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# MAGNESIUM, "THE UNSUNG HERO"


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**ABSTRACT** Magnesium participates in more than 600 enzymatic reactions in the body. Its role in the treatment of cardiac arrhythmias and pre-eclampsia is already well established. Magnesium`s role in preventive medicine is not very well described in medicine literature. We have carefully studied the pathophysiology of magnesium and explained its role in hypertension, chronic kidney disease, vascular calcification, metabolic syndrome and mortality from cardiovascular disease. Through this article we hope to add to the existing knowledge of magnesium metabolism, its role in cardiovascular pathology and potential benefits of magnesium supplements on health.

**KEYWORDS :** Magnesium, physiology, hypertension, vascular calcification, cardiovascular morbidity, pain, dementia.

## INTRODUCTION:

Magnesium is the most abundant mineral in the earth`s crust and has been recognized since ancient times. It has been in use in the form of Epsom salts for treating abdominal pain, muscle strains and cerebral edema since the 16th century. We now know that magnesium is also the second most abundant intracellular cation in the human body and plays a cofactor for more than 300 enzymatic reactions vital to metabolic pathway[i] Its importance in treatment of pre-eclampsia and cardiac arrhythmias is already well established. However, this divalent cation has received little attention when it comes to the preventive medicine and overall well-being. In this review we discuss the role of magnesium at the molecular level and its impact of subclinical magnesium deficit on human health. We have conducted a thorough literature review and selected the articles with statistically significant results and impacting information.

**Defining magnesium deficit:** In common clinical practice a magnesium deficiency is defined as a serum magnesium level of 0.8 mmol/L [ii]. But magnesium is primarily an intracellular cation, and extracellular magnesium levels do not always correlate with magnesium deficiency. Various studies have shown a depleted magnesium levels in erythrocytes, myocytes and body fluids including CSF, while measuring normal serum concentrations [iii]. Chronic low intake of magnesium in the diet can result in the subclinical magnesium deficit [iv].

**Prevalence of subclinical magnesium deficit:** Since serum magnesium measurements don't effectively co-relate with total magnesium deficit, true prevalence of hypomagnesemia is derived from nutritional surveys. During the last century, with increased consumption of processed foods, dietary magnesium intake in US and Europe has declined from 500 mg/day to 175-200 mg/day. Dietary surveys reveal that the average daily requirement for magnesium is not met in Europe and US[v]. In addition to this, an alarming trend of increased cardiovascular disease, metabolic disorders and hypertension were associated with dietary deficits of magnesium in both adolescent and adult population [v] . Increased medicinal use of proton pump inhibitors and diuretics is associated with an inverse relationship to the total body stores of magnesium and contribute to increased prevalence of magnesium deficit [vi,vii].

**Magnesium Balance in the body:** The main source of magnesium for humans is diet. Daily recommended intake of magnesium is recommended to be 350-400 milligrams a day[ii].

Magnesium is absorbed in the small and large bowel via 2 pathways. Passive absorption via paracellular movement of magnesium down a concentration gradient and active absorption via cell membrane proteins, identified as transient receptor potential melastatins (TRPM) 6 and 7[viii]. On average, approximately 30% of dietary magnesium is absorbed into the bloodstream, although this percentage can increase to nearly 80% in times of dietary magnesium restriction. 60% of the absorbed magnesium gets stored in the bones at the surface of hydroxyapatite crystals. Kidney forms the next regulator of the circulating free magnesium ions and reabsorb 95% of the filtered magnesium ions. 20%-30% reabsorption occurs at proximal convoluted tubule(PCT), 65% at loop of Henle mainly at thick ascending limb [ix]. Only 10% of the filtered magnesium is delivered to distal convoluted tubule where only a fraction of filtered magnesium is reabsorbed [ix].
*(Refer to the table1)*

**Table 1:** TRPM6, transient receptor potential melastatin 6 (*TRPM6*); NKCC2, sodium–potassium·chloride transporter 2 (*SLC12A1*); ROMK, renal outer·medullary potassium channel (*KCNJ1*), ClC·Kb, chloride channel Kb (*CLCNKB*); CaSR, calcium·sensing receptor (*CASR*); Kv1.1, potassium voltage·gated channel subfamily A member 1 (*KCNA1*); Kir4.1/Kir5.1, inward rectifier·type potassium channel 4.1/5.1 (*KCNJ10/KCNJ16*); NCCT, sodium·chloride symporter (*SLC12A3*); FXYD2, sodium·potassium ATPase subunit gamma (*FXYD2*); HNF1B, hepatocyte nuclear factor·1 beta (*HNF1B*); EGF, epidermal growth factor (*EGF*); PCBD1, pterin·4·alpha·carbinolamine dehydratase 1(*PCBD1*); claudin·16 (*CLDN16*); claudin·19 (*CLDN19*); cyclin M2 (*CNNM2*).*Taken by permission. BL.*

| Hypomagnesemia | Mechanism | Potential etiologies |
|---|---|---|
| ***(Gastrointestinal)*** Passive absorption (small intestine) | Decreased electrochemical gradient and bulk transport | Low dietary magnesium intake, short·gut syndrome, proton pump inhibitors |
| Active absorption (large intestine) | Impaired transporter function | TRPM6 protein defects |
| ***(Renal)*** Glomerular filtration | Hyperfiltration leading to overwhelming of renal magnesium reabsorption capacity | Diabetes mellitus, acute tubular necrosis diuresis, excessive volume expansion |

| | | |
|---|---|---|
| Proximal tubular reabsorption | Nephron cellular injury impairing passive reabsorption | Fanconi's syndrome, drug toxicity (aminoglycosides, cisplatin) |
| Thick ascending limb of Loop of Henle | Acquired or inherited impaired transporter function | Claudin-16, Claudin-19, NKCC2, ROMK, ClC-Kb, or CaSR protein defects |
| Distal convoluted tubule | Acquired or inherited impaired transporter function | TRPM6, Kv1.1, Kir4.1/Kir5.1, NCCT, FXYD2, HNF1B, PCBD1, EGF, CaSR, or Cyclin M2 protein defects |

**Physiological function of magnesium:**
Magnesium serves as a cofactor for more than 300 enzyme reactions in a body. Magnesium is a key element determining the excitability of the muscles , endothelial cells and neurons. It not only impacts the endocrine function with its influence on Parathyroid hormone(PTH), insulin, aldosterone levels but also through its direct impact on calcium exchange between the intracellular and extracellular space, hydroxyapatite deposition and calcium phosphate crystallization. Hence a magnesium deficit can directly or indirectly impact multiple organ systems in the body.

**Magnesium`s role in Hypertension:** It has already been well established that a low potassium diet or chronic hypokalemia is associated with development of hypertension. This principal form the basis of low Na/K ratio(sodium potassium ratio) in the DASH diet as an effective life-style modification in hypertensive patients. Magnesium serves as the main co factor in the magnesium dependent ATP channel and ensures proper functioning of the Na/K pump[x]. A low magnesium state causes inhibition of the Na/k pump affecting the intracellular Na/K ratio and membrane potential of the aorta and cardiac muscle. [xi].Intracellular magnesium deficiency may also cause an increase in intracellular sodium and calcium, which predisposes to arterial vasospasm, increased catecholamine release, increased fatty acids and lipids, as well as intravascular hypercoagulability. [xii]

Animal experiments have shown a reduced production of Aldosterone, Angiotensin ii and increased production of atrial natriuretic peptide(ANP) with magnesium infusion. It is notable that the suppression of aldosterone by magnesium can occur independent of its effect on potassium[xiii,xiv]. In addition, magnesium deficit causes increased calcium influx leading to excitability of the cell, muscle, neuron and vasoconstriction. The elevated intracellular calcium can also cause indirect increase in release of aldosterone in hypertensive patients [xv,xvi]

**Vascular calcification and Atherosclerosis:** Hydroxyapatite, also known as mature form of amorphous calcium phosphate (ACP) is the most reviewed compound in pathology of vascular calcification. In patients prone to vascular calcification, phosphorus ions combine with calcium ion to form ACP crystal which further matures into hydroxyapatite after meeting extracellular ATP. The nidus of the ACP crystals acts a Randall plaque and initiates a process of successive rounds of mineral deposition[xvii] . The maturation of ACP crystals in the matrix cause metastatic calcification in the blood vessels and tissues. Magnesium slows down progression of vascular calcification by relegating the production as well as maturation of ACP. The formation of amorphous calcium phosphate depends on the levels of Phosphorus, PTH( parathyroid hormone) and FGF23( fibroblast growth factor 23) in the body [xviii] . Magnesium ions bind very strongly with the phosphorus ions in the intestine hence preventing excessive circulating levels of ionized phosphorus and reducing the formation of amorphous ACP crystals. Furthermore, magnesium shields the ACP surface from extracellular ATP preventing its breakdown and enhancing the formation of pyrophosphate which inhibits hydroxyapatite formation[xix].

Low magnesium and high phosphorus levels in the body can induce a vascular muscle cell trans-differentiation by increasing the gene expression of Runt Related Transcription Factor 2 (RUNX2) and Bone Morphogenic Protein 2( BMP2) [xx] . This transformed vascular smooth muscle cell(VSMC) has low contractility and is prone to deposition of ACP in the matrix.[xxi] Magnesium not only inhibits the vessel wall transdifferentiating by reducing osteoblastic gene expression but also causes increases production of prostaglandin I2 and nitric oxide in individual endothelial cells [xxii] . These beneficial effects of magnesium are studied in many randomized control trials which concluded a positive impact of magnesium supplementation on hypertension, atherosclerosis and cardiovascular morbidity [xxiii].

**Chronic kidney Disease :** The benefits of magnesium also extend to the chronic kidney disease. Vascular calcification (VC) is prevalent in patients suffering from chronic kidney disease. Factors promoting calcification include abnormalities in mineral metabolism, particularly high phosphate levels. Magnesium plays a very important role in a normal mineral metabolism. A subclinical magnesium deficiency presents with increased phosphorus levels, PTH levels and FGF23 levels in the vitro and nurtures a pernicious environment for accelerated atherosclerosis, cardiac dysrhythmias and chronic myocardial ischemia [xxiv,xxv] . In addition, magnesium antagonizes phosphate-induced apoptosis of vascular smooth muscle cells and prevents vascular calcification [xxvi] . In vitro studies done by Sakaguchi et al. also showed a protective effect of magnesium against phosphate induced kidney injury and phosphate toxicity. The same experiment also showed that a low magnesium medium increased apoptosis and expression levels of profibrotic and proinflammatory cytokines [xxvii].

Indirect evidence gathered from use of magnesium carbonate as phosphate binders in CKD patients show an added benefit of decline in progression of atherosclerosis and vascular calcification. The same effect was seen with sevelamer, which partly works by reducing phosphorus absorption and increasing serum magnesium levels in the process[xxviii] . The positive impact of magnesium on vascular calcification and progression of atherosclerosis is true in all stages of CKD including patients on maintenance hemodialysis as well as after renal transplantation.
*(Refer to Table 2)*

**Metabolic Syndrome:** Metabolic syndrome is a syndrome of abnormal metabolism of carbohydrates and fats. Magnesium is required for proper functioning of both metabolic pathways. The insulin producing beta cells are electrically excitable. These cells require a stimulation from change in cellular membrane potential to sense the variation in blood glucose and cause insulin secretion. The process of insulin secretion in response to blood glucose levels depends on the generation of magnesium dependent ATP, activation of magnesium dependent Glucokinase and production of Glucose 6 Phosphate. The resulting influx of calcium ion cause depolarization of the membrane and insulin release[xxix]. A chronic magnesium deficit impairs this mechanism and cause a disruption in the coupling of glucose levels in blood and subsequent insulin release. Intracellular $Mg^{2+}$ concentration is also critical for the phosphorylation of insulin receptors and the activity of other signal kinases. A magnesium deficit causes an abnormal signaling from the insulin receptors and

kinases and reduce insulin sensitivity. This theory was also investigated in a clinical study conducted by Milagros G. Huerta, where a direct relationship was derived between magnesium deficiency and insulin resistance in obese children [xxx]. Another study that followed was done by Martha Rodríguez-Morán which concluded an improvement in insulin sensitivity and metabolic control with magnesium supplementation in type 2 Diabetes Mellitus [xxxi].

Similarly, magnesium is necessary for proper functioning of Lecithin Cholesterol Acyltransferase (LCAT) and Lipoprotein Lipase (LPL), which lowers triglyceride levels and raises HDL-cholesterol levels. Magnesium dependent ATP is also the controlling factor for the rate-limiting enzyme in the cholesterol biosynthesis which if impaired causes elevated cholesterol levels [xxxii,xxxiii] . Many clinical studies have shown an inverse relationship of magnesium with incidence of diabetes and metabolic syndrome in both men and women.
*(Refer to table 3)*

**Bone health:** Magnesium influences bone health by playing a key role in normal functioning of Parathyroid hormone (PTH), phosphorus levels as well as mineralization of the bone. On the basis of experimental and epidemiological studies, both low and high magnesium have harmful effects on the bones [xxxiv].

While calcium and vitamin D have been the master focus of nutritional prevention of osteoporosis, a significant association has been found between bone density and the intake of Mg [xxxv].

Magnesium deficiency contributes to osteoporosis directly by forming impaired hydroxyapatite crystals, increasing osteoclastic activity on bone cells and indirectly by impacting Parathyroid levels and promoting low grade inflammation. Chronic low Mg intake also retards cartilage and bone differentiation as well as matrix calcification[xxxvi].

Magnesium acts as a co factor for PTH hormone synthesis and release, and its deficiency causes both reduced release as well as PTH resistance in vivo[xxxvii]. The 25-hydroxycholecalciferol-1-hydroxylase enzyme also requires Mg for conversion of inactive vitamin D 25 to active vitamin d 1,25 in kidneys[xxxviii]. A resulting abnormal vitamin D and PTH homeostasis impacts bone in a negative way. Bone differentiation continues to happen in a magnesium deficit environment but there is a delay in the onset of mineralization, bone remodeling and also an impairment in the bone marrow differentiation. In addition, a low magnesium state can cause delay in fracture healing
*(Refer to Table 4)*

**Neuroprotection:** Magnesium plays an essential role in nerve transmission and neuromuscular conduction. It also functions in a protective role against excessive excitation that can lead to neuronal cell death (excitotoxicity). It has been implicated in many neurological disorders and has gained an immense interest in multiple research studies. Glutamate is the most abundant excitatory neurotransmitter. NMDA receptor is a specific type of glutamate receptor and plays vital role in synaptic plasticity and memory function. One of the main functions of magnesium, is its interaction with NMDA receptor serving as a blockade to calcium influx in the NMDA receptor. Magnesium is the key ion required for the suppression of glutamatergic neuronal excitation especially NMDA receptors[xxxix]. Low magnesium potentiates glutamatergic neurotransmission, leading to excitotoxicity, which accentuates oxidative stress and neuronal cell death.

Abnormal glutamatergic neurotransmission has been implicated in many neurological and psychiatric disorders including migraine, chronic pain, epilepsy, Alzheimer's, Parkinson's, and stroke. Depression and anxiety are common comorbidities in most of the neurological disorders [xl]. Magnesium participates in several physiological processes in the psycho-neuro-endocrine system and modulates the hypothalamic pituitary adrenal (HPA) axis, along with blocking the calcium influx of NMDA glutamatergic receptors, all of which help prevent feelings of stress and anxiety [xli,xlii,xliii]

Pathophysiology behind protective effect of magnesium after a brain injury both traumatic and ischemic.

1. Preventing Excitotoxicity : Magnesium is a key metabolic factor in noncompetitive blockage of NMDA receptor. Thus, it prevents excess calcium influx and preventing excitotoxicity.
2. Mitochondrial function: Oxidative stress directly contributes to mitochondrial dysfunction, promoting the release of cytochrome c, which triggers an apoptotic cascade. Mitochondria have also been implicated in glutamate-mediated excitotoxicity, by participating in the release of glutamate, $Ca^{2+}$ sequestration and the generation of reactive oxygen species (ROS) [xliv]. Magnesium regulates mitochondrial membrane permeability and reduce the mitochondrial dysfunction.
3. Neuroinflammation: Hypomagnesemia in CNS injury can stimulate substance P production which plays a potential role in neuroinflammation. Substance P stimulates the release of histamine and serotonin (5HT) from mast cells, which can compromise the blood-brain barrier (BBB). Magnesium deficit stimulates immune cells to release pro-inflammatory cytokines, including TNF-$\alpha$ and potentiates $Ca^{2+}$ influx by stimulating NMDA receptors. [xlv]
4. TRPM7 channels: (transient receptor potential ion channel.sub family M7)TRPM7 is one of the few mammalian Magnesium transporters described to date, playing an important role in regulating $Mg^{2+}$ entry into cells. Activation of TRPM7 during ischemia has been proposed as a key factor contributing to excitotoxicity and other deleterious processes. A decline in intracellular $Mg^{2+}$ concentration, can lead to the generation of reactive oxygen and nitrogen species, which could further activate TRPM7, thereby exacerbating oxidative stress and cell death pathways[xlvi]

Molecular studies and animal studies have shown neuronal protection from pre-treatment with magnesium, making this mineral of intense interest for its potential neuroprotective role in humans. Large sized randomized control trials are still lacking but multiple small studies and metanalysis show a promising role of magnesium in neuroprotection.
*(Refer to tables 5-9)*

## CONCLUSIONS:

Magnesium seems to have a very important role in maintain normal physiological function and overall wellbeing. Dietary magnesium deficiency in modern world has been linked to multiple medical problems. Magnesium`s benefit and adverse effects in both primary and secondary prophylaxis for cardiovascular disease and neurological disease has been studied extensively both in experimental models as well as human trials. Current available data in literature supports a benefit of daily magnesium supplement or a magnesium rich diet for maintenance of good cardiovascular, neurological, bone health. However due to lack of a consistent dose of magnesium supplements used across all studies, it is difficult to recommend a fixed daily dose for prescription of magnesium supplements. Also, little is known if a certain composition of magnesium is better than the other. A reassuring fact is that so far, none of the studies reported any side effects at doses ranging from 200 mg to 400 mg once a day supplementation of oral magnesium. In our opinion patients should be counselled about taking a magnesium rich diet in addition to low sodium high potassium diet to prevent

cardiovascular disease and maintaining bone health. In addition, a daily oral supplement of magnesium 200- 400 mg once a day can be considered in patients who endorse poor dietary intake of magnesium and suffer from metabolic syndrome or cardiovascular diseases.

***Abbreviations :*** *ECF- extracellular fluid; ACP- amorphous calcium phosphate, RUNX2: runt related transcription factor 2, BMP2: bone morphogenic protein 2,* PTH parathyroid hormone, FGF23: fibroblast growth factor 23, *DASH- Dietary Approaches to Stop Hypertension, ANP: atrial natriuretic peptide, LCA: lecithin cholesterol acyltransferase, LPL: lipoprotein lipase, reactive oxygen species (ROS), TRPM 6receptors(transient receptor potential ion channel sub family M6 TRPM7receptors:*transient receptor potential ion channel.*sub family M7;PCT : proximal convoluted tubule, DCT: distal convoluted tubule; VSMC: vascular smooth muscle cell*

**Table2 : Studies showing association of magnesium with vascular stiffness, hypertension and cardiac mortality.**

| AUTHORS | SAMPLE SIZE | TYPE OF STUDY | RESULTS |
|---|---|---|---|
| Kieboom et al. 2016 J Am Heart Assoc. 2016 Jan 22;5(1):e002707. Serum Magnesium and the Risk of Death from Coronary Heart Disease and Sudden Cardiac Death.. | n= 9882 f/u 8. Years | prospective cohort study | increased risk of CHD mortality hazard ratio: 1.36, 95% CI 1.09-1.69) SCD hazard ratio: 1.54, 95% CI (1.12-2.11) accelerated subclinical atherosclerosis and increased carotid intima-media thickness: +0.013 mm, 95% CI 0.005-0.020) |
| Sakaguchi Y et al. Association between Density of Coronary Artery Calcification and Serum Magnesium Levels among Patients with Chronic Kidney Disease *PLoS One*. 2016;11(9):e0163673. Published 2016 Sep 23. doi:10.1371/journal.pone.0163673 | 109 CKD | Randomized controlled trial | CAC density was inversely associated with serum magnesium levels, particularly in patients with higher serum phosphate levels. |
| Turgut F, Kanbay M, Metin MR, Uz E, Akcay A, Covic A. Magnesium supplementation helps to improve carotid intima media thickness in patients on hemodialysis. Int Urol Nephrol. 2008;40(4):1075-82. doi: 10.1007/s11255-008-9410-3. Epub 2008 Jun 21. PMID: 18568412. | N=47 HD patients | Randomized controlled trial | Serum parathyroid significantly decreased with magnesium replacements p=0.003 Bilateral carotid IMT was significantly improved in patients treated with magnesium citrate compared to initial values p=0.002 for right and p =0.001 for left carotid |
| Tzanakis I, Virvidakis K, Tsomi A, Mantakas E, Girousis N, Karefyllakis N, Papadaki A, Kallivretakis N, Mountokalakis Intra- and extracellular magnesium levels and atheromatosis in hemodialysis patients. Magnes Res. 2004 Jun;17(2):102-8. PMID: 15319142. | N=93 HD | Prospective cohort | A strong negative association of both extracellular and intracellular magnesium with common carotid intima-media thickness exists in haemodialysis patients, p=0.001 |
| Zhang X, Li Y, Del Gobbo LC, Rosanoff A, Wang J, Zhang W, Song Y. -. Hypertension. 2016 Aug;68(2):324-33. doi: Effects of Magnesium Supplementation on Blood Pressure:10.1161/HYPERTENSIONAHA.116.07664. Epub 2016 Jul 11. PMID: 27402922. | N=2028 | Meta-analysis of RCT trials | Mg supplementation with a dose of 300 mg/d or duration of 1 month is sufficient to elevate serum Mg and reduce BP; and serum Mg was negatively associated with diastolic BP but not systolic BP (all P<0.05). |
| Kass L, Weekes J, Carpenter L. Effect of magnesium supplementation on blood pressure: a meta-analysis. Eur J Clin Nutr. 2012 Apr;66(4):411-8. doi: 10.1038/ejcn.2012.4. Epub 2012 Feb 8. PMID: 22318649. | 22 trials n=1173 | Metanalysis | Daily intake of magnesium 350 mg decreased SBP by 4- 5 mm hg |
| Han H, Fang X, Wei X, et al. Dose-response relationship between dietary magnesium intake, serum magnesium concentration and risk of hypertension: a systematic review and meta-analysis of prospective cohort studies. *Nutr J*. 2017;16(1):26. Published 2017 May 5. doi:10.1186/s12937-017-0247-4 | 10 cohort studies N = 180,566 | systematic review and meta-analysis of prospective cohort studies. | inverse dose-response relationship between dietary magnesium intake and the risk of hypertension. 100 mg/day increment in magnesium intake was associated with a 5% reduction in the risk of hypertension (RR = 0.95; 95% CI: 0.90, 1.00). The association of serum magnesium concentration with the risk of hypertension was marginally significant (RR = 0.91; 95% CI: 0.80, 1.02). |
| Tin A, Grams ME, Maruthur NM, Astor BC, Couper D, Mosley TH, Selvin E, Coresh J, Kao WH. Results from the Atherosclerosis Risk in Communities study suggest that low serum magnesium is associated with incident kidney disease. Kidney Int. 2015 Apr;87(4):820-7. doi: 10.1038/ki.2014.331. Epub 2014 Oct 1. PMID: 25272232; PMCID: PMC4382401. | N= 13226 | Observational study | + Dose response relationship between serum mag levels and progression of CKD and ESRD independent association. |

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| Joosten MM, Gansevoort RT, Bakker SJ; PREVEND Study Group. Low plasma magnesium and risk of developing chronic kidney disease: results from the PREVEND Study. Kidney Int. 2015 Jun;87(6):1262-3. doi: 10.1038/ki.2015.33. PMID: 26024037. | N=5113 | Prospective cohort study | Independent association of Hypomagnesemia and incidence of CKD even after adjusted for albuminuria |
| Sakaguchi Y, Shoji T, Hayashi T, Suzuki A, Shimizu M, Mitsumoto K, Kawabata H, Niihata K, Okada N, Isaka Y, Rakugi H, Tsubakihara Y. Hypomagnesemia in type 2 diabetic nephropathy: a novel predictor of end-stage renal disease. Diabetes Care. 2012 Jul;35(7):1591-7. doi: 10.2337/dc12-0226. Epub 2012 Apr 12. PMID: 22498805; PMCID: PMC3379604. | N=455 | Retrospective cohort study | Hypomagnesemia in type 2 diabetic nephropathy predicts ESRD , increased incidence by 2-fold. |
| Sakaguchi Y, Fujii N, Shoji T, Hayashi T, Rakugi H, Iseki K, Tsubakihara Y, Isaka Y; PLoS One. 2014<br>Magnesium modifies the cardiovascular mortality risk associated with hyperphosphatemia in patients undergoing hemodialysis | N= 142,069 | Cohort study | Serum Mg levels significantly modified the mortality risk associated with hyperphosphatemia in patients undergoing hemodialysis. |
| Peacock JM, Ohira T, Post W, Sotoodehnia N, Rosamond W, Folsom AR.. *Am Heart J*. 2010;160(3):464-470. doi:10.1016/j.ahj.2010.06.012<br>Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study | N=14 232 | | Association of low serum magnesium with sudden cardiac dealth<br>0.78–0.8 (HR, 0.97; 95% CI, 0.71–1.33) |

**Table 3: Relationship of Magnesium and incidence of Diabetes Mellitus.**

| Study | Name of the study | Number of participants | Type of study | Results | Conclusion |
|---|---|---|---|---|---|
| Lopez-Ridaura R, Hu FB et al. Diabetes Care. 2004 Jan;27(1):134-40. doi: 10.2337/diacare.27.1.134. PMID: 14693979. | Magnesium intake and risk of type 2 diabetes in men and women | 85,060 women and 42,872 men | Prospective trial | (RR) of type 2 diabetes was 0.66 (95% CI 0.60-0.73; P for trend <0.001) in women and 0.67 (0.56-0.80) P<0.001) in men | significant inverse association between magnesium intake and diabetes risk |
| Ju SY, Choi WS, Ock SM, Kim CM, Kim DH. *Nutrients*. 2014;6(12):6005-6019. Published 2014 Dec 22. doi:10.3390/nu6126005 | Dietary Magnesium Intake and Metabolic Syndrome in the Adult Population: Dose-Response Meta-Analysis and Meta-Regression | 30,092 participants<br>10 observational studies<br>8 cross sectional studies | Meta-analysis | 12% reduction in the risk of metabolic syndrome for an increment in magnesium intake of 150 mg/day, RR, 0.88; 95% CI, 0.84–0.93 RR 0.9 95% CI in women. | lower levels of magnesium intake were associated with the risk of metabolic syndrome in observational studies, which is consistent with the results from an analysis using linear regression methods |
| Nizzal sarrafzadegan Salehi-Abargouei et al. Nutrition. 2016 Apr;32(4):409-17. doi: 10.1016/j.nut.2015.09.014. Epub 2015 Oct 23. PMID: 26919891. | Magnesium status and the metabolic syndrome: A systematic review and meta-analysis | 31 876 participants 9 articles | Meta-analysis | 0.73; 95% confidence interval: 0.62, 0.86; $P < 0.001$); | Inverse relationship to dietary magnesium consumption and metabolic syndrome |
| Rodríguez-Morán M, Guerrero-Romero F. Diabetes Care. 2003 Apr;26(4):1147-52. doi: 10.2337/diacare.26.4.1147. PMID: 12663588. | Oral Magnesium Supplementation Improves Insulin Sensitivity and Metabolic Control in Type 2 DM | 63 participants with low serum magnesium and DM2 | randomized double-blind controlled trial | HOMA-IR index (3.8 +/- 1.1 vs. 5.0 +/- 1.3, P = 0.005) HbA(1c) (8.0 +/- 2.4 vs. 10.1 +/- 3.3%, P = 0.04) than control | Oral supplementation with MgCl(2) = improves insulin sensitivity and metabolic control |
| Dong JY, Xun P, He K, Qin LQ. Magnesium intake and risk of type 2 diabetes*Diabetes Care*. 2011;34(9):2116-2122. doi:10.2337/dc11-0518 | Magnesium Intake and Risk of Type 2 Diabetes | 536,318 participants 13 studies | Meta-analysis of prospective cohort studies | 0.86 (95% CI 0.82–0.89) with evidence of heterogeneity among studies ($P$= 0.02, $I^2$ = 48.4%). | significant inverse relation between magnesium intake and risk of type 2 diabetes in dose-response manner |

**Table 4 :magnesium`s association with abnormal bone mineralization**

| Study | Sample size | Type of study | Results | conclusions |
|---|---|---|---|---|
| Tonya S Orchard, et al 2014 Magnesium intake, bone mineral density, and fractures: results from the Women's Health Initiative Am J Clin Nutr. 2014 Apr;99(4):926-33. doi: 10.3945/ajcn.113.067488. Epub 2014 Feb 5. PMID: 24500155; PMCID: PMC3953885. | 73,684 postmenopausal women | Observational Study | Baseline hip BMD was 3% higher ($P < 0.001$), and whole-body BMD was 2% higher ($P < 0.001$), in women who consumed >422.5 compared with <206.5 mg Mg/d. | Lower magnesium intake is associated with lower BMD of the hip and whole body, but this result does not translate into increased risk of fractures |
| Bo Yu, jinlei chang et al Chang J, Yu D, Ji J, Wang N, Yu S, Yu B. The Association Between the Concentration of Serum Magnesium and Postmenopausal Osteoporosis. *Front Med (Lausanne)*. 2020;7:381. Published 2020 Aug 4. doi:10.3389/fmed.2020.00381 2020 | 2,776 postmenopausal women 11 studies | Metanalysis | (SMD = −0.56, 95% CI = −1.02 to −0.09). The 16 sets of results showed a statistically significant heterogeneity ($I^2$ = 96.6%, $P <$ 0.001 | postmenopausal women with osteoporosis had a lower concentration of serum Mg than the healthy controls; |
| Kunutsor SK, Whitehouse MR, Blom AW, Laukkanen JA. Low serum magnesium levels are associated with increased risk of fractures: a long-term prospective cohort study. *Eur J Epidemiol*. 2017;32(7):593-603. doi:10.1007/s10654-017-0242-2 | 2245 men aged 42–61 years | a long-term prospective cohort study | Total fractures 0.80 (0.49–1.31) HR 95% CI. Femoral fractures: 0.93 (0.48–1.80) HR CI 95% | Low serum magnesium is independently associated with an increased risk of total and femoral fractures in middle-aged Caucasian men |

**Table 5: Studies showing relationship between Magnesium and Migraine prophylaxis and treatment:**

| Name of the study | Type of study | Authors | No. of participants/ studies | Results | Conclusion |
|---|---|---|---|---|---|
| Effects of intravenous and oral magnesium on reducing migraine. | Meta-analysis | Chiu HY, Yeh TH, Huang YC, Chen PY 2016 | 21 studies included. 11 studies on effect of IV magnesium. 10 studies on Oral magnesium. | Intravenous magnesium significantly relieved acute migraine within 15 - 45 minutes, 120 minutes, and 24 hours after the initial infusion (Odd ratios [ORs] = 0.23, 0.20, and 0.25, respectively). Oral magnesium significantly alleviated the frequency and intensity of migraine (ORs = 0.20 and 0.27). | Intravenous magnesium reduces acute migraine attacks within 15 - 45 minutes, 120 minutes, and 24 hours after the initial infusion and oral magnesium alleviates the frequency and intensity of migraine. |
| Intravenous caffeine citrate vs. magnesium sulfate for reducing pain in patients with acute migraine headache | prospective experimental study | Baratloo A, Mirbaha S, Kasmaei HD, Payandemehr P, Elmaraezy A, Negida A 2016 | 70 patients | Both IV caffeine citrate and IV magnesium sulfate reduced pain scores significantly, but the magnesium sulfate group showed more improvement than the Caffeine citrate group after one hour ($P < 0.001$) and after two hours ($P < 0.001$). | IV magnesium sulfate at a dose of 2 g might be superior to IV caffeine citrate 60 mg for the short-term management of migraine headache in emergency departments. |
| Magnesium in migraine prophylaxis—is there an evidence-based rationale? | Systematic review. | Von Luckner A, Riederer F | Five clinical trials published from 1990 to 2016 | One out of two Class I evidence trials showed a significant reduction of the number of migraine attacks compared with placebo, while two out of three Class III trials evinced a statistically significant reduction of the primary efficacy parameters compared with placebo. | Grade C (possibly effective) evidence for prevention of migraine with magnesium |
| Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura. | Randomized, double-blind, placebo-controlled study | Bigal ME, Bordini CA, Tepper SJ, Speciali JG 2002 | 60 patients | In the migraine with aura group patients receiving magnesium sulphate presented a statistically significant improvement of pain and of all associated symptoms compared with controls. The analgesic therapeutic gain was 36.7% and NNT was 5.98 at 1 hour. | Magnesium sulphate can be used for the treatment of all symptoms in migraine with aura, or as an adjuvant therapy for associated symptoms in patients with migraine without aura. |

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| Intravenous magnesium sulphate vs. metoclopramide in the management of acute migraine attacks in the Emergency Department | Randomized, double-blind, placebo-controlled study | Cete Y, Dora B, Ertan C, Ozdemir C, Oktay C 2005 | 113 patients | No difference in age, gender or baseline VAS scores between the groups (P > 0.05) | IV magnesium and metoclopramide are no more effective than placebo in the treatment of acute migraine attacks |
| Intravenous magnesium for acute benign headache in the emergency department | Randomized double-blind placebo-controlled trial | Frank LR, Olson CM, Shuler KB, Gharib SF 2004 | 44 patients | no statistically significant difference between groups for any secondary outcomes | No benefit to using IV magnesium to treat patients with acute benign headache who present to the ED. |

**Table 6 : Studies showing Magnesium role in Chronic Pain and Fibromyalgia:**

| Name of the study | Type of study | Authors | N=No. of participants | Results | Conclusion |
|---|---|---|---|---|---|
| Value of sequential intravenous and oral magnesium therapy in patients with chronic low back pain with a neuropathic component. PMID: 23384256. | Randomized controlled trial | Yousef AA, Al-deeb AE *[38]* 2013 | N= 80 | Statistically significant reduction in pain intensity throughout the 6-month follow-up period, with mean (SD) pre-treatment NRS values of 7.5 (2.2) compared with 4.7 (1.8) at 6 months. | Magnesium presents a viable treatment option for patients with refractory chronic back pain who have failed to respond to conventional treatment. |
| I.V. infusion of magnesium sulphate during spinal anesthesia improves postoperative analgesia. | Randomized controlled trial | Hwang JY, Na HS, Jeon YT, Ro YJ, Kim CS, Do SH [39]. 2010 | N=40 | Postoperative pain scores and cumulative postoperative PCA consumptions were significantly lower in Group M at 4, 24, and 48 h after surgery (P<0.05). | I.V. magnesium sulphate administration during spinal anesthesia improves postoperative analgesia. |
| Postoperative magnesium sulphate infusion reduces analgesic requirements in spinal anesthesia | Randomized controlled trial | Apan A, Buyukkocak U, Ozcan S, Sari E, Basar H [40] 2004 | N=50 | When compared to the control group, time to analgesic need was increased and total analgesic consumption was reduced in the magnesium group (meperidine consumption 60.0 +/- 73.1 mg control group, 31.8 +/- 30.7 mg magnesium group, P = 0.02). | Magnesium sulphate infusion may be used as an adjunct for reducing analgesic consumption after spinal anesthesia. |
| Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? | Clinical trial | Bagis S, Karabiber M, As I, Tamer L, Erdogan C, Atalay A [41] 2013 | N= 60 | Serum magnesium levels (P = 0.021) and erythrocyte magnesium levels (P = 0.000) were significantly lower in the fibromyalgia patients than in the control group. | The magnesium citrate treatment was only effective tender points and the intensity of fibromyalgia. However, it was effective on all parameters when used in combination with amitriptyline. |

**Table 7; Studies showing role of Magnesium in Anxiety and Depression:**

| Name of the study | Type of study | Authors | N=No. of participants studies | Results | Conclusion |
|---|---|---|---|---|---|
| Association between magnesium intake and depression and anxiety in community-dwelling adults | Prospective cohort | Jacka FN, Overland S, Stewart R, Tell GS, Bjelland I, Mykletun A [42] 2009 | 5708 participants | Inverse association between standardized energy-adjusted magnesium intake and standardized depression scores. statistically significant (β=−0.16, 95% confidence interval (CI)=−0.22 to −0.11). | Inverse association between standardized energy-adjusted magnesium intake and standardized depression scores. |

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| The effects of magnesium supplementation on subjective anxiety and stress | Systematic review | Boyle NB, Lawton C, Dye L<br><br>2017 | 8 studies reviewed. | Four/eight studies in anxious samples, four/seven studies in PMS samples, and one/two studies in hypertensive samples reported positive effects of Mg on subjective anxiety outcomes. Mg had no effect on postpartum anxiety. | Existing evidence is suggestive of a beneficial effect of Mg on subjective anxiety in anxiety vulnerable samples. |
| Nutritional and herbal supplements for anxiety and anxiety-related disorders | Systematic review | Lakhan SE, Vieira KF<br><br>2010 | 24 studies with 2619 participants | Of the randomized controlled trials reviewed, 71% (15 out of 21) showed a positive direction of evidence | Combination nutritional supplements containing lysine or magnesium has positive effect on decreasing anxiety and stress levels. |
| Dietary magnesium and calcium intake and risk of depression in the general population | Meta-analysis | Li B, Lv J, Wang W, Zhang D<br><br>2017 | 17 epidemiological studies | The pooled relative risks of depression were 0.81 (95% confidence interval = [0.70, 0.92]) for Mg.<br>Inverse relation also found when studies conducted in Asia (relative risk = 0.57; 95% confidence interval = [0.44, 0.74]) | Moderate Mg intake may be inversely associated with the risk of depression |
| Magnesium and depression | Systematic review | Derom ML, Sayón-Orea C, Martínez-Ortega JM, Martínez-González MA 2013 | 21 cross-sectional studies, 3 intervention trials, 1 prospective study, 1 case only study, and 1 case series study | A higher intake of dietary magnesium seems to be associated with lower depression symptoms though reverse causality cannot be excluded. The results assessing the association between blood and cerebrospinal fluid magnesium and depression are inconclusive. | Oral magnesium supplementation may prevent depression and might be used as an adjunctive therapy. |

**Table 8: Studies showing role of magnesium on Alzheimer's disease(AD)**

| Name of study | Type of study | Authors | No of participants /studies | Results | Conclusion |
|---|---|---|---|---|---|
| Magnesium status in Alzheimer's disease | Systematic review | Veronese N, Zurlo A, Solmi M, Luchini C, Trevisan C, Bano G, Manzato E, Sergi G, Rylander R 2015 | 13 studies | Significantly lower Mg in cerebrospinal fluid (2 studies; SMD = −0.35; $P$ = .02) and in hair (2 studies; SMD = −0.75; $P$ = .0001). No differences between AD and controls were evident for serum Mg. | AD seems to be associated with a lower Mg status when compared to controls. |
| Dietary mineral intake and risk of mild cognitive impairment | PATH through life project | Cherbuin N, Kumar R, Sachdev P, Anstey KJ 2014 | N =1406 | Higher magnesium intake was associated with a reduced risk of developing Mild cognitive impairment/disorders (MCI: HR 0.07, 95% confidence interval (CI) 0.01–0.56, $p$ = 0.013; MCD: HR 0.47, 95% CI 0.22–0.99, $p$ = 0.046) | dietary intake of minerals may contribute to vascular and Alzheimer's disease progression earlier in the disease process |
| Serum magnesium is associated with the risk of dementia | Prospective study | Kieboom BC, Licher S, Wolters FJ, Ikram MK, Hoorn EJ, Zietse R, Stricker BH, Ikram MA 2017 | N= 9,569 | Both low serum magnesium levels (≤0.79 mmol/L) and high serum magnesium levels (≥0.90 mmol/L) were associated with an increased risk of dementia (hazard ratio [HR] 1.32, 95% confidence interval [CI] 1.02–1.69, and HR 1.30, 95% CI 1.02–1.67, respectively). | Both low and high serum magnesium levels are associated with an increased risk of all-cause dementia |

**Table 9: Association of magnesium with risk of stroke**

| Name of the study | Type of study | Authors | No of participants/studies | Results | Conclusion |
|---|---|---|---|---|---|
| Serum magnesium concentrations and all-cause, cardiovascular, and cancer mortality among US adults | Prospective cohort | Zhang X, Xia J, Del Gobbo LC, Hruby A, Dai Q, Song Y | N=14,353 | Elevated risk for stroke mortality was observed among participants with serum Mg < 0.70 mmol/L (HR: 2.55, 95% CI: 1.18, 5.48). | Significant increase in stroke mortality rate in patients with low Mg levels. |

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| Dietary magnesium intake and the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality | Meta-analysis | Fang X, Wang K, Han D, He X, Wei J, Zhao L, Imam MU, Ping Z, Li Y, Xu Y, Min J, Wang F 2016 | 40 prospective cohort studies; N >1million | Incremental increase in magnesium intake was associated with 7% reduction in the risk of stroke (RR: 0.93; 95% CI, 0.89–0.97) | Increasing dietary magnesium intake is associated with a reduced risk of stroke |
| Dietary magnesium intake and risk of stroke | Meta-Analysis | Larsson S.C., Orsini N., Wolk A 2012 | 7 Prospective studies N=241378 | Increment of 100 mg Magnesium per day was associated with an 8% reduction in risk of total stroke (combined RR: 0.92; 95% CI: 0.88, 0.97) | Dietary magnesium intake is inversely associated with risk of stroke, specifically ischemic stroke. |
| Magnesium intake and incidence of stroke | Meta-analysis | Nie Z.-L., Wang Z.-M., Zhou B., Tang Z.-P., Wang S.-K 2013 | 8 studies N=304,551 | Highest magnesium intake and reduced risk of total stroke (summary RR: 0.89; 95% CI: 0.82, 0.97) significant inverse association between highest magnesium intake and the risk of ischemic stroke (summary RR: 0.88; 95% CI: 0.80, 0.98) | Higher magnesium intake is associated with reduced risk of total and ischemic stroke |
| Association between intakes of magnesium, potassium, and calcium and risk of stroke | Meta-analysis | Adebamowo S.N., Spiegelman D., Willett W.C., Rexrode K.M 2015 | 86,149 women in the NHS I 94,715 women in the NHS II | Combined RR of total stroke was 0.87 (95% CI: 0.83, 0.92) for a 100-mg/d increase in magnesium intake, 0.91 (95% CI: 0.88, 0.94) for a 1000-mg/d increase in potassium intake, and 0.98 (95% CI: 0.94, 1.02) for a 300-mg/d increase in calcium intake. | High intakes of magnesium and potassium but not calcium was also significantly associated with reduced risk of stroke in women. |
| Intake of potassium- and magnesium-enriched salt improves functional outcome after stroke | Randomized controlled trial | Pan WH, Lai YH, Yeh WT, Chen JR, Jeng JS, Bai CH, Lin RT, Lee TH, Chang KC, Lin HJ, Hsiao CF 2017 | 291 participants | The K/Mg salt group had a significantly increased OR (2.25; 95% CI: 1.09, 4.67) of achieving good neurologic performance compared with the Na salt group. But the effect of K salt alone (OR: 1.58; 95% CI: 0.77, 3.22) was not significant | Providing the Dietary recommended intake (DRI) amount of magnesium and potassium together long term is beneficial for stroke patient recovery from neurologic deficits. |
| Plasma magnesium and risk of ischemic stroke among women. | Retrospective case-control analysis | Adebamowo SN, Jiménez MC, Chiuve SE, Spiegelman D, Willett WC, Rexrode KM 2014 | 32,826 participants | Women with magnesium levels<0.82 mmol/L had significantly greater risk of total ischemic stroke (multivariable relative risk, 1.57; 95% confidence interval, 1.09-2.27; P=0.01) and thrombotic stroke (multivariable relative risk, 1.66; 95% confidence interval, 1.03-2.65; P=0.03) compared with women with magnesium levels≥0.82 mmol/L. | Lower plasma magnesium levels may contribute to higher risk of ischemic stroke among women. |

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