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The role of magnesium deficiency in the pathogenesis of hypertension and the influence of magnesium supplementation on blood pressure – literature review

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Summary:

Magnesium is a macronutrient that is very important for the proper functioning of the human body. Deficiency of this element is crucial in the development of many disorders in the proper functioning of many organ systems. The optimal level of magnesium has a significant influence on the functioning of the cardiovascular system, among others. Although the factors showing the mechanism of lowering blood pressure by magnesium ions are not fully understood, the influence of the correct concentration of magnesium in the human body on cardiovascular protection is beyond doubt. Magnesium supplementation produces positive effects in the functioning of blood vessels and in maintaining blood

pressure within the normal range. In our article, we focused on the role of magnesium in maintaining normal blood pressure at the molecular, cellular and tissue levels, as well as on the impact of magnesium supplementation on reducing blood pressure.

Key words: magnesium, hypertension, deficiency, supplementation

INTRODUCTION AND PURPOSE

Essential arterial hypertension is a chronic disease, the causes of which are not fully understood. It is estimated that by 2025 there will be more than 1.5 billion people in the world with this disease. [3] [12] The number of sick people keeps growing. Hypertension is the leading cause of the development of cardiovascular diseases such as stroke and coronary artery disease. [10] Many factors influence the genesis of arterial hypertension. The main behavioral factors are: improper lifestyle with limited physical activity and a sedentary lifestyle, and a diet based on unhealthy, processed foods and an increased consumption of simple sugars. Hypertension can be diagnosed when the blood pressure is higher than the current norm. [15] In a meta-analysis of 137,260 patients, a significant reduction in mortality was observed in those treated with the drug for hypertension compared to those treated with placebo. [13]

Magnesium is a common element in the human body. Its greatest resources are in legumes, nuts and leafy green plants. [4] Mineral water can also be a considerable source of magnesium. Its main storage in the human body is bones, where approximately 60% of this element is stored. [7] [8] Magnesium is a constituent of many enzyme systems. Its role as a cofactor has been proven in 325 enzyme systems. [9] The level of magnesium in the blood serum is not a good indicator of its amount in the human body, as it accumulates mainly intracellularly.

Magnesium plays an important role in maintaining homeostasis and the proper function of the circulatory system, however, the role of its deficiency in the genesis of hypertension is not fully understood. [1] Magnesium deficiency has a negative effect on nearly all systems in the human body. It causes anxiety, irritability, reduced appetite and headaches. In the muscular system, muscle contractions and tetany can be observed. The impact of magnesium deficiency is also visible in the nervous system. Memory impairment, nervousness, tremors, and convulsions were observed. In the cardiovascular system, it causes cardiac arrhythmias, endothelial dysfunction and vasospasm. In addition, hypokalemia, hypocalcemia and constipation can be observed when the magnesium level is lowered. Magnesium deficiency has been associated with a higher incidence of gestational eclampsia in pregnant women. Chronic magnesium deficiency can cause many disorders in the human body, such as insulin resistance, diabetes, disorders of lipid metabolism, atherosclerosis, osteoporosis, depression and arterial hypertension. [10] Studies have found a link between magnesium intake and cardiovascular risk. A reduction in this risk has been shown when the magnesium intake is increased to recommended levels or higher. [16] It should be noted, however, that the majority of people with reduced magnesium levels do not have any symptoms.

Research in the US and European studies have found magnesium intake below the recommended level. [10] The daily recommendation for Mg2 + intake is 420 mg for men and 320 mg for women. [11] It has been shown that in the British population the daily intake is 270 mg for men and 221.4 mg for women [17], indicating a deficiency of this element in the diet. Magnesium intake has fallen in recent years, possibly due to the use of fertilizers and a higher proportion of processed foods in the diet and cooking foods that contain significant amounts of Mg2 + [10]. There is evidence that the intake of K +, Ca2 +, Mg2 + and fiber is inversely related to blood pressure. The reduction of blood pressure was

achieved by using a vegetarian and Mediterranean diet, which are characterized, among others, by a high content of fiber and Mg2 +, which has been proven in studies. [19]

The most numerous group of people who are deficient in this element are the elderly - it has been shown that over 80% of people over 71 years of age have a magnesium deficiency. [16] Intestinal absorption of magnesium ions decreases with age and its loss in urine increases. If insufficient magnesium is supplied with the food, it can be recovered significantly in the Henle loop. [14]

The main goal of our work is to summarize the knowledge about the influence of magnesium and its deficiency in the genesis of hypertension and the role of magnesium supplementation on blood pressure changes. When writing our article, we consulted the most up-to-date sources of knowledge on this topic. A review of the literature shows a significant relationship between magnesium deficiency and the development of hypertension, as well as the positive role of magnesium supplementation in predisposed individuals and those already suffering from hypertension.

DESCRIPTION OF THE STATE OF KNOWLEDGE

The role of magnesium deficiency in the genesis of arterial hypertension can be considered at the molecular level. The influx of Mg2 + into the cell is regulated, inter alia, by the cationic channels of melastatin-6 and -7. [22] Melastatin-6 cation channels are found mainly in the large intestine and kidneys, where they are involved in the reabsorption of magnesium ions. Cellular outflow occurs mainly with the participation of the Na + / Mg2 + and Mg2 + / Ca2 + pumps and the Mn2 + / Mg2 + Cl- / Mg2 + cotransporter. There are reports that disturbance of the inflow and outflow of cells may contribute to the genesis of arterial hypertension and, consequently, to cardiovascular diseases. [1] [22] Melastatin-7 cation channels ensure arterial integrity. [23] Malfunctioning of these channels in the arterial walls may lead to an abnormal inflow of Mg2 + [24] and, as a consequence, to a change in its concentration in the vascular wall and the development of arterial hypertension. [22] [24] Melastatin-6 and -7 cation channels are present in the vascular endothelium and play an important role in maintaining the correct concentration of magnesium cations within the cell. [26] The melastatin-7 cation channel is also involved in the formation of new blood vessels and remodeling of the existing ones. [27] As a result of oxidative stress or decreased magnesium concentration, the expression of melastatin-7 cation channels on the endothelial wall is increased [23]. activity of these channels, which causes vasoconstriction, remodeling and fibrosis, and angiogenesis, which in turn leads to arterial hypertension. [20] Estrogens also influence the cationic channels of melastatin-6. The decreased level of estrogen after menopause causes an increase in the loss of magnesium cations, which may contribute to the genesis of arterial hypertension and osteoporosis.

The role of Mg2 + ions is also based on the antagonistic effect of Ca2 + cations, which are a factor leading to an increase in blood pressure. Magnesium cations act antagonistically to calcium ions in vascular smooth muscle cells. Extracellular Mg2 + ions inhibit the influx of Ca2 + into the cell by neutralizing the negative electric charge on the cell membrane and by binding to the Ca2 + channel. Increasing the level of Mg2 + in the cell accelerates the breakdown of inositol-1,4,5-triphosphate in the endoplasmic reticulum, which inhibits the release of Ca2 + ions from it. [34] The decreased level of magnesium ions causes the mobilization of calcium ions from the endoplasmic reticulum, which in turn causes an increase in the concentration of calcium in the cytosol of smooth muscle cells of blood vessels and their contraction. [35] The vessels then contract. Blood pressure rises.

Magnesium cations, in addition to their direct effect on vascular smooth muscle, also act through the synthesis of prostacyclin (PGI2) and nitric oxide (NO), which dilate blood vessels. [5] [22] [34] The human body contains natural substances that constrict blood vessels, such as vasopressin, endothelin 1 and angiotensin II. Mg2 + ions are involved in the intracellular transmission of the signal of vasoactive

peptides. After these compounds bind to their receptors, the increased level of Mg2 + in the cell reduces the contractile potential of these substances, and the lowered level increases the contractile potential. [36] It has also been shown that reduced magnesium levels reduce the synthesis of prostaglandin E1, which causes vasodilatation. It follows from the fact that the deficiency of this element causes narrowing of blood vessels and, consequently, an increase in blood pressure. The Renin-angiotensin-aldosterone system plays a key role in the regulation of blood pressure. [2] The deficiency of Mg2 + increases the intracellular influx of Ca2 +, which causes an increase in the synthesis of aldosterone. [37] Magnesium deficiency also increases the synthesis of vasoconstrictor prostaglandins and thromboxane A2. All these changes caused by the deficiency of Mg2 + ions cause an increase in blood pressure.

Calcium ions play a key role in the release of catecholamines from the adrenal medulla. Mg2 + ions act in an antagonistic way to Ca2 +, their increased concentration inhibits the release of catecholamines from the adrenal glands. There are reports of a positive effect of magnesium supplementation in people with pheochromocytoma of the adrenal gland. [38] The substance that stimulates the release of catecholamines from the adrenal cortex is acetylcholine. Magnesium ions antagonize the action of calcium ions, which increase acetylcholine secretion. [41] This results in a reduction in catecholamines, which increase blood pressure. [39] Magnesium activates the enzyme that breaks down catecholamines (COMT), while calcium deactivates it. Magnesium deficiency causes a decrease in COMT, which increases the concentration of catecholamines [2] [41], which increase blood pressure.

Psychological stress is a potential factor in the development of hypertension. On the pathophysiological level, it is caused by stimulation of the hypothalamic-pituitary-adrenal axis. [45] Mg2 + are ions that significantly influence the functioning of this neurohormonal system. Magnesium deficiency increases levels of corticotropin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). [44] These hormones significantly increase blood pressure.

Decreased magnesium levels interfere with the parathyroid gland's response to decreased serum calcium levels. Under conditions of hypomagnesaemia and hypocalcaemia, PTH secretion is reduced. PTH causes an increase in Mg2 + reabsorption in the kidneys and Mg2 + absorption in the intestines, which increases the concentration of this element in the body. Disruption of Mg2 + homeostasis affects fluctuations in PTH and Ca2 +, which are known factors that increase blood pressure. [thirty]

There are complex relationships between vitamin D and its metabolites and magnesium in the human body. 1,25-dihydroxyvitamin D stimulates the absorption of Mg2 + in the intestine. Mg2 + cations, on the other hand, support the process of vitamin D hydroxylation to a biologically active form. These processes take place in the liver and kidneys. [29] Magnesium deficiency leads to a reduction in the amount of biologically active vitamin D.

Proper flexibility of blood vessels ensures optimal blood flow and proper perfusion in peripheral tissues. Vascular elasticity disorders resulting in an increase in their stiffness result in an increase in blood pressure and the workload of the heart, which are necessary for the proper blood supply to peripheral tissues. The concentration of magnesium ions plays a key role in the regulation of vascular tone. In the course of arterial hypertension, the reconstruction of blood vessels occurs. They are overgrown both inwards and outwards. [43] A key role in this mechanism is played by tissue transglutaminase, which is activated by Ca2 and deactivated by Mg2 +. [46] Metalloproteinases in blood vessels degrade elastin and collagen, which causes fibrosis and vascular stiffness. The vessels then become dysfunctional. It has been proven that with magnesium deficiency the expression of metalloproteinases increases, and with magnesium supplementation the concentration of metalloproteinases in the vascular endothelium decreases. [28]

The cause of arterial hypertension is also the calcification of blood vessels, which we divide into medial and internal. Internal calcification occurs in the course of atherosclerosis, while medial calcification reduces the elasticity of the vessels, which in turn causes stiffening of the arteries and an increase in blood pressure. Vascular calcification leads to isolated systolic hypertension and is mainly observed in the elderly. [48] Studies have shown that Mg2 + cations reduce the arterial calcification process. [31] It has been proven that magnesium supplementation reduces the calcification of the coronary arteries. [47]

Magnesium deficiency affects the genesis of inflammation and increases the amount of free radicals, which generates vascular endothelial dysfunction. Mg2 + deficiency increases the amount of CRP, interleukin 1, interleukin 6 and tumor necrosis factor α, which are pro-inflammatory molecules [6] [42] and reduces the amount of antioxidants - selenium, vitamin E, vitamin C and glutathione. [21] Inflammatory factors make the endothelium dysfunctional, which contributes to the development of arterial hypertension.

Older people have a predisposition to reduce the concentration of magnesium in the body. The reason for this is reduced absorption of this element in the gastrointestinal tract and its increased loss by the kidneys. In elderly people, the process of calcification of the vessels is accelerated. They stiffen and develop isolated systolic arterial hypertension. [2] In the blood vessels of the elderly, the amount of free radicals increases and the amount of pro-inflammatory factors increases. On the other hand, the amount of nitric oxide, which has a vasodilating effect, is reduced. The process of vascular fibrosis also intensifies. All of the factors leading to an increase in blood pressure are influenced by magnesium deficiency.

The correct concentration of magnesium is believed to be helpful in the treatment of high blood pressure. The positive effects of magnesium supplementation on blood pressure have been shown. Magnesium citrates, gluconates and aspartates are the compounds with the highest bioavailability, therefore they are recommended in the treatment of Mg2 + deficiency. [10] Mg2 + supplementation causes an increase in the amount of high-density lipoproteins (HDL) and a reduction of low-density lipoproteins (LDL). The use of magnesium preparations in the prophylaxis of hypertension may be recommended as well as in the adjuvant therapy of the treatment of this disease. [32]

In a study of 15,248 participants, it was proved that the concentration of magnesium in the blood serum was inversely related to the systolic blood pressure. [40] Another study showed a positive effect of magnesium supplementation on both systolic and diastolic blood pressure [33], while another study showed that magnesium supplementation had positive effects in patients with secondary or refractory arterial hypertension and in people using diuretics. [25] People with magnesium deficiency have been shown to need higher doses of drugs to lower blood pressure than people with normal magnesium levels. [33]

CONCLUSIONS:

Hypertension is a chronic disease that develops in hidden places. It is one of the world's most common diseases. The number of patients is constantly increasing. Currently, about one fifth of people in the world suffer from hypertension. [12] Untreated high blood pressure leads to many complications.

We know that magnesium enhances the production of vasodilating factors: nitric oxide and prostacyclin. Deficiency of this element lowers the level of antioxidants and increases inflammation and the production of aldosterone. [2] [37] Mg2 + deficiency may affect the metabolism of carbohydrates and lipids, which in turn leads to the development of insulin resistance and progressive atherosclerotic changes resulting in progressive arterial stiffness. Magnesium as a calcium antagonist keeps the elastic fibers of the arteries free from calcium deposits, thus maintaining the natural

elasticity of the vessels. It takes part in the regulation of blood pressure by changing the reactivity and tension of blood vessels. [20] All these relationships demonstrate the key function of Mg2 + in maintaining normal blood pressure.

A healthy diet with the optimal amount of magnesium is very important. It has been shown that in Western countries the magnesium intake is low and is in the range of 30% -50% of the daily requirement. [18] An optimal diet with the correct magnesium content may be a determinant of normal blood pressure. It allows for functionally correct multiple systems. Magnesium supplementation has been shown to be effective in reducing both systolic and diastolic blood pressure. [33] A diet high in magnesium is recommended both for people suffering from hypertension and for those who have risk factors for hypertension due to the participation of magnesium ions in preventing the development of hypertension. [25]

There is no doubt about the relationship between magnesium deficiency and hypertension. Consuming adequate amounts of magnesium from both the diet and drinking water seems to be appropriate management both for people suffering from hypertension or those at risk for the disease, but also for all people who do not have high blood pressure.

LIST OF REFERENCES:

1. Kostov K, Halacheva L. *Role of Magnesium Deficiency in Promoting Atherosclerosis, Endothelial Dysfunction, and Arterial Stiffening as Risk Factors for Hypertension.* Int J Mol Sci. 2018 Jun 11;19(6):1724. doi: 10.3390/ijms19061724. PMID: 29891771; PMCID: PMC6032400.

2. Dominguez L, Veronese N, Barbagallo M. *Magnesium and Hypertension in Old Age. Nutrients.* 2020 Dec 31;13(1):139. doi: 10.3390/nu13010139. PMID: 33396570; PMCID: PMC7823889.

3. Patni N, Fatima M, Lamis A, Siddiqui SW, Ashok T, Muhammad A. *Magnesium and Hypertension: Decoding Novel Anti-hypertensives.* Cureus. 2022 Jun 10;14(6):e25839. doi: 10.7759/cureus.25839. PMID: 35836446; PMCID: PMC9273175.

4. Dominguez LJ, Gea A, Ruiz-Estigarribia L, Sayón-Orea C, Fresán U, Barbagallo M, Ruiz-Canela M, Martínez-González MA. *Low Dietary Magnesium and Overweight/Obesity in a Mediterranean Population: A Detrimental Synergy for the Development of Hypertension. The SUN Project.* Nutrients. 2020 Dec 31;13(1):125. doi: 10.3390/nu13010125. PMID: 33396318; PMCID: PMC7824180.

5. Maier JA, Bernardini D, Rayssiguier Y, Mazur A. *High concentrations of magnesium modulate vascular endothelial cell behaviour in vitro*. Biochim Biophys Acta. 2004 May 24;1689(1):6-12. doi: 10.1016/j.bbadis.2004.02.004. PMID: 15158908.

6. Carbone F, Elia E, Casula M, Bonaventura A, Liberale L, Bertolotto M, Artom N, Minetti S, Dallegri F, Contini P, Verzola D, Pontremoli R, Viazzi F, Viviani GL, Bertolini S, Pende A, Pisciotta L, Montecucco F. *Baseline hs-CRP predicts hypertension remission in metabolic syndrome*. Eur J Clin Invest. 2019 Aug;49(8):e13128. doi: 10.1111/eci.13128. Epub 2019 Jun 3. PMID: 31091356.

7. Rude R.K., Shils M.E. Magnesium. In: Shils M.E., Shike M., Ross A.C., Caballero B., Cousins R.J., eds. *Modern nutrition in health and disease.* Baltimore: Lippincott Williams & Wilkins; 2006. 10th ed223-247

8. Hashizume N, Mori M: *An analysis of hypermagnesemia and hypomagnesemia.* Jpn J Med, 1990, 29, 368-372.

9. Choi MK, Bae YJ. *Association of Magnesium Intake with High Blood Pressure in Korean Adults:* Korea National Health and Nutrition Examination Survey 2007-2009. PLoS One. 2015 Jun 15;10(6):e0130405. doi: 10.1371/journal.pone.0130405. PMID: 26075385; PMCID: PMC4468246.

10. Gröber U, Schmidt J, Kisters K. *Magnesium in Prevention and Therapy.* Nutrients. 2015 Sep 23;7(9):8199-8226. doi: 10.3390/nu7095388. PMID: 26404370; PMCID: PMC4586582.

11. de Baaij JH, Hoenderop JG, Bindels RJ. *Regulation of magnesium balance: lessons learned from human genetic disease.* Clin Kidney J. 2012 Feb;5(Suppl 1):i15-i24. doi: 10.1093/ndtplus/sfr164. PMID: 26069817; PMCID: PMC4455826.

12. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. *Global burden of hypertension: analysis of worldwide data.* Lancet. 2005 Jan 15-21;365(9455):217-23. doi: 10.1016/S0140-6736(05)17741-1. PMID: 15652604.

13. Elliott WJ, Czarny HR. *Farmakologia kliniczna i terapia nadciśnienia, Podręcznik nadciśnienia.* Tom. 25. Edynburg; Nowy Jork: Elsevier; 2008. Podstawa dowodowa leczenia nadciśnienia tętniczego; s. 413–452.

14. Ismail A.A., Ismail N.A. *Magnesium: A mineral essential for health yet generally underestimated or even ignored*. J. Nutr. Food Sci. 2016;6:2. doi: 10.4172/2155-9600.1000523.

15. Giles TD, Berk BC, Black HR, Cohn JN, Kostis JB, Izzo JL Jr, Weber MA. *Expanding the definition and classification of hypertension.* J Clin Hypertens (Greenwich). 2005 Sep;7(9):505-12. doi: 10.1111/j.1524-6175.2005.04769.x. PMID: 16227769; PMCID: PMC8109641.

16. Qu X, Jin F, Hao Y, Li H, Tang T, Wang H, Yan W, Dai K. *Magnesium and the risk of cardiovascular events: a meta-analysis of prospective cohort studies.* PLoS One. 2013;8(3):e57720. doi: 10.1371/journal.pone.0057720. Epub 2013 Mar 8. PMID: 23520480; PMCID: PMC3592895.

17. Kass L., Sullivan K.R. *Low Dietary Magnesium Intake and Hypertension.* World J. Cardiovasc. Dis. 2016;6:447. doi: 10.4236/wjcd.2016.612048.

18. Altura B.M., Li W., Zhang A., Zheng T., Shah N.C. *Sudden cardiac death in infants, children and young adults: Possible roles of dietary magnesium intake and generation of platelet-activating factor in coronary arteries.* J. Heart Health. 2016;2:1–5.

19. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. *A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group.* N Engl J Med. 1997 Apr 17;336(16):1117-24. doi: 10.1056/NEJM199704173361601. PMID: 9099655.

20. Touyz RM, Yao G. *Modulation of vascular smooth muscle cell growth by magnesium-role of mitogen-activated protein kinases.* J Cell Physiol. 2003 Dec;197(3):326-35. doi: 10.1002/jcp.10393. PMID: 14566962.

21. Belin RJ, He K. *Magnesium physiology and pathogenic mechanisms that contribute to the development of the metabolic syndrome.* Magnes Res. 2007 Jun;20(2):107-29. PMID: 18062585.

22. Houston M. *The role of magnesium in hypertension and cardiovascular disease*. J Clin Hypertens (Greenwich). 2011 Nov;13(11):843-7. doi: 10.1111/j.1751-7176.2011.00538.x. Epub 2011 Sep 26. PMID: 22051430; PMCID: PMC8108907.

23. Baldoli E, Castiglioni S, Maier JA. *Regulation and function of TRPM7 in human endothelial cells: TRPM7 as a potential novel regulator of endothelial function*. PLoS One. 2013;8(3):e59891. doi: 10.1371/journal.pone.0059891. Epub 2013 Mar 22. PMID: 23533657; PMCID: PMC3606311.

24. Paravicini TM, Chubanov V, Gudermann T. *TRPM7: a unique channel involved in magnesium homeostasis.* Int J Biochem Cell Biol. 2012 Aug;44(8):1381-4. doi: 10.1016/j.biocel.2012.05.010. Epub 2012 May 24. PMID: 22634382.

25. Touyz RM. *Role of magnesium in the pathogenesis of hypertension.* Mol Aspects Med. 2003 Feb-Jun;24(1-3):107-36. doi: 10.1016/s0098-2997(02)00094-8. PMID: 12537992.

26. Baldoli E, Maier JA. *Silencing TRPM7 mimics the effects of magnesium deficiency in human microvascular endothelial cells.* Angiogenesis. 2012 Mar;15(1):47-57. doi: 10.1007/s10456-011-9242-0. Epub 2011 Dec 20. PMID: 22183257.

27. Di A, Malik AB. *TRP channels and the control of vascular function.* Curr Opin Pharmacol. 2010 Apr;10(2):127-32. doi: 10.1016/j.coph.2009.11.010. Epub 2010 Jan 7. PMID: 20060363.

28. Dolinsky BM, Ippolito DL, Tinnemore D, Stallings JD, Zelig CM, Napolitano PG. *The effect of magnesium sulfate on the activity of matrix metalloproteinase-9 in fetal cord plasma and human umbilical vein endothelial cells.* Am J Obstet Gynecol. 2010 Oct;203(4):371.e1-5. doi: 10.1016/j.ajog.2010.06.012. Epub 2010 Aug 16. PMID: 20719294.

29. Ritchie G, Kerstan D, Dai LJ, Kang HS, Canaff L, Hendy GN, Quamme GA. *1,25(OH)(2)D(3) stimulates Mg2+ uptake into MDCT cells: modulation by extracellular Ca2+ and Mg2+*. Am J Physiol Renal Physiol. 2001 May;280(5):F868-78. doi: 10.1152/ajprenal.2001.280.5.F868. PMID: 11292630.

30. Hagström E, Ahlström T, Ärnlöv J, Larsson A, Melhus H, Hellman P, Lind L. *Parathyroid hormone and calcium are independently associated with subclinical vascular disease in a community-based cohort.* Atherosclerosis. 2015 Feb;238(2):420-6. doi: 10.1016/j.atherosclerosis.2014.12.027. Epub 2014 Dec 20. PMID: 25562577.

31. Louvet L, Bazin D, Büchel J, Steppan S, Passlick-Deetjen J, Massy ZA. *Characterisation of calcium phosphate crystals on calcified human aortic vascular smooth muscle cells and potential role of magnesium*. PLoS One. 2015 Jan 21;10(1):e0115342. doi: 10.1371/journal.pone.0115342. PMID: 25607936; PMCID: PMC4301909.

32. Zhang X, Li Y, Del Gobbo LC, Rosanoff A, Wang J, Zhang W, Song Y. *Effects of Magnesium Supplementation on Blood Pressure: A Meta-Analysis of Randomized Double-Blind Placebo-Controlled Trials. Hypertension.* 2016 Aug;68(2):324-33. doi: 10.1161/HYPERTENSIONAHA.116.07664. Epub 2016 Jul 11. PMID: 27402922.

33. Whang R, Chrysant S, Dillard B, Smith W, Fryer A. *Hypomagnesemia and hypokalemia in 1,000 treated ambulatory hypertensive patients.* J Am Coll Nutr. 1982;1(4):317-22. doi: 10.1080/07315724.1982.10719001. PMID: 7185863.

34. Kolte D, Vijayaraghavan K, Khera S, Sica DA, Frishman WH. *Role of magnesium in cardiovascular diseases.* Cardiol Rev. 2014 Jul-Aug;22(4):182-92. doi: 10.1097/CRD.0000000000000003. PMID: 24896250.

35. Cunha AR, Umbelino B, Correia ML, Neves MF. *Magnesium and vascular changes in hypertension.* Int J Hypertens. 2012;2012:754250. doi: 10.1155/2012/754250. Epub 2012 Feb 29. PMID: 22518291; PMCID: PMC3299255.

36. Sontia B, Touyz RM. *Role of magnesium in hypertension.* Arch Biochem Biophys. 2007 Feb 1;458(1):33-9. doi: 10.1016/j.abb.2006.05.005. Epub 2006 May 24. PMID: 16762312.

37. Laurant P, Dalle M, Berthelot A, Rayssiguier Y. *Time-course of the change in blood pressure level in magnesium-deficient* Wistar rats. Br J Nutr. 1999 Sep;82(3):243-51. PMID: 10655971.

38. James MF, Beer RE, Esser JD. *Intravenous magnesium sulfate inhibits catecholamine release associated with tracheal intubation.* Anesth Analg. 1989 Jun;68(6):772-6. PMID: 2735543.

39. Douglas WW, Rubin RP. *The mechanism of catecholamine release from the adrenal medulla and the role of calcium in stimulus-secretion coupling*. J Physiol. 1963 Jul;167(2):288-310. doi: 10.1113/jphysiol.1963.sp007150. PMID: 16992152; PMCID: PMC1359395.

40. Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, Hutchinson RG, Metcalf PA. *Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness:* the ARIC study. Atherosclerosis Risk in Communities

41. Torshin IIu, Gromova OA, Gusev EI. *Mechanisms of antistress and antidepressive effects of magnesium and pyridoxine*. Zh Nevrol Psikhiatr Im S S Korsakova. 2009;109(11):107-11. Russian. PMID: 20120072.

42. Kim DJ, Xun P, Liu K, Loria C, Yokota K, Jacobs DR Jr, He K. *Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes*. Diabetes Care. 2010 Dec;33(12):2604-10. doi: 10.2337/dc10-0994. Epub 2010 Aug 31. PMID: 20807870; PMCID: PMC2992198.

43. Heagerty AM, Aalkjaer C, Bund SJ, Korsgaard N, Mulvany MJ. *Small artery structure in hypertension. Dual processes of remodeling and growth. Hypertension.* 1993 Apr;21(4):391-7. doi: 10.1161/01.hyp.21.4.391. PMID: 8458640.

44. Pochwat B, Szewczyk B, Sowa-Kucma M, Siwek A, Doboszewska U, Piekoszewski W, Gruca P, Papp M, Nowak G. *Antidepressant-like activity of magnesium in the chronic mild stress model in rats: alterations in the NMDA receptor subunits*. Int J Neuropsychopharmacol. 2014 Mar;17(3):393-405. doi: 10.1017/S1461145713001089. Epub 2013 Sep 26. PMID: 24067405.

45. Agyei B, Nicolaou M, Boateng L, Dijkshoorn H, van den Born BJ, Agyemang C. *Relationship between psychosocial stress and hypertension among Ghanaians in Amsterdam, the Netherlands--the GHAIA study*. BMC Public Health. 2014 Jul 7;14:692. doi: 10.1186/1471-2458-14-692. PMID: 25001592; PMCID: PMC4099212.

46. Torshin I.Y., Gromova O.A. *Connective tissue dysplasia, cell biology and molecular mechanisms of magnesium exposure.* RMZh. 2008;16:230–238.

47. Hruby A, O'Donnell CJ, Jacques PF, Meigs JB, Hoffmann U, McKeown NM. *Magnesium intake is inversely associated with coronary artery calcification: the Framingham Heart Study*. JACC

Cardiovasc Imaging. 2014 Jan;7(1):59-69. doi: 10.1016/j.jcmg.2013.10.006. Epub 2013 Nov 27. PMID: 24290571; PMCID: PMC3957229.

48. Kalra SS, Shanahan CM. *Vascular calcification and hypertension: cause and effect.* Ann Med. 2012 Jun;44 Suppl 1:S85-92. doi: 10.3109/07853890.2012.660498. PMID: 22713153.