The Effect Of Magnesium On Hypertension And Kidney Transplant Patients

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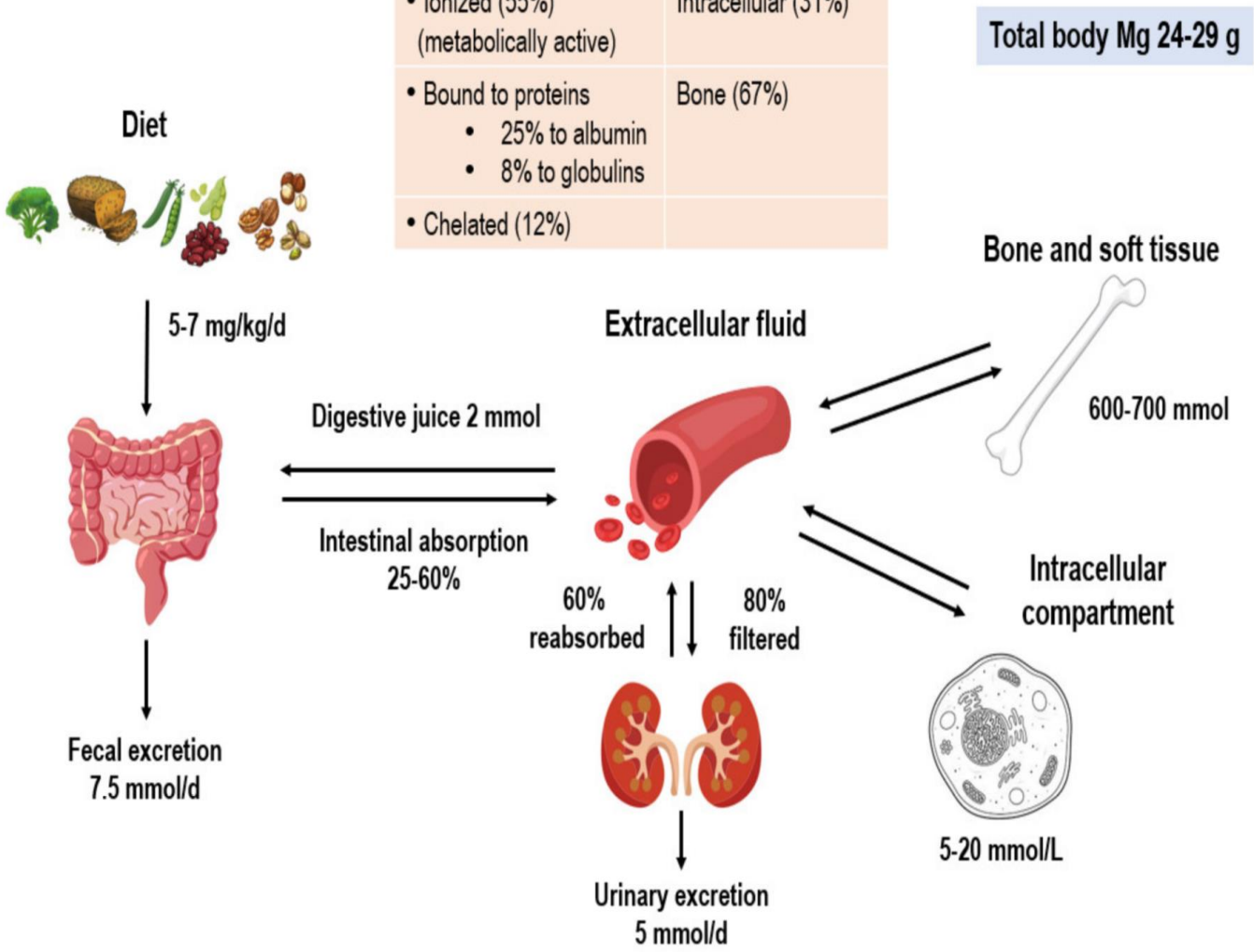
Introduction

- Magnesium (Mg) is the fourth cation of the body and the second most prevalent intracellular cation.
- Approximately half of total body Mg is located in bone, the remainder being contained in skeletal muscles and soft tissues.

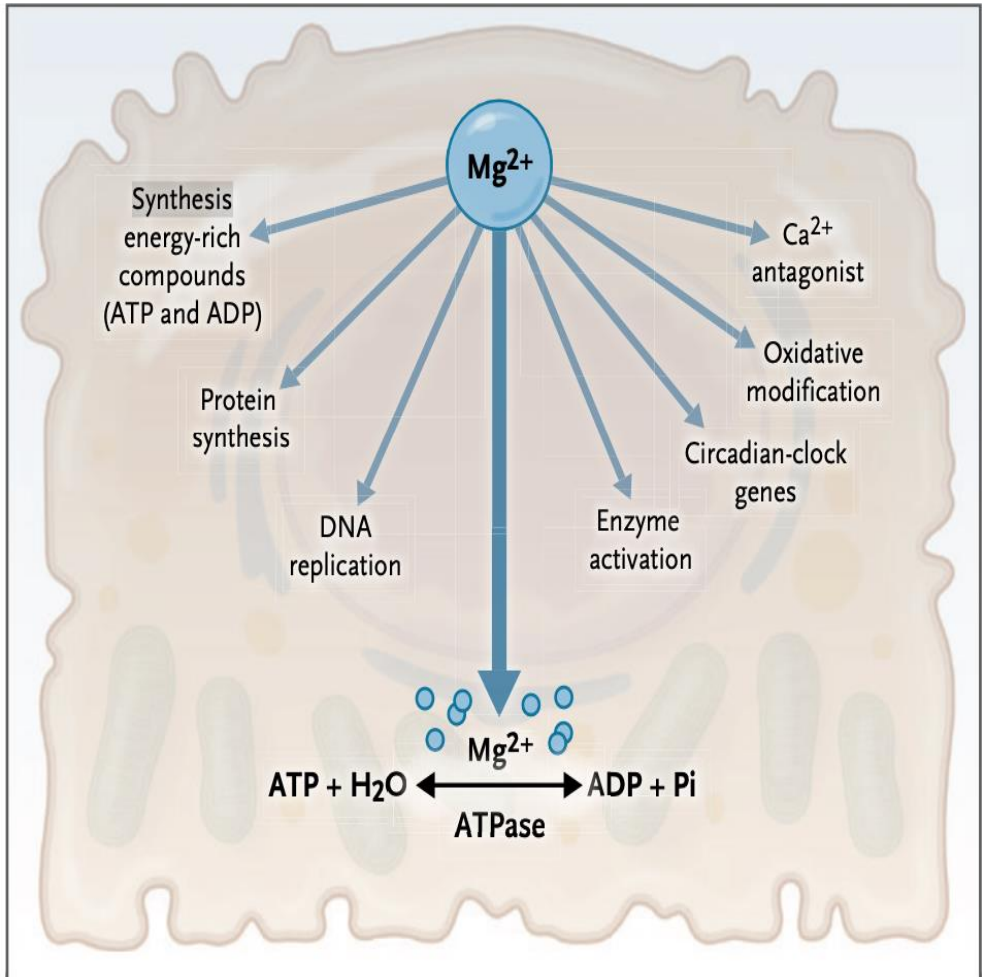
Distribution of magnesium in the body.

Extracellular (2%)	Intracellular (98%)
• Ionized (55%) (metabolically active)	Intracellular (31%)
• Bound to proteins • 25% to albumin • 8% to globulins	Bone (67%)
• Chelated (12%)	



Magnesium and the Hallmarks of Aging,2024

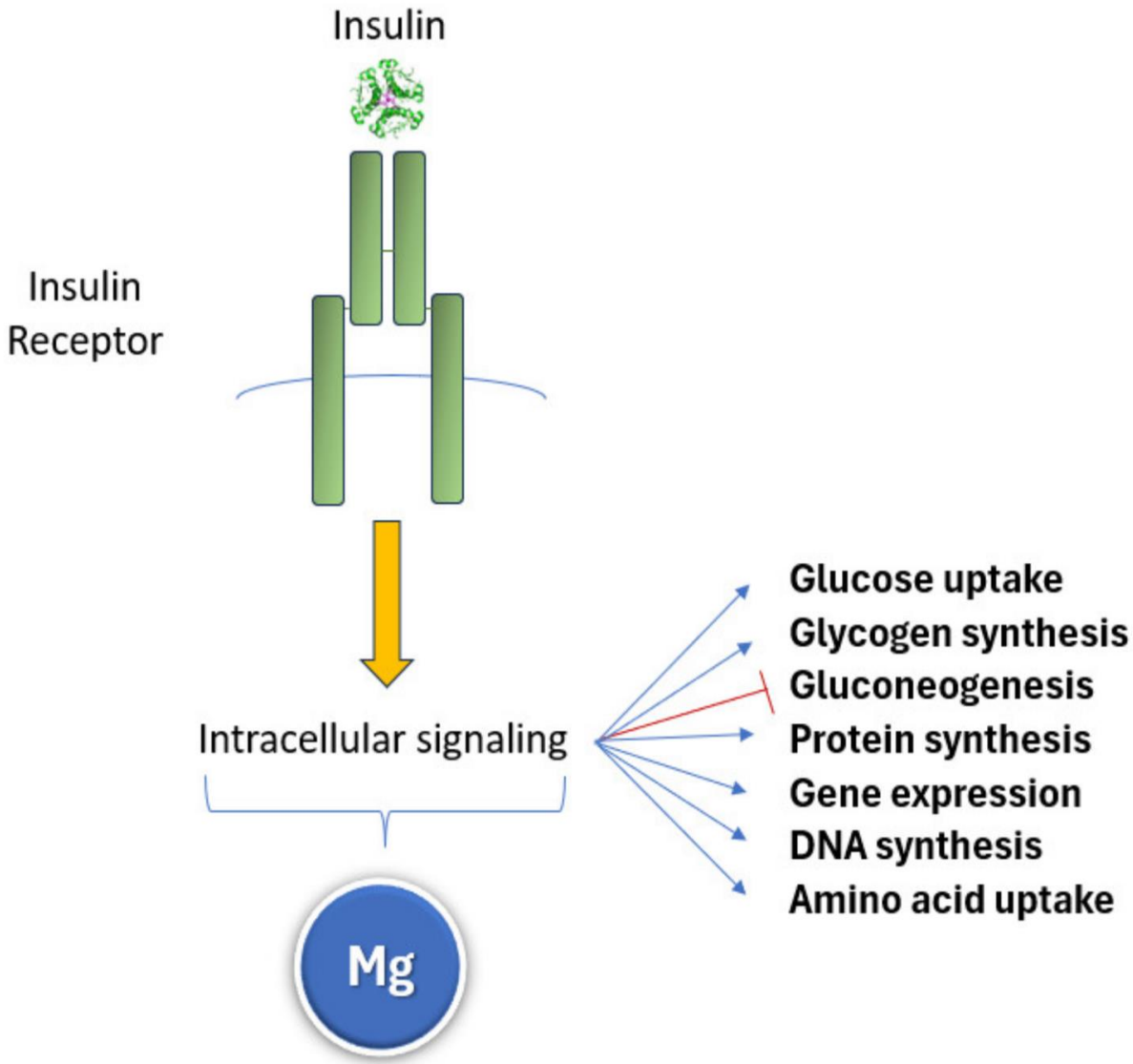
- Magnesium (Mg) is an essential mineral in the human body, which acts as a co-factor in more than 300 enzymatic reactions. Mg plays an important role in energy production, oxidative phosphorylation, glycolysis and nucleic acid synthesis.
- All ATPase reactions require Mg2+–ATP, including those involved in RNA and DNA bio-logic functions.
- Magnesium influences circadian-clock genes, which control circadian rhythm in biologic systems.



- Mg also interacts with other ions (such as potassium and calcium) which maintains nerve impulse conduction, cardiac electrical properties and muscle contraction .

- Thus, Mg is indicated in the physiological function of the heart, brain and skeletal muscle.

Magnesium influences all insulin signaling intracellular pathways as a cofactor of the enzymatic systems involved; hence, it modulates the effects on glucose metabolism and protein and DNA synthesis.



Magnesium and the Hallmarks of Aging,2024

- The primary dietary sources of Mg include whole grains and grain products, nuts, fish and seafood, legumes and berries.

- it is practically absent in processed food and sugar sweetened beverages.

Some Food Sources of Magnesium

Food	Serving	Magnesium (mg)
Cereal all bran	1/2 cup	112
Cereal oat bran	1/2 cup dry	96
Brown rice, medium-grain, cooked	1 cup	86
Fish, mackerel, cooked	3 ounces	82
Spinach, frozen, chopped, cooked	1/2 cup	78
Almonds	1 ounce (23 almonds)	77
Swiss chard, chopped, cooked	1/2 cup	75
Lima beans, large, cooked	1/2 cup	63
Cereal, shredded wheat	2 biscuits	61
Peanuts	1 ounce	48
Molasses, blackstrap	1 tablespoon	48
Hazelnuts	1 ounce (21 hazelnuts)	46
Walnuts	1 ounce (14 walnuts)	44
Okra, frozen, cooked	1/2 cup	37
Milk, 1% fat	8 fluid ounces	34
Banana	1 medium	32

Magnesium and Hypertension in Old Age, MDPI, 2020

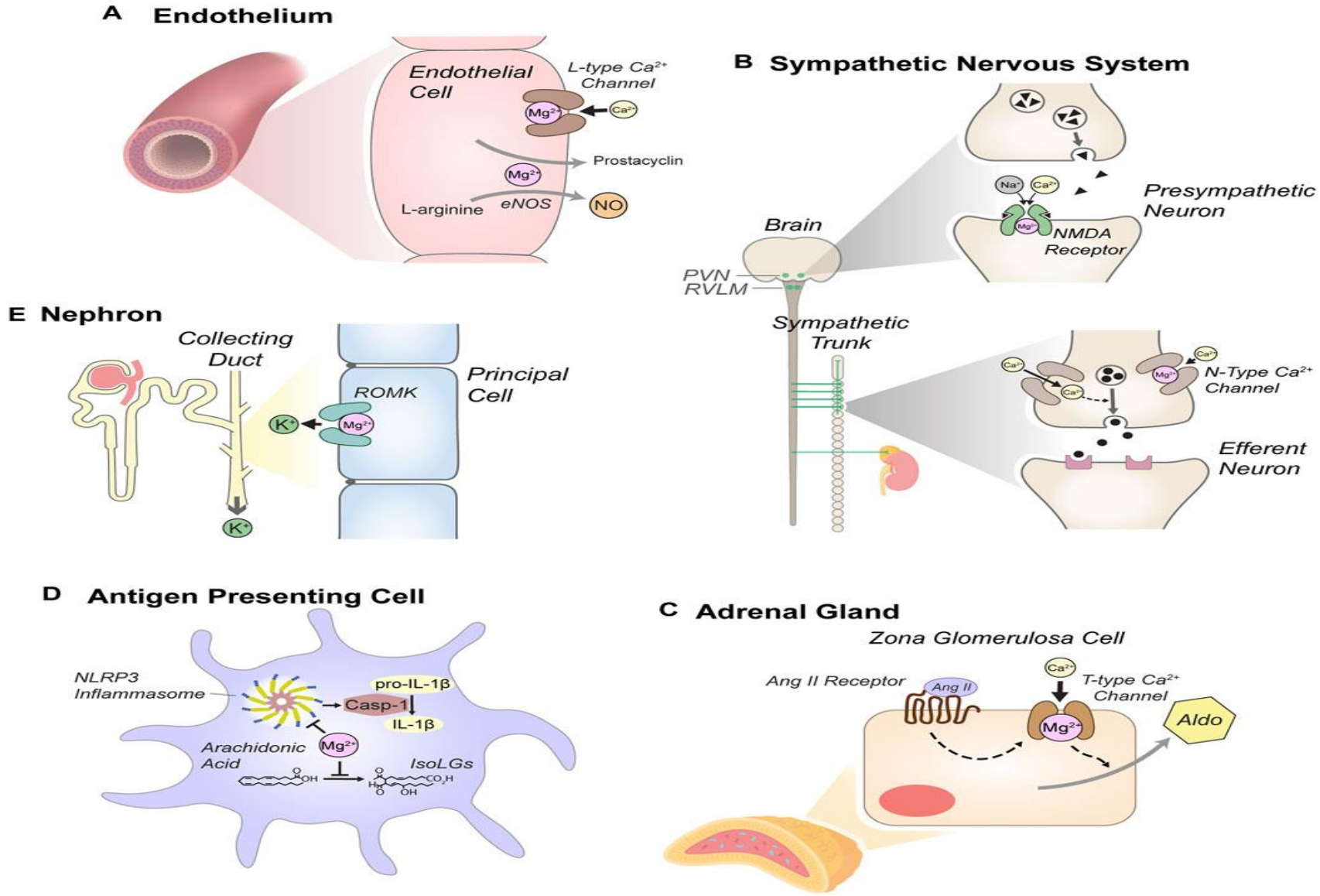
- The recommended Mg intake is 350 mg/d for men and 300 mg/d for females.
- this requirement may be increased in several physiological conditions (i.e., exercise, aging, pregnancy, etc.), as well as in some pathological conditions (diabetes, infections, etc).

Mg and hypertension

Table 2. Main Mechanisms of Magnesium-related Blood Pressure Regulation.

- Regulation of vascular tone and contraction
  - Calcium antagonism
  - Endothelial function
  - RAAS
  - Catecholamine secretion
  - Vascular calcification
- Insulin resistance
- Oxidative stress and inflammation

RASS: Renin-Angiotensin-Aldosterone System.



Magnesium in hypertension: mechanisms and clinical implications, Aprill2024

Main Mechanisms of Magnesium-related Blood Pressure Regulation:

❖Regulation of Vascular Tone and Contraction

- Magnesium is a major physiological regulator of vascular tone, and modulates peripheral vascular resistance by enhancing relaxation responses and mitigating agonist-induced vasoconstriction.

- Mg can directly stimulate the production of prostacyclin and nitric oxide and thus influence endothelium-dependent and independent vasodilation subsequently impacting upon BP control.

- Furthermore, Mg has also been reported to influence vascular tone and reactivity and to prevent by exerting antioxidant and anti-inflammatory functions.

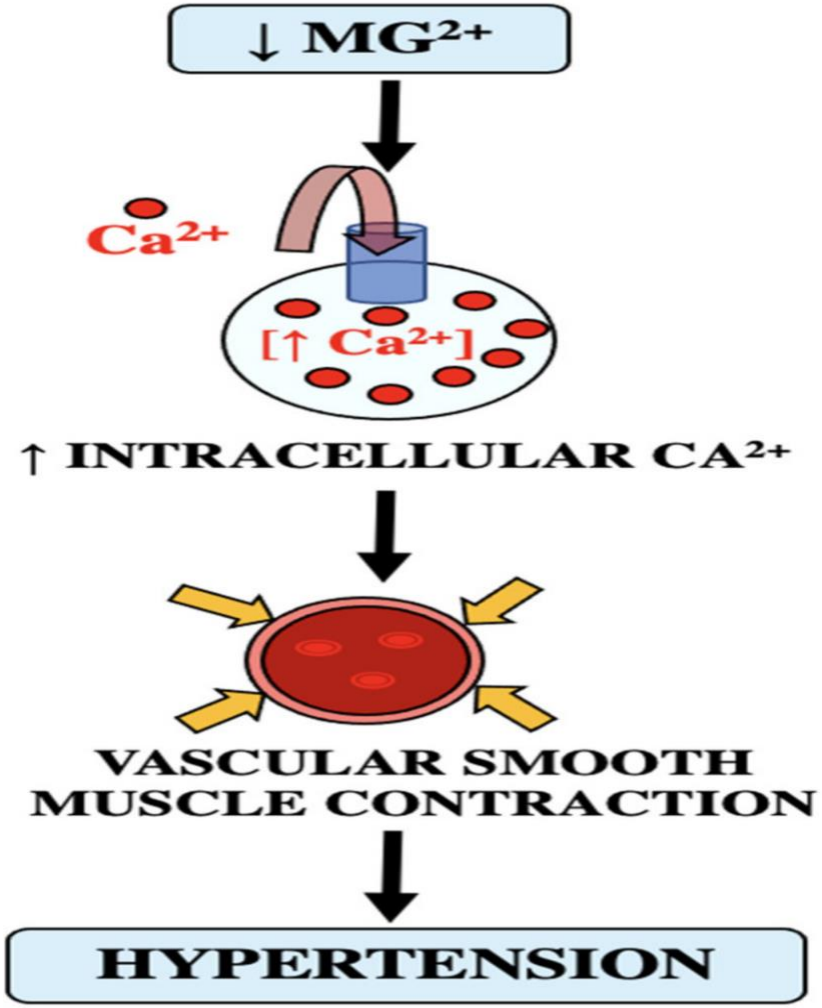
Trace element magnesium: a key player in hypertension management

•Rajesh ParsanathanPublished: 15 August 2023

1. Magnesium as a Calcium Antagonist

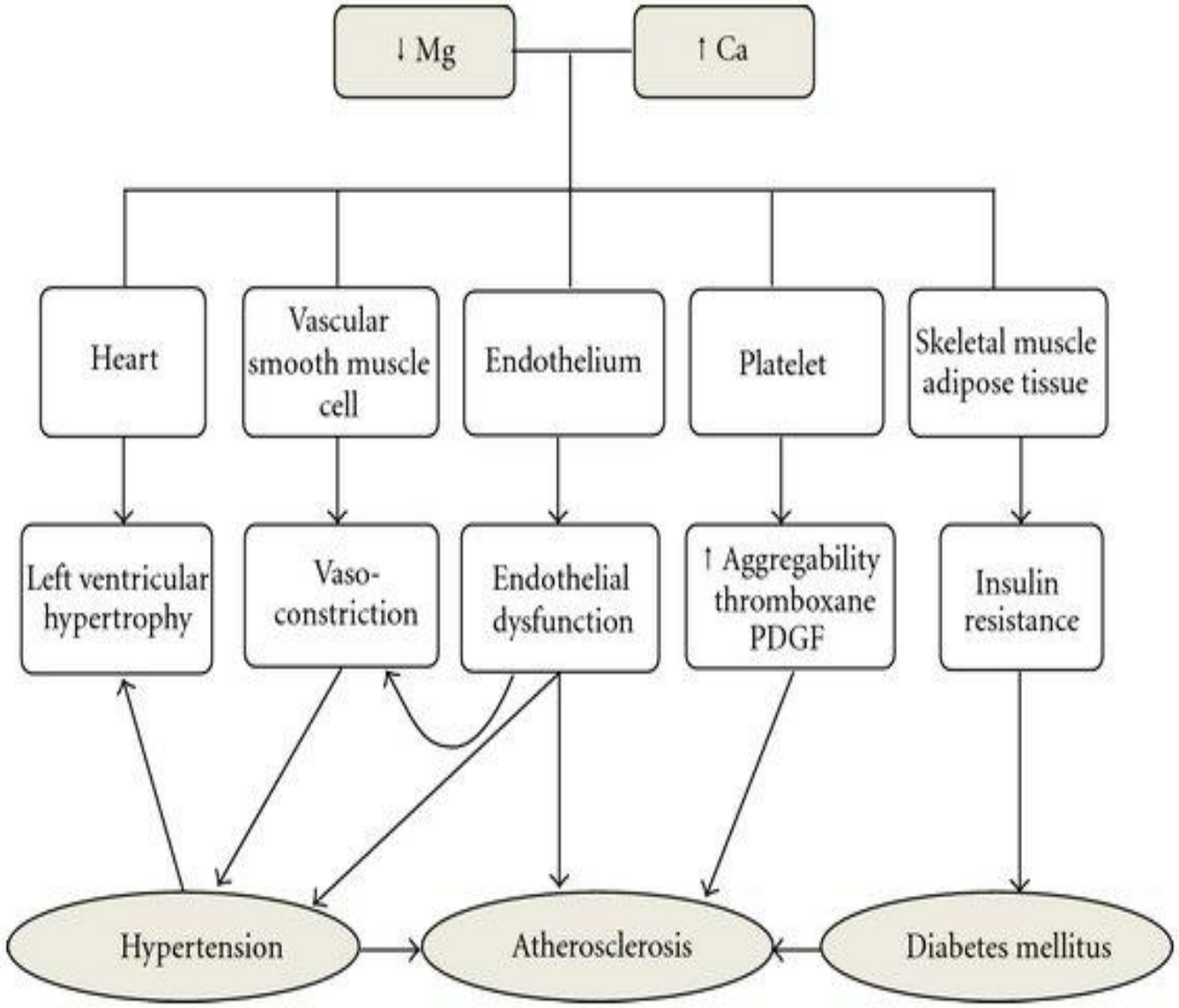
- Calcium ion plays a crucial role in the control of vascular smooth muscle cells excitation, contraction and impulse propagation.

- Extracellular magnesium levels and cellular-free magnesium concentrations modulate vascular smooth muscle cells tone by voltage-dependent L-type calcium channels .



- Furthermore, magnesium can itself function as a natural physiologic calcium channel blocker , modulating the activity of the calcium-channels.

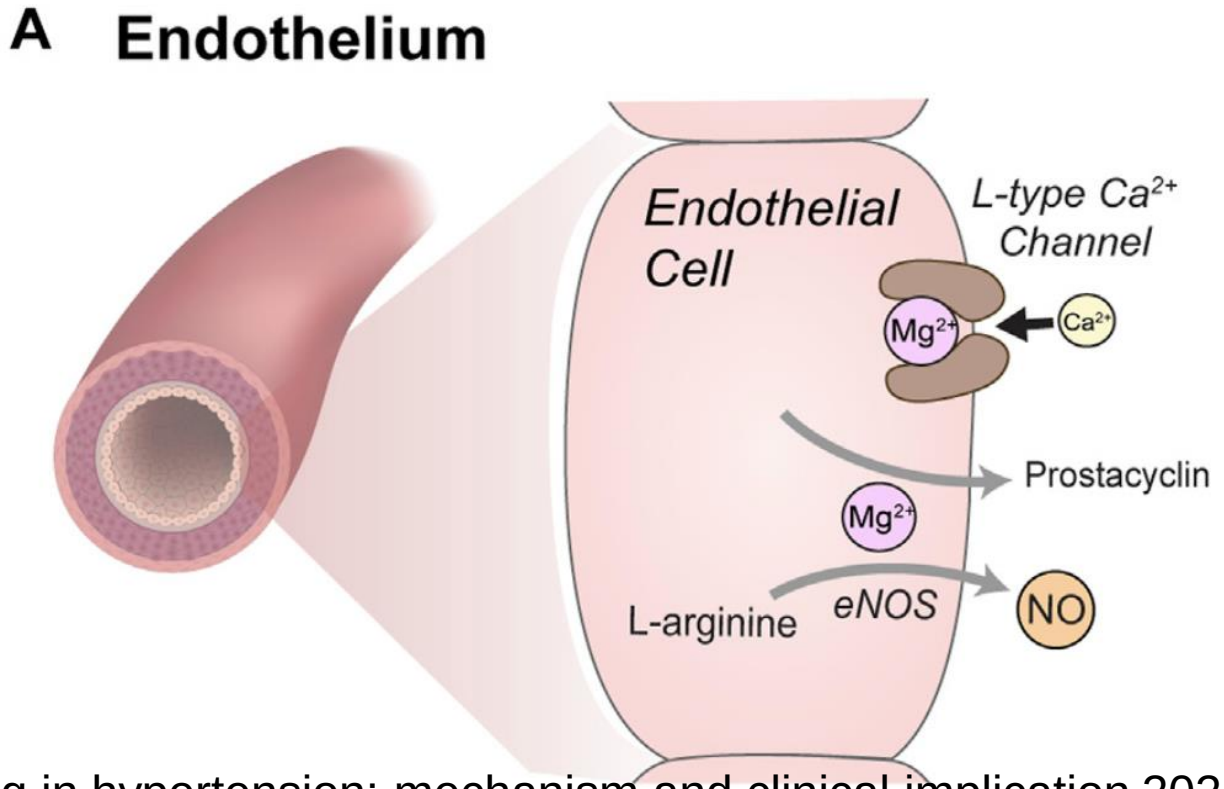
- Thus, magnesium counteracts calcium and functions as physiological calcium blocker, similarly to synthetic calcium antagonists.



2. Magnesium and Endothelial Function

- Magnesium stimulates vascular endothelial functions by affecting the release of nitric oxide, endothelin-1, and prostacyclin.
- Magnesium ions directly trigger the production of prostacyclin and nitric oxide.

- Mg2+ reduces vascular tone through actions in endothelial cells, including blockade of L-type Ca2+ channels and by supporting secretion of prostacyclin and nitric oxide (NO).



Mg in hypertension: mechanism and clinical implication,2024

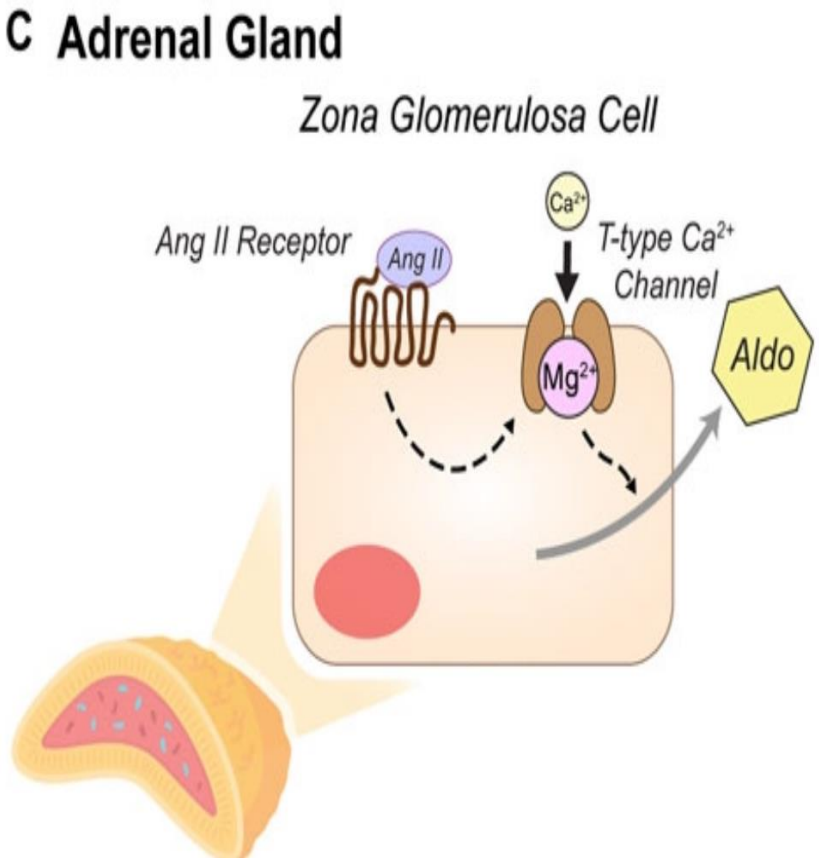
Effects of Oral Magnesium Supplementation on Vascular Function: A Systematic Review and Meta-analysis of Randomized Controlled Trials Bianca Cristina Antunes Alves Marques [1] [2], Márcia Regina Simas Torres Klein [3], 2020

- This meta-analysis suggest that oral Mg supplementation may improve endothelial function when conducted at least for 6 months and in unhealthy, overweight or older individuals.

3. Magnesium and the Renin-Angiotensin-Aldosterone System (RAAS)

- In experimental models, it has been shown that magnesium has some direct effects on the synthesis of aldosterone and indirect effects through the RAAS.
- Aldosterone secretion is a calcium-dependent process, which can be affected by magnesium due to its calcium antagonist properties.

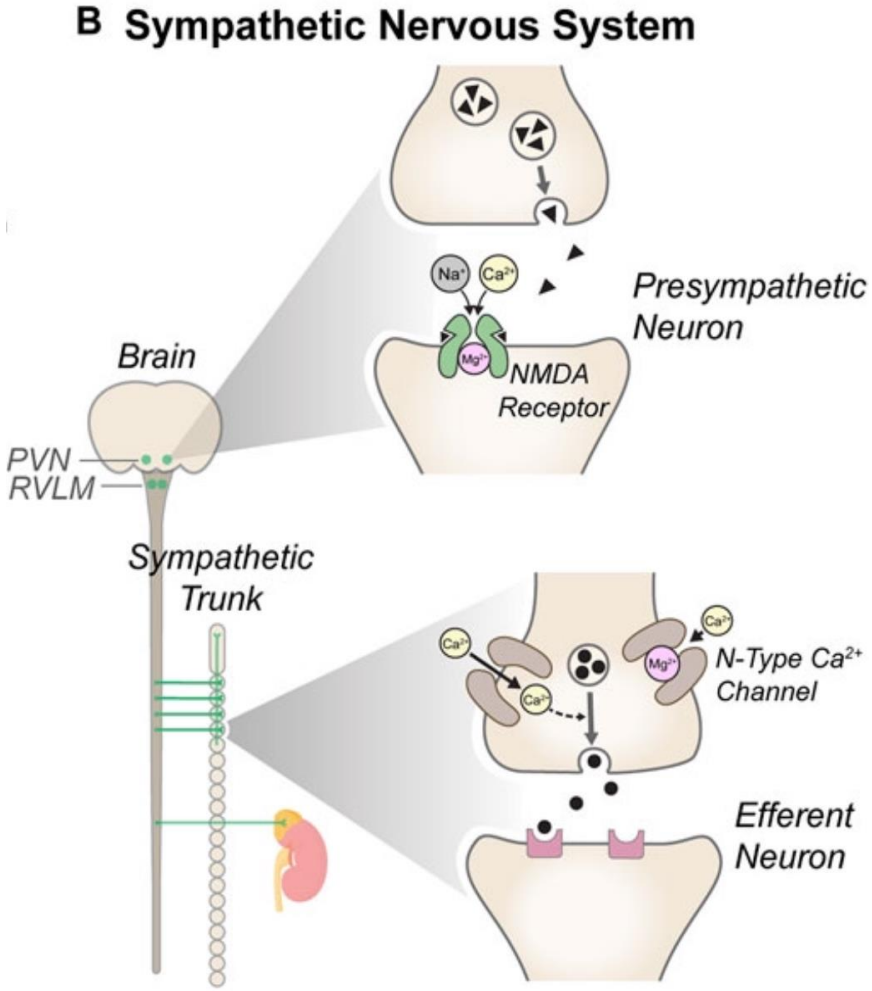
- Mg2+ reduces aldosterone secretion in the adrenal cortex. Mg2+ blockade of T-type Ca2+ channels in zona glomerulosa cells modulates stimulation of aldosterone (Aldo) secretion by angiotensin II (Ang II).



Mg in hypertension: mechanism and clinical implication,2024

4. Magnesium and Catecholamines

The release of catecholamines from the adrenal gland and from adrenergic nerve terminals in response to sympathetic stimulation is a calcium-mediated process. magnesium competes with calcium for membrane channels, blocking the calcium entrance, and consequently modifying these calcium-linked responses.



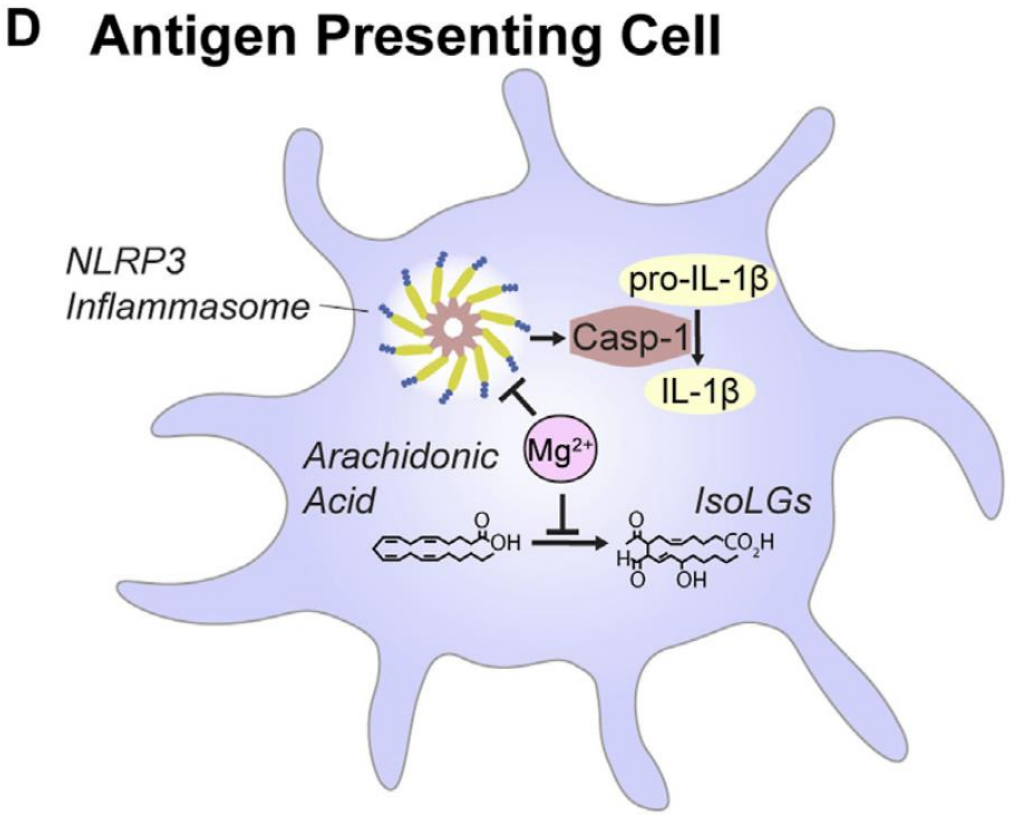
Mg in hypertension: mechanism and clinical implication,2024

5. Magnesium and Vascular Calcification

- Vascular calcification refers to the deposit of calcium in the arterial wall and is closely linked to high blood pressure. Hypertension is a risk factor for atherosclerosis and intimal calcification.
- The calcification of the vessel media is associated with reduced elasticity and arterial stiffness, a major cause of isolated systolic hypertension particularly frequent in old age.
- Some studies have indicated a protective effect of magnesium against vascular calcification, attributable to its calcium antagonistic effects including hydroxyapatite formation and calcium transport into the cells.
- The possible mechanism to explain such protective effect has not been yet fully clarified.

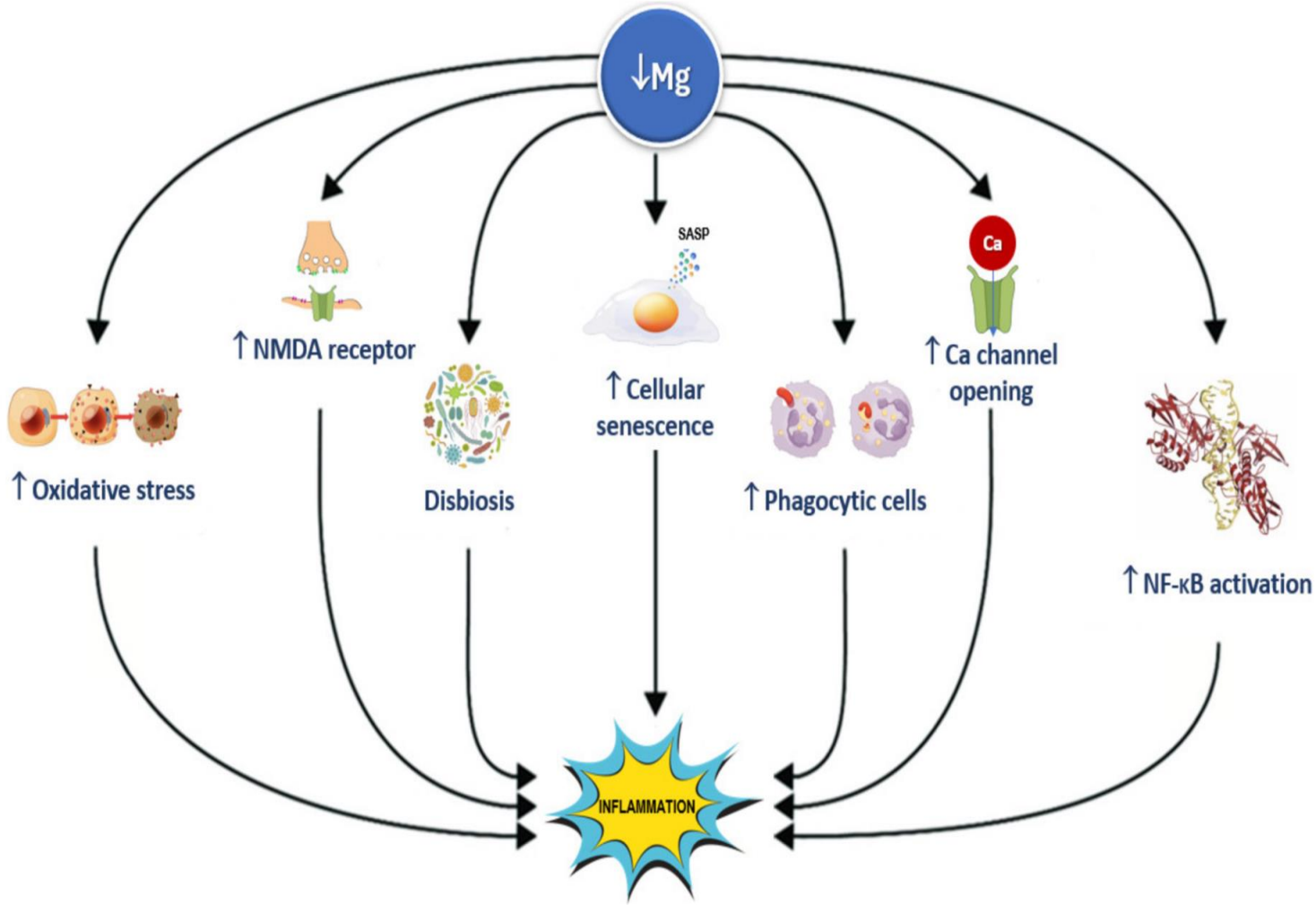
❖ Oxidative stress and inflammation

- Mg2+-depletion stimulates antigen presenting cells (dendritic cells and monocytes).
- Mg2+ depletion enhances expression of NLR family pyrin domain containing 3 (NLRP3), a key component of the inflammasome, which activates caspase-1 (Casp-1).
- Casp-1 stimulates production of pro-inflammatory cytokines, including IL-1β. .



Mg in hypertension: mechanism and clinical implication,2024

Magnesium deficiency induces inflammation through several signaling pathways.



Magnesium and the Hallmarks of Aging,2024

Effect of magnesium supplements on serum C-reactive protein: a systematic review and meta-analysis 2017

Mohsen Mazidi[1,2], Peyman Rezaie[3], Maciej Banach[4–6], on behalf of Lipid

- Systematic review and meta-analysis of randomised controlled trials (RCTs).
- This study evaluated the impact of Mg supplementation on CRP.
- This meta-analysis suggests that Mg supplementation significantly reduces serum CRP level.

nutrients

MDPI

Review

The Effect of Electrolytes on Blood Pressure: A Brief Summary of Meta-Analyses

17 June 2019

Sehar Iqbal, Norbert Klammer and Cem Ekmekcioglu *

- Overall, 32 meta-analyses evaluating the effect of sodium, potassium, calcium and magnesium on human blood pressure.
- The major findings of this review were especially that sodium (salt) reduction and a higher intake of potassium have convincing blood pressure lowering effects. In addition, higher magnesium intake is suggested to possibly reduce blood pressure, especially in patients with hypertension.
- magnesium showed a moderate blood pressure reducing effect in general. The potential antihypertensive effects of magnesium are for example suggested to be related to calcium channel blockage, increases in nitric oxide, and better endothelial function.

Nutr Res Pract. 2022 Feb;16(1):74-93
https://doi.org/10.4162/nrp.2022.16.1.74
pISSN 1976-1457·eISSN 2005-6168

Nutrition Research and Practice

Original Research

Association of dietary calcium, magnesium, sodium, and potassium intake and hypertension: a study on an 8-year dietary intake data from the National Health and Nutrition Examination Survey

As compared to men, women increased their risk of hypertension even with a lower sodium intake. Women would also reasonably reduce their risk of developing hypertension by increasing calcium and magnesium intake. High calcium, magnesium, potassium, and low sodium intake somewhat reduces the risk of developing hypertension in all individuals.

Magnesium Depletion Score and Metabolic Syndrome in US Adults: Analysis of NHANES 2003 to 2018

Xiaohao Wang,[1,2,3] Zhaohao Zeng,[4] Xinyu Wang,[5] Pengfei Zhao,[1,2,3] Lijiao Xiong,[1,2,3]

The Journal of Clinical Endocrinology & Metabolism, 2024, 109, e2324–e2333

THey analyzed data from 15 565 adults participating in the National Health and Nutrition Examination Survey (NHANES) 2003 to 2018.
The MDS is a scoring system developed to predict the status of magnesium deficiency

This study identified a significant association between MDS and metabolic syndrom.
It is possible to prevent and reduce MetS by supplementing with magnesium supplements or encouraging higher magnesium intake diet.

Dose-response relationship between dietary magnesium intake, serum magnesium concentration and risk of hypertension: a systematic review and meta-analysis of prospective cohort studies

Hedong Han[1†], Xin Fang[2*†], Xin Wei[3†], Yuzhou Liu[3], Zhicao Jin[1], Qi Chen[1], Zhongjie Fan[4], Jan Aaseth[5,6]

Nutrition Journal (2017)

- Nine articles, including 20,119 cases of hypertension and 180,566 participates, were included in the meta-analysis.

They found an inverse association between dietary magnesium intake and the risk of hypertension .

- A 100 mg/day increment in magnesium intake was associated with a 5% reduction in the risk of hypertension
- The association of serum magnesium concentration with the risk of hypertension was marginally significant.
- The evidence supports the inverse dose-response relationship between dietary magnesium intake and the risk of hypertension.

Conclusion

- optimal management of hypertension should include attention to Mg^{2+} balance. Clinicians should have a high index of suspicion for Mg^{2+} depletion in hypertensive patients, given that

1) dietary Mg^{2+} deficiency is common.

2) hypertension is associated with Mg^{2+} depletion, even in untreated patients.

3) common comorbidities (such as diabetes mellitus) are also associated with Mg^{2+} depletion.

4) commonly prescribed medications promote Mg^{2+} deficiency,

including thiazide-type and loop diuretics, and proton pump inhibitors .

❖Clinicians should consider prescription of a well-absorbed oral Mg^{2+} supplement. Well-absorbed supplements include most organic salts and possibly the chloride salt.

❖Clinicians should have a low threshold for prescribing agents that oppose urinary Mg^{2+}-wasting, such as K^+ and Mg^{2+}-sparing diuretics (e.g., spironolactone or amiloride), and SGLT2 inhibitors.

It is likely that improved Mg^{2+} balance associated with SGLT2 inhibitors contributes to improved cardiovascular benefits associated with their use.

SGLT2 Inhibitors for Treatment of Refractory Hypomagnesemia: A Case Report of 3 Patients

Evan C. Ray, Cary R. Boyd-Shiwarski, Pengfei Liu, Danica Novacic, and David Cassiman

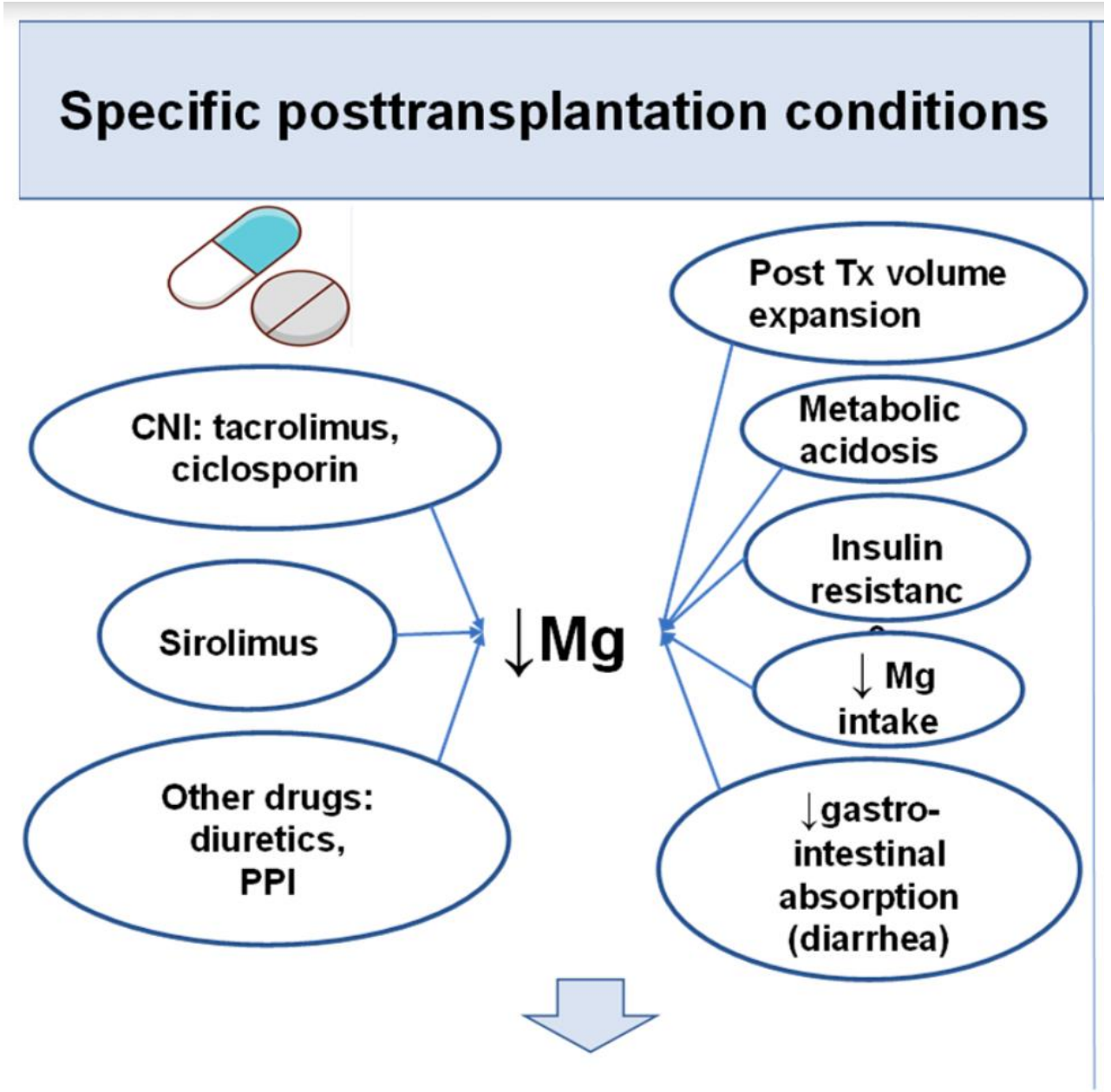
Mg and Kidney transplantation

- Hypomagnesemia is frequently observed after kidney transplantation, Hypomagnesemia was reported to develop frequently within the first few weeks following transplantation , with a serum Mg level nadir in the second month post-transplantation .

- Hypomagnesemia may persist for several years after kidney transplantation.

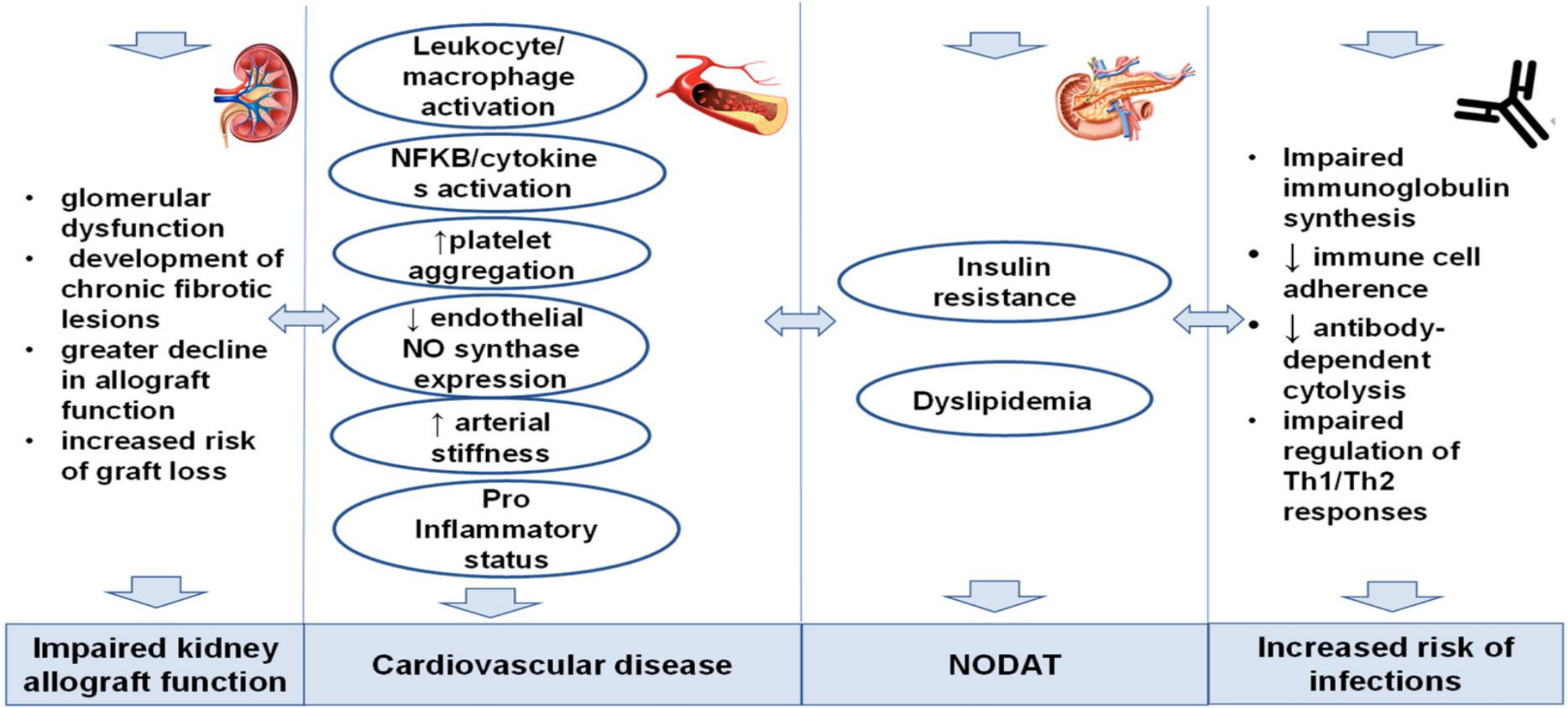
Causes:

- calcineurin inhibitors (CNI): cyclosporine or tacrolimus
- MTOR inhibitors
- post-transplantation volume expansion
- metabolic acidosis
- insulin resistance
- decreased gastro-intestinal absorption due to diarrhea
- low Mg intake
- medication such as diuretics or proton pump inhibitors



The Impact of Hypomagnesemia on the Long-Term Evolution After Kidney Transplantation

The Impact of Hypomagnesemia after Kidney Transplantation



The Impact of Hypomagnesemia on the Long-Term Evolution After Kidney Transplantation, 2024

Mg and graft function

- The relationship between serum Mg and graft function has been poorly evaluated in literature.
- These data in human and mice converge to suggest that hypomagnesemia is not only associated with accelerated decline of graft function but is also an active contributor to renal lesions.
- Data from the literature indicates a bi -directional relashion ship between hypomagnesemia and renal function. Impairment of renal graft function results in increased magnesium loss due to tubular fibrosis; conversely, reduced magnesium levels negatively influence graft function.

Mg and NODAT

- Post-transplant diabetes mellitus (PTDM) affects both patient and graft survival .Hypomagnesemia has recently been identified as an independent risk factor for PTDM, however with some conflicting data in literature.

- The diabetogenic effects of hypomagnesemia are not yet well understood and have been attributed to several mechanisms:

➢altered cellular glucose transport,

➢reduced pancreatic insulin secretion,

➢defective post-receptor insulin signaling

➢altered insulin–insulin receptor interactions.

- Mitochondrial dysfunction has a central role in hypomagnesemia and NODAT

Review

Serum Magnesium after Kidney Transplantation: A Systematic Review June 2018

Anne-Sophie Garnier [1,2], Agnès Duveau [1,2], Martin Planchais [1,2], Jean-François Subra [1,2,3],

- In cohort of 154 kidney transplant recipients, 28 patients (18.2%) developed a PTDM within the first year of transplantation, and in most patients within the first 2 months.The pre-transplant Mg level was significantly lower in patients that developed PTDM (p = 0.014).
- While most studies converge to confirm that hypomagnesemia is an independent risk factor for PTDM, the impact of hypomagnesemia correction after kidney transplantation has not yet been fully explored.
- Literature analysis also highlights the need for studies in order to determine the best Nutrients routes for Mg supplementation, formulations and doses to achieve normal serum Mg concentration in these patients.

Association Between Pre-Transplant Magnesemia and Post-Transplant Dysglycemia in Kidney Transplant Recipients

Azam Alamdari [1], Ghazal Asadi [2], Farzaneh Sadat Minoo [1], Mohammad-Reza Khatami [1], Seyed Mansour Gatmiri [1], Simin Dashti-Khavidaki [1], Saba Heydari Seradj [3] and Neda Naderi [1,*]

- In this retrospective cohort, 89 first-time kidney transplant recipients with 6 months of follow-up were included. None of the participants had a positive history of rejection, pre-transplant history of diabetes mellitus or fasting plasma glucose ≥ 100 mg/dL.

- Pre-transplant hypomagnesemia may be considered a risk factor for developing post-transplant glycemic disturbances, and patients with lower pre-transplant Mg concentration could be at a higher risk for developing IFG.

- Animal studies and clinical trials with non-transplant diabetic patients indicate that hypomagnesemia is an independent risk factor for this condition, although in most studies magnesium supplementation improves glucose tolerance and insulin sensitivity .

The Impact of Hypomagnesemia on the Long-Term Evolution After Kidney Transplantation 2024

Ioana Adela Ratiu [1,2], Corina Moisa [1,*], Luciana Marc [3,4], Nicu Olariu [3,4], Cristian Adrian Ratiu [1],

- A retrospective study on 87 patients who have had a transplant for more than 5 years, a period considered immunologically stable.

- Although the existing literature supports the notion that hypomagnesemia may often trigger the onset of T2DM, this study found no correlation between hypomagnesemia and glycemic imbalanc.

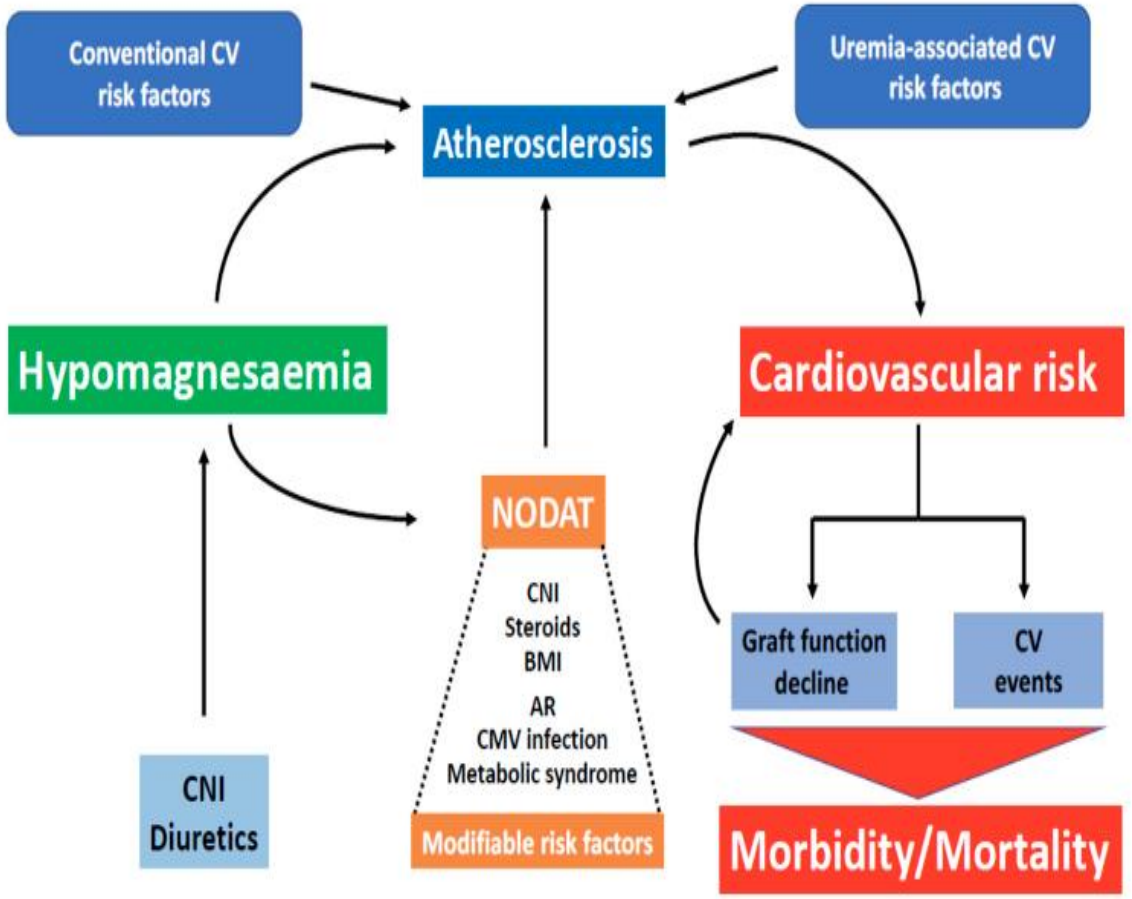
Mg and cardiovascular

- Hypomagnesemia has been shown to play a role in the pathogenesis of arterial hypertension, endothelial dysfunction, dyslipidemia and inflammation, with all these factors contributing to coronary heart disease (CHD).

- The relationship between CHD and serum Mg concentrations was studied in a cohort of 13,922 middle-age adults in 1998. patients who developed CHD had a lower serum Mg concentration than the controls, suggesting that low serum Mg was an independent risk factor for CHD.

- In a Japanese cohort of 728 subjects, lower serum Mg was significantly and independently associated with mean intima-media thickness ($p = 0.004$) and risk of ≥2 carotid plaques ($p = 0.03$) .
- Hypomagnesemia was also reported to directly or indirectly affect vascular stiffness in the general population .
- In another study, Mg supplementation improved endothelial dysfunction in patients with CHD.

Despite relying on retrospective studies, a body of evidence link hypomagnesemia to PTDM and cardiovascular risk in kidney transplant patients .
Given the frequency of PTDM and its relationship with cardiovascular risk, correcting hypomagnesemia soon after transplantation could translate into a significant decrease in vascular disease, which today is the primary cause of death in kidney transplant recipients.



Serum Magnesium after Kidney Transplantation: A Systematic Review
Anne-Sophie Garnier.2018

SGLT2 Inhibitors

Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study 2017

Anna Solini[1*], Livia Giannini[2], Marta Seghieri[2], Edoardo Vitolo[2], Stefano Taddei[2], Lorenzo Ghiadoni[2] and Rosa Maria Bruno[2]

The use of SGLT2 inhibitors leads to an increase in serum magnesium levels, an improvement in endothelial dysfunction, a reduction in arterial stiffness, and decreased resistance in the arterial circulation of the renal graft .

As most clinical trials involving SGLT2 inhibitors have excluded transplant populations, further data are needed to clarify their effects in post-Tx organ recipients.

Hypomagnesemia and infection

- Accumulating evidence suggests a possible link between Mg^{2+} and the immune system. Mg^{2+} plays an essential role in controlling immune function by exerting an extended effect on several immune processes, such as immunoglobulin synthesis, immune cell adherence, antibody-dependent cytolysis, and regulation of Th1/Th2 responses

X-linked immunodeficiency with magnesium defect (XMEN):

- a mild form of combined immune deficiency
- mutations in Mg^{2+} transport systems,
- Mg^{2+} signaling is critical for natural killer (NK) and $CD8^{+}$ T-cell function.

- Unlike infectious occurring in KTRs in the first months post-Tx, which are often pre-xisting or nosocomially acquired, infections arising several years after transplantation are a consequence of immunosuppressive therapy.
- Infectious episodes represent a major cause of mortality in KT patients,

Hypomagnesemia Is a Risk Factor for Infections after Kidney Transplantation: A Retrospective Cohort Analysis
by **Balazs Odle,2024**

- a single-center retrospective cohort study of KTRs transplanted between 2005 and 2015

- 376 KTRs of whom 229 patients (60.9%) suffered from Mg^{2+} deficiency defined as a serum $Mg^{2+} < 0.7$ mmol/L.

- KTRs suffering from Mg^{2+} deficiency are at increased risk of UTIs and viral infections in the first year after KT.
- Interventional studies investigating the effect of Mg^{2+} supplementation on Mg^{2+} deficiency and viral infections in KTRs are needed.

The Impact of Hypomagnesemia on the Long-Term Evolution After Kidney Transplantation 2024

Ioana Adela Ratiu [1,2], Corina Moisa [1,*], Luciana Marc [3,4], Nicu Olariu [3,4], Cristian Adrian Ratiu [1],

- They focused on CMV reactivation and the presence of HBV, HCV, papilloma, herpes virus, and COVID-19 infection within the spectrum of post-Tx viral infections.
- The study revealed no significant increase in the incidence of CMV reactivation among KTRs experiencing hypomagnesemia.
- the incidence of SARS-CoV-2 infection is twice as high in KTRs with hypomagnesemia when compared to those with normal magnesium levels.

Mg and sleep quality

Sleep quality, fatigue, societal participation and health-related quality of life in kidney transplant recipients: a cross-sectional and longitudinal cohort study

Nephrol Dial Transplant,2024,

Tim J. Knobbe [1,†], Daan Kremer [1,†], Michele F. Eisenga [1], Marco van Londen [1], Coby Annema [2], Ute Bültmann [3], Ido P. Kema [4],

We included872KTR(39% female, age 56±13years) and 335 healthy controls. In total, 33% of male KTR and 49% offe male KTR reported poor sleep quality, which was higher compared with male and female healthy controls for both).

In logistic regression analyses, female sex, anxiety, active smoking, low protein intake, physically inactive lifestyle, low plasma magnesium concentration, using calcineurin inhibitors, not using mTOR inhibitors and using benzodiazepine agonists were associated with poor sleep quality.

thanks