on cardiovascular hemodynamics in the neurally intact dog. *J Pharmacol Exp Ther*.1987;243(1):126-130.
76. Wu F, Zou LY, Altura BT, Barbour RL, Altura BM. Low extracellular magnesium results in cardiac failure. *Magnes Trace Elem*.1992;10(5-6):409-419.
77. Altura BM, Barbour RL, Dowd TL, Wu F, Altura BT, Gupta RK. Low extracellular magnesium induces intracellular free Mg deficits, ischemia, depletion of high-energy phosphates and cardiac failure in intact working rat hearts: A <sup>31</sup>P-NMR study. *Biochim Biophys Acta*.1993;1182(3):328-332.
78. Altura BM, Gebrewold A, Altura BT, Brautbar N . Magnesium depletion impairs carbohydrate and lipid metabolism and cardiac bioenergetics and raises myocardial calcium content in vivo: relationship to etiology of cardiac diseases. *Biochem Mol Biol Int*.1996;40(6):1183-1190.
79. Zou LY, Altura BT, Wu F, Jellicks LA, Wittenberg BA, et al. (1997) Roles of Mg<sup>2+</sup> and Ca<sup>2+</sup> in beneficial vs. detrimental actions of alcohol on heart. *Advances in Magnesium Res*. Smetana, ed. John Libbey, London, 211-214.



80. Rayssiguier Y, Gueux E. Magnesium and lipids in cardiovascular disease. *J Am Coll Nutr.*1956;5(6):507-519.
81. Altura BM, Altura BT. New perspectives on the role of magnesium in pathophysiology of the cardiovascular system .I. Clinical Aspects. *Magnesium.*1958;4(5-6):226-244.
82. Altura BM. Ischemic heart disease and magnesium. *Magnesium.*1988;7(2):57-67.
83. Rasmussen HS. Justification for magnesium therapy in acute ischemic heart disease. Clinical and experimental studies. *Danish Med Bull.*1993;40(1):84-89.
84. Orlov MW, Brodsky MA, Douban S. A review of magnesium, acute myocardial infarction and arrhythmia. *J Am Coll Nutr.*1994;13(2):127-132.
85. Simko F. Pathophysiological aspects of the protective effect of magnesium in myocardial infarction (review). *Acta Med Hung.*1994;50(1-2):55-64.
86. Satur CM. Magnesium and cardiac surgery. *Ann Roy Coll Surg Engl.*1997;79(5):349-354.
87. Altura BM, Gebrewold A, Shah NC, Shah GJ, Altura BT. Potential roles of magnesium deficiency in inflammation and atherogenesis: Importance and cross-talk of platelet-activating factor and ceramide. *J Clin Exp Cardiol.*2016;7(3): 1000427.
88. Altura BM, Shah NC, Shah GJ, Altura BT. Why is alcohol-induced atrial arrhythmias and sudden cardiac death difficult to prevent and treat: Potential roles of unrecognized ionized hypomagnesemia and release of ceramides and platelet-activating factor. *Cardiovasc Pathol: Open Access.*2016;1(3):1000112.
89. Altura BT, Altura BM. Measurement of ionized magnesium in whole blood, plasma and serum with a new ion-selective electrode in healthy and diseased human subjects. *Magnes Trace Elem.*1992;10(2-4):90-98.
90. Altura BT, Shirey TL, Young CC, Hiti J, Dell'Orfano K, Handwerker SM et al. A new method for the rapid determination of ionized Mg<sup>2+</sup> in whole blood , serum and plasma. *Methods Find Exp Clin Pharmacol.*1992;14(4):297-304.
91. Handwerker SM, Altura BT, Royo B, Altura BM. Ionized magnesium in umbilical cord serum of pregnant women with transient hypertension. *Am J Hypertens.*1993;6(6):542-545.
92. Markell MS, Altura BT, Barbour RL, Altura BM. Ionized and total magnesium levels in cyclosporin-treated renal transplant recipients: relationship with cholesterol and cyclosporin levels . *Clin Sci.*1993;85(3):315-318.
93. Markell MS, Altura BT, Sarn Y, Delano BG, Hudo O, Friedman EA et al. Deficiency of serum ionized magnesium receiving hemodialysis or peritoneal dialysis. *ASAIO J.*1993;39(3):M801-M804.
94. Altura BM, Lewenstam A, eds (1994) Unique Magnesium -Sensitive Ion Selective Electrodes. *Scand J Clin Lab Invest* 56: 211-234.
95. Muneyyirci -Delale O, Nacharaju VI, Jalou S, Rahman M, Altura BM, Altura BT et al. Divalent cations in women with PCOS: Implications for cardiovascular disease. *Gynecol Endocrinol.*2001;15(3):198-201.
96. Handwerker SM, Altura BT, Jones KY, Altura BM. Maternal-fetal transfer of ionized serum magnesium during stress of labor and delivery: a human study. *J Am Coll Nutr.*1995;14(4):376-381.
97. Scott VL, DeWolf AM, Kang Y, Altura BT, Virji MA, Cook DR et al. Ionized hypomagnesemia in patients undergoing orthotopic liver transplantation: a complication of citrate intoxication. *Liver Transpl Surg.*1996;2(5):343-347.
98. Fogh-Andersen N, Altura BM, Altura BT, Sigaard-Andersen O . Changes in plasma ionized calcium and magnesium in blood donors after donation of 450 ml blood. Effects of hemodilution and Donnan equilibrium. *Scand J Clin Lab Invest.*1996;56:245-250.
99. Djurhuus S, Kligaard NA, Pedersen KK, Blaabjerg O, Altura BM, Altura BT et al. Magnesium induces insulin-stimulated glucose uptake and serum lipid concentrations in type 1 diabetes. *Metabolism.*2001;50(12):1409-1417. DOI:10.1053/meta.2001.28072.
100. Altura RA, Wang WC, Wynn L, Altura BM, Altura BT . Hydroxyurea therapy associated with declining serum levels of magnesium in children with sickle cell anemia. *J Pediatr.*2002;140(5):565-569. DOI:10.1067/mpd.2002.122644
101. Zehtabchi S, Sinert R, Rinnert S, Chang B, Hennis R, Rachel A, Altura et al. Serum ionized magnesium levels and ionized calcium to magnesium ratio in adult patients with sickle cell anemia. *Am J Hematol.*2004;77:215-222. DOI: 10.1002/ajh.20187.
102. Apostol A, Apostol R, Ali E, Choi A, Ehsuni N, Hu B et al. Cerebral spinal fluid magnesium and calcium levels in preeclamptic women during administration of magnesium sulfate. *Fertil Steril.*2010;94(1):276-282. doi: 10.1016/j.fertnstert.2009.02.024.
103. Muneyyirci-Delale O, Nacharaju VL, Altura BM, Altura BT. Sex steroid hormones modulate serum ionized magnesium and calcium levels throughout the menstrual cycle in women. *1998;69(5):958-962.*
104. Muneyyirci-Delale O, Nacharaju VL, Dalloul M, Altura BM, Altura BT. Serum ionized magnesium and calcium and sex hormones in healthy young men: importance of serum progesterone level. *Fertil Steril.*1999;72(5):817-822.
105. Seelig MS, Altura BM, Altura BT. Benefits and risks of sex hormone replacement in postmenopausal women. *J Am Coll Nutr.*2004;23(5):482S-496S.
106. Resnick LM, Bardicof D, Altura BT, Aldermam MH, Altura BM. Serum ionized magnesium: Relation to blood pressure and racial factors. *Am J Hypertens.*1997;10(12pt 1):1420-1424.
107. Altura BT, Shirey TL, Young CC, Dell'Orfano K, Altura BM (1992) Characterization and studies of a new ion selective electrode for free extracellular magnesium ions in whole blood, plasma and serum. In: *Electrolytes, Blood Gases and Other Critical Analytes: The Patient, The Measurement, and The Government.* Vol 14. P. D'Orazio , M.F. Burritt, S.F. Sena. Omni Press, Wisconsin, pp 152-173.
108. Altura BM, Altura BT, Gebrewold A, Ising H, Gunther T. Magnesium deficiency and hypertension: correlation between magnesium deficiency diets and microcirculatory changes in situ. *Science.*1984;223(4642):1315-1317.
109. Altura BM, Altura BT, Gebrewold A, Ising H, Gunther T. Noise-induced hypertension and magnesium in rats: relationship to microcirculation and calcium. *J Appl Physiol.*1992;72(1):194-202.
110. Altura BM, Altura BT. Magnesium in cardiovascular biology. *Sci & Med Scientific Am.*1995;2(3):28-37.
111. Altura BM, Altura BT (1996) Magnesium as an extracellular signal in cardiovascular pathobiology. *J Jap Soc Magnes Res* 15: 17-32.
112. Altura BM, Altura BT, Carella A. Magnesium deficiency- induced spasms of umbilical vessels: relation to preeclampsia, hypertension, growth retardation. *Science.*1983;221(4608):376-378.

113. Kimura T, Yasue H, Sakaino N, Rokutanada M, Jougasaki M, Araki H. Effect of magnesium on the tone of isolated human coronary arteries. Comparison with diltiazem and nitroglycerin. *Circulation*.1980;79(5):1118-1124.
114. Goto K, Yasue H, Okumura K, Matsuyama K, Kugiyama K, Hiroo Miyagi et al. Magnesium deficiency detected by intravenous loading test in variant angina pectoris. *Am J Cardiol*.1990;65(11):709-712. doi.org/10.1016/0002-9149(90)91375-G.
115. Satake K, Lee JD, Shimizu H, Ueda T, Nakamura T. Relation between severity of magnesium deficiency and frequency of angina attacks in men with variant angina. *J Am Coll Cardiol*.1996;28: 897-902.
116. Sueda S, Fukuda H, Watanabe K, Suzuki J, Saeki H, Ohtani T, et al. Magnesium deficiency in patients with recent myocardial infarction and provoked coronary artery spasm. *Jpn Circ J*.2001;65(7):643-648.
117. Wu F, Altura BT, Gao J, Barbour RL, Altura BM. Ferrylmyoglobin formation induced by acute magnesium deficiency in perfused rat heart causes cardiac failure. *Biochim Biophys Acta*.1994;1225(2):158-164.
118. Morrill GA, Gupta RK, Kostellow AB, Ma GY, Zhang A, et al. (1997) Mg<sup>2+</sup> modulates membrane lipids in vascular smooth muscle cells: a link to atherogenesis. *FEBS Lett*.1997;408(2):191-194. doi.org/10.1016/S0014-5793(97)00420-1.
119. Morrill GA, Gupta RK, Kostellow AB, Ma GY, Zhang A, Altura BT, et al. Mg<sup>2+</sup> modulates membrane sphingolipids and lipid messengers in vascular smooth muscle cells. *FEBS Lett*.1998;440(1-2):167-171.
120. Altura BM, Shah NC, Jiang XC, Perez-Albela JL, Sica AC, Altura BT. Short-term magnesium deficiency results in decreased levels of serum sphingomyelin, lipid peroxidation, and apoptosis in cardiovascular tissues. *Am J Physiol Heart Circ Physiol*.2009;297(1):H86-H92. doi: 10.1152/ajpheart.01154.2008.
121. Altura BM, Shah Nc, Li Z, Jiang XC, Perez-Albela JL, Altura BT. Magnesium deficiency upregulates serine palmitoyl transferase (SPT 1 and SPT 2) in cardiovascular tissues: relationship to serum ionized Mg<sup>2+</sup> and cytochrome C. *Am J Physiol Heart Circ Physiol*.2010;299(3):H932-H938. doi: 10.1152/ajpheart.01076.2009.
122. Shah NC, Liu JP, Iqbal J, Hussain M, Jiang XC, Zhiqiang Li et al. Mg deficiency results in modulation of serum lipids, glutathione, and NO synthase isozyme activation in cardiovascular tissues : relevance to de novo synthesis of ceramide, serum Mg and atherogenesis. *Int J Clin Exp Med*.2011;4(2):103-118.
123. Zheng T, Li W, Altura BT, Shah NC, Altura BM. Sphingolipids regulate [Mg<sup>2+</sup>]<sub>o</sub> uptake and [Mg<sup>2+</sup>]<sub>i</sub> content in vascular smooth muscle cells: potential mechanisms and importance to membrane transport of Mg<sup>2+</sup>. *Am J Physiol Heart Circ Physiol*.2011;300(2):H486-H492. doi: 10.1152/ajpheart.00976.2010.
124. Altura BM, Shah NC, Shah GJ, Zhang A, Li W, Zheng T et al. Short-term magnesium deficiency upregulates ceramide synthase in cardiovascular tissues and cells: cross-talk among cytokines, Mg<sup>2+</sup>, NF-κB and de novo ceramide. *Am J Physiol Heart Circ Physiol*.2012;302(1):319-332. doi: 10.1152/ajpheart.00453.2011.
25. Altura BM, Shah NC, Shah GJ, Li W, Zhang A, et al. (2013) Magnesium deficiency upregulates sphingomyelinases in cardiovascular tissues and cells: cross-talk among proto-oncogenes, Mg<sup>2+</sup>, NF-κB, and ceramide and their potential relationships to resistant hypertension, atherogenesis and cardiac failure. *Int J Clin Exp Med*.2013;6(10):861-879.
126. Altura BM, Shah NC, Shah GJ, Zhang A, Li W, Zheng Tet al. Short-term magnesium deficiency upregulates protein kinase C isoforms in cardiovascular tissues and cells; relation to NF-κB, cytokines, ceramide salvage sphingolipid pathway and PKC-zeta: hypothesis and review. *Int J Clin Exp Med*.2014;7(1):1-21.
127. Altura BM, Li W, Zhang A, Zheng T, Shah NC, Gatha J. Shah et al. The expression of PAF is induced by low extracellular Mg<sup>2+</sup> in aortic, cerebral and piglet coronary arterial vascular smooth muscle cells; cross-talk with ceramide production, DNA, nuclear factor-κB and proto-oncogenes: possible links to inflammation, atherogenesis, hypertension, sudden cardiac death in children and infants, stroke, and aging: hypothesis and review. *Int J Cardiol Res*.2016;3(1):47-67. doi.org/10.19070/2470-4563-1600011.
128. Altura BM, Shah Nc, Shah GJ, Perez-Albela JL, Altura BT. Magnesium deficiency results in oxidation and fragmentation of DNA, downregulation of telomerase activity, and ceramide release in cardiovascular tissues and cells: potential relationship to atherogenesis, cardiovascular diseases and aging. *Int J Diabetol & Vasc Dis Res*. 2016;4(1):1-5. doi.org/10.19070/2328-353X-1600011e.
129. Majno G, Joris I. *Cells, Tissues, and Disease: Principles of General Pathology*. (2nd Edn.) Oxford, Oxford Univ Press.2004;307-424.
130. Kumar V, Abbas AK, Aster JC. *Robbins and Cotran Pathologic Basis of Disease*. (9th Edn.) . Philadelphia, Elsevier-Saunders . 2015:496-501.
131. Merrill AH Jr, Jones DD. An update of the enzymology and regulation of sphingomyelin metabolism. *Biochim Biophys Acta*.1990;1044(1):1-12.
132. Merrill AH Jr (1992) De novo sphingolipid biosynthesis: a necessary but dangerous , pathway. *J Biol Chem*.2002; 277:25843-25846. doi: 10.1074/jbc.R200009200.
133. Aguilera-Romero A, Gehin C , Reizman H. Sphingolipid homeostasis in the web of metabolic routes. *Biochim Biophys Acta*.2014;1841(5):647-656. doi: 10.1016/j.bbailip.2013.10.014.
134. Bielawska AE, Shapiro JF, Jiang L, Melkonyan HS, Piot C, Wolfe CL et al. Ceramide is involved in triggering of cardiomyocyte apoptosis induced by ischemia and reperfusion. *Am J Pathol*.1997;151(5):1257-1263.
135. Getz GS. The two Cs: ceramide and cardiomyopathy. *J Lipid Res*.2008;49(10):2077-2078. DOI:10.1194/jlr.E800015-JLR200.
136. Empinado HM, Deevska GM, Nokolova-Karakashian M, Yoo JK, Cristou DD, Ferreira LF. Diaphragm dysfunction in heart failure is accompanied by increases in neutral sphingomyelinase activity and ceramide. *Europ J Heart Failure*.2014; 16(5):519-525. doi: 10.1002/ehf.73.
137. Yu J, Pan W, Shi R, Yang T, Li Y, Yu G et al . Ceramide is upregulated and associated with mortality in patients with chronic heart failure. *Canad J Cardiol*.2015;31(3):357-363. doi: 10.1016/j.cjca.2014.12.007.
138. Fruwirth GO, Loidi A, Hermetter A. Oxidized phospholipids: from molecular properties to disease. *Biochim Biophys Acta* .2007;1772(7):718-736. doi.org/10.1016/j.bbadis.2007.04.009.
139. Prescott SM, Zimmerman GA, Stafforini DM, McIntyre TM (2000) Platelet-activating factor and related lipid mediators. *Annu Rev Biochem*.2000;69:419-445. DOI:10.1146/annurev.biochem.69.1.419.
140. Montrucchio G, Alloatti G, Camussi G. Role of platelet-activating factor

- in cardiovascular pathophysiology. *Physiol Rev.*2000;80(4):1669-1699.
141. Altura BM, Gebrewold A, Zheng T, Altura BT. Sphingomyelinase and ceramide analogs induce vasoconstriction and leukocyte-endothelial interactions in cerebral blood vessel venules in the intact rat brain: insight into mechanisms and possible relation to brain injury. *2002; 58(3):271-278.*
142. Dillon PK, Ritter AB, Duran WN. Vasoconstrictor effects of platelet-activating factor in the hamster cheek pouch microcirculation: dose-related relations and pathways of action. *Circ Rec.*1988;62(4):722-731.
143. Uhl E, Pickelmann S, Baethmann A, Schürer L. Influence of platelet-activating factor on cerebral microcirculation in rats. Part I . Systemic application. *Stroke.*1999;30(4):873-879.
144. Dillon PK, Fitzpatrick MF, Ritter AB, Duran WN (1988) Effect of platelet-activating factor on leukocyte adhesion to micro vascular endothelium: time course and dose-response relationships. *Inflamm.*1988;12(6): 563-573.
145. Bekker AY, Dillon PK, Paul J, Duran WN, Ritter AB. Dose-response relationships between platelet-activating factor and permeability: surface area product of FITC-dextran 150 in the hamster cheek pouch. *Microcirc Endothel Lymphatics.*1988;4(6):433-446.
146. Moschos MM, Pantazis P, Gatzoulas Z, Panos GD, Gazouli M, Nitoda E et al. Association between platelet activating factor acetylhydrolase and diabetic retinopathy: Does inflammation affect the retinal status? *Prostagl & Other Lipid Med.*2016;122:69-72. doi: 10.1016/j.prostaglandins.2016.01.001.