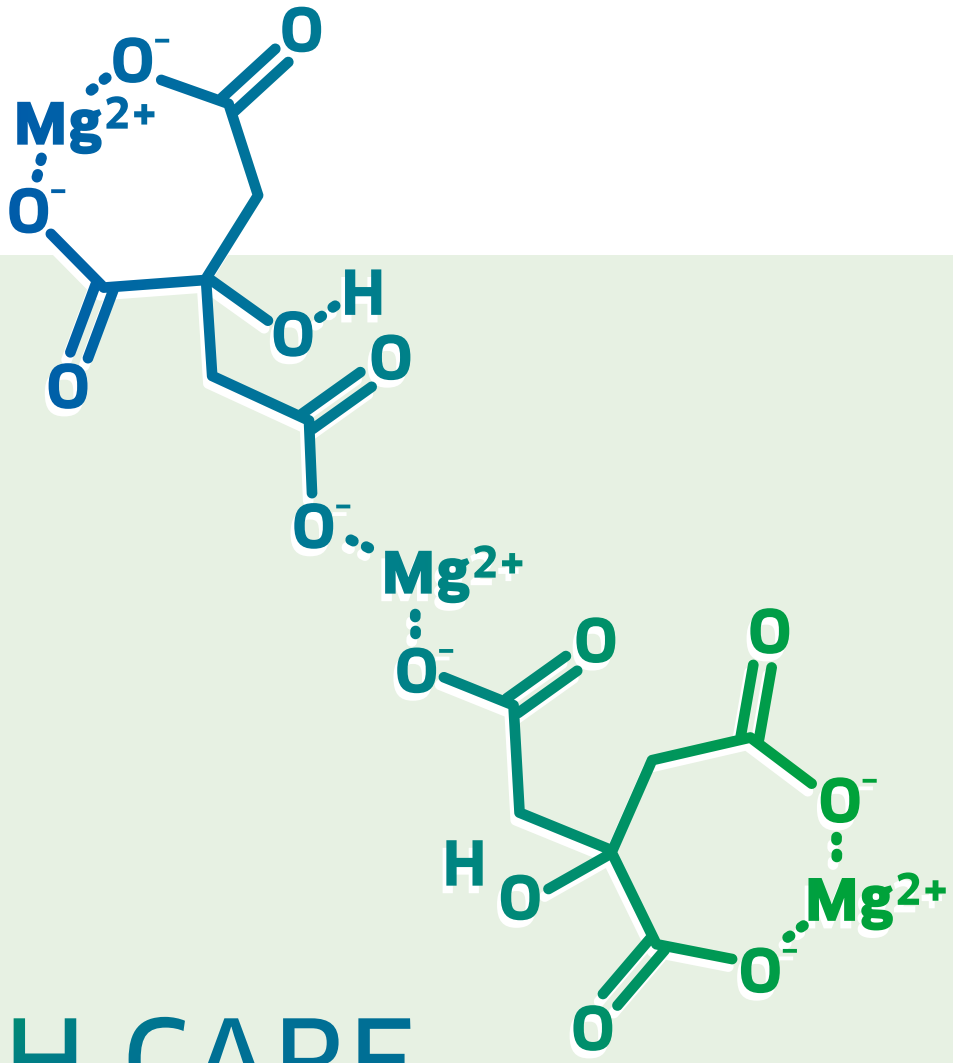
MAGNESIUM Diasporal®



SCIENTIFIC INFORMATION

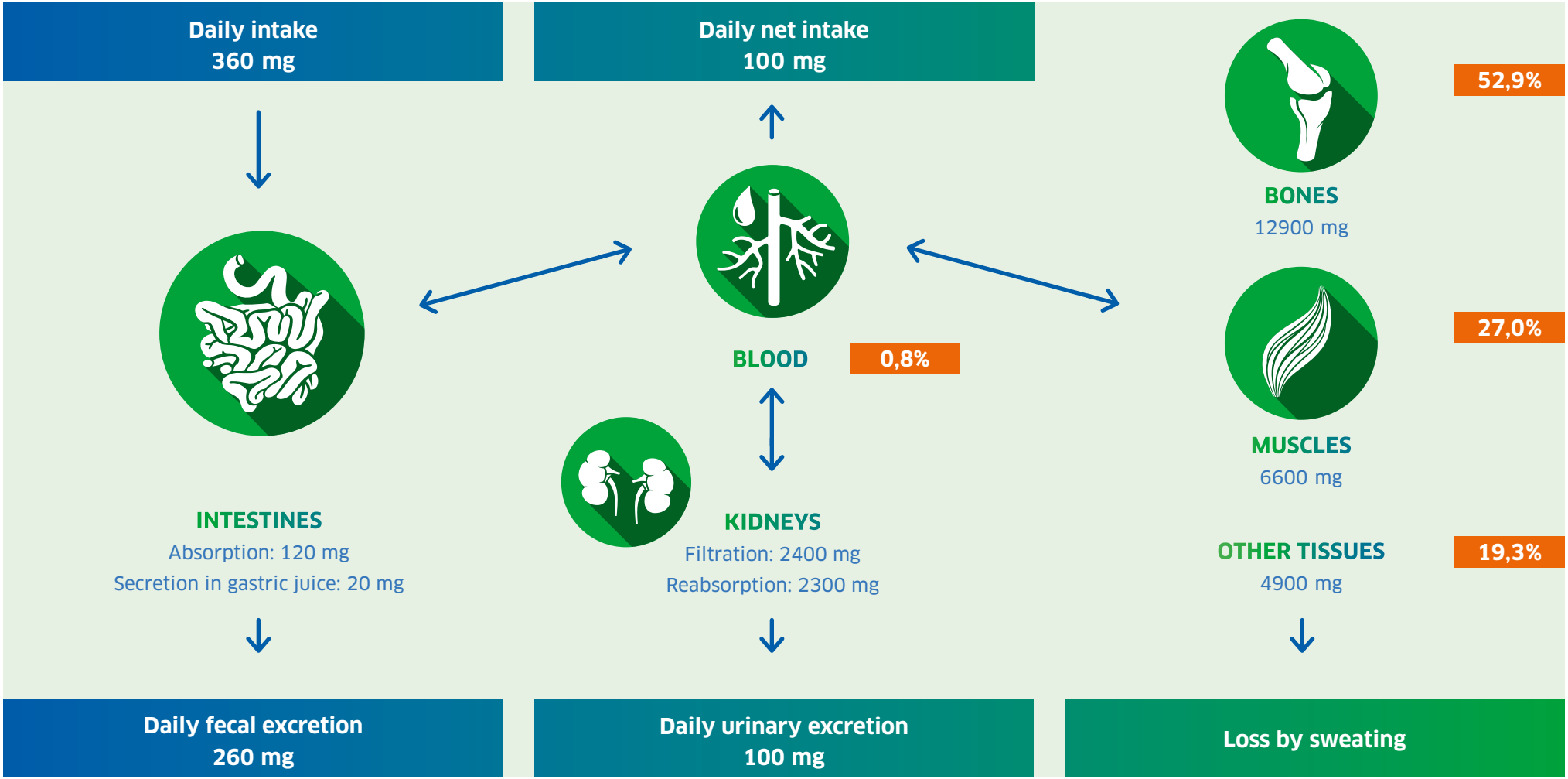
FOR HEALTH CARE PROFESSIONALS

Table of Contents

Magnesium homeostasis

The magnesium (Mg) content in the blood is less than 1% of the body's total Mg.

Measurements of serum Mg are therefore of very little relevance for the diagnosis of Mg deficiency.[1, 2]



Magnesium homeostasis

The intracellular role of magnesium

Key role of Mg in cellular physiology:[1, 3]

- The complex Mg-ATP is required for the activity of many enzymes. In general, Mg acts as a cofactor in all reactions involving the utilisation and transfer of ATP
- Mg is essential in DNA replication and DNA repair (thus maintaining stability of the genome), RNA transcription, and protein formation
- Mg participates in controlling the activity of some ionic channels in many tissues and works as a Ca antagonist
- Neuronal Mg concentrations downregulate the excitability of the N-methyl-D-aspartate (NMDA) receptor, which is essential for excitatory synaptic transmission and neuronal plasticity in learning and memory
- Daily changes in Mg concentration regulate cellular circadian rhythms and energy balance[4]

Energy metabolism (ATP)

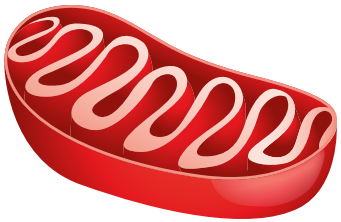
Protein synthesis

Cell division (DNA replication)

Free Mg as a calcium antagonist

Key role of Mg in cellular physiology

ATP



Glycolysis

Citric acid cycle

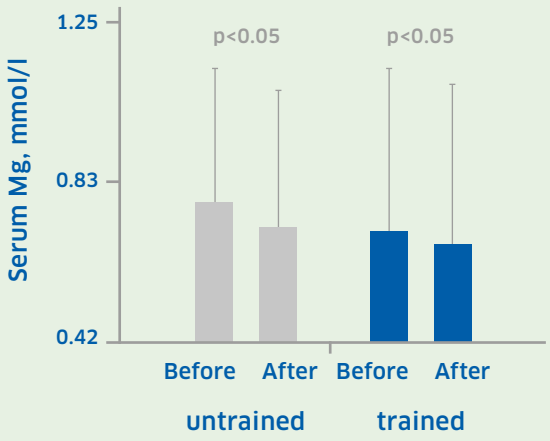
Electron transport chain

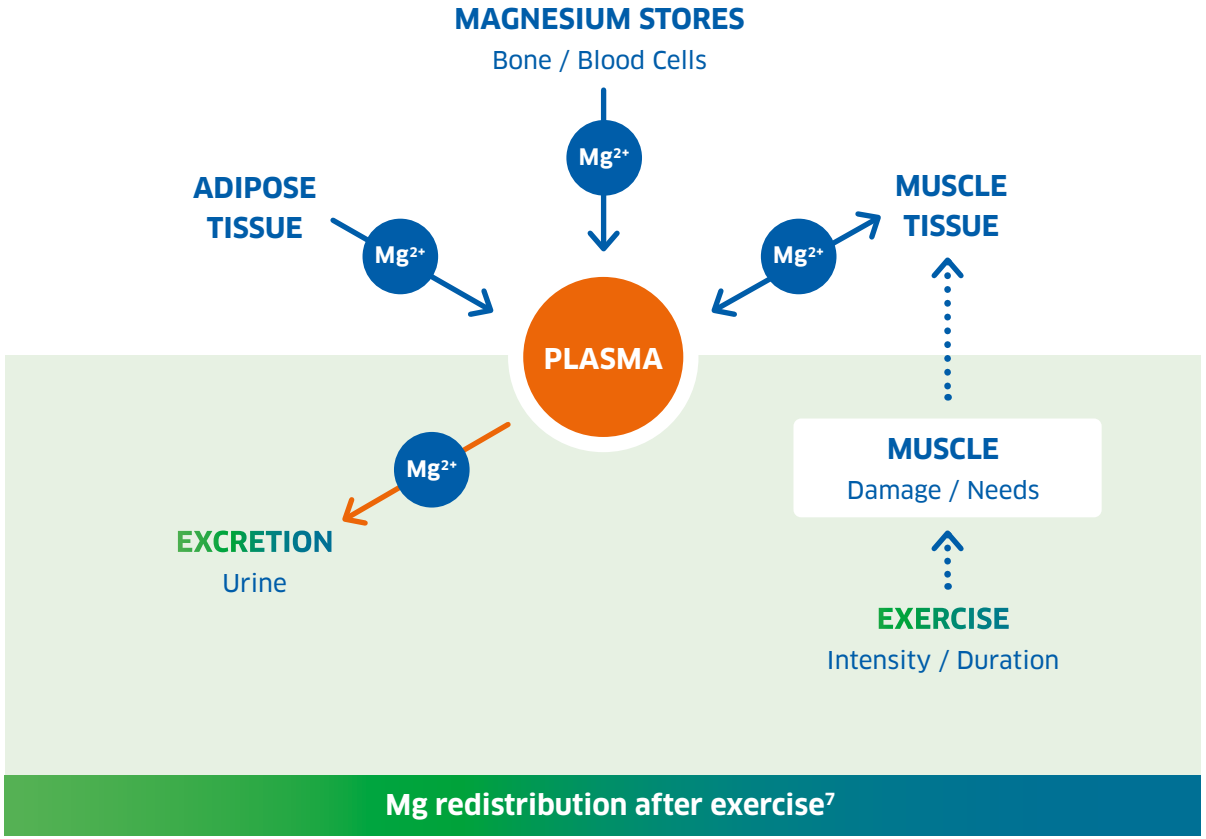
In form of Mg-ATP, Mg is a cofactor for the intracellular energy supply

Magnesium and sweating

- Depending on the intensity of physical exercise, the physical condition, the fitness level, the climatic conditions, prior fluid/food intake and the body surface area, the body may produce several hundred millilitres to more than two litres of sweat per hour[5]
- Under normal conditions, the mean Mg concentration in sweat is 0.5-9.6 mg/L[6], but it can increase upon exercise
- Cells lose Mg during physical activity. The consumption of ATP results in the release of Mg, which is then transported out of the cell (Mg redistribution)
- Mg supplementation is indicated in sports and occupational medicine to compensate for the increased loss[7]
- Exhaustive training leads to a significant decrease in serum Mg in people[8]

Decrease in serum Mg after training[8]



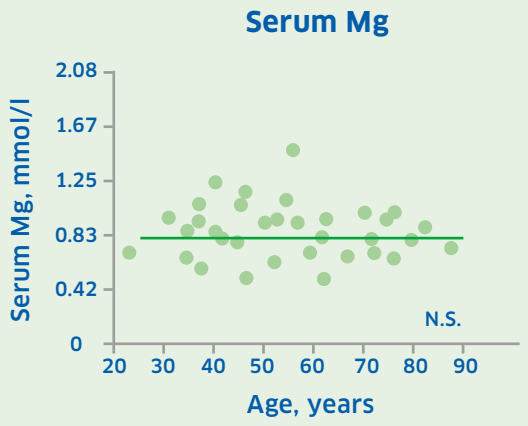


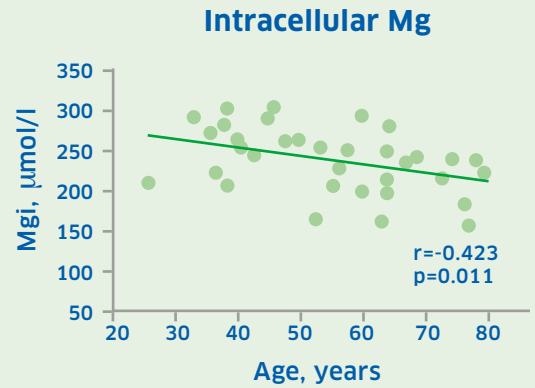
Mg redistribution after exercise[7]

Magnesium and aging

Whereas serum Mg remains unchanged with age, the intracellular Mg concentration decreases[9]

Serum and intracellular Mg in elderly people[9]

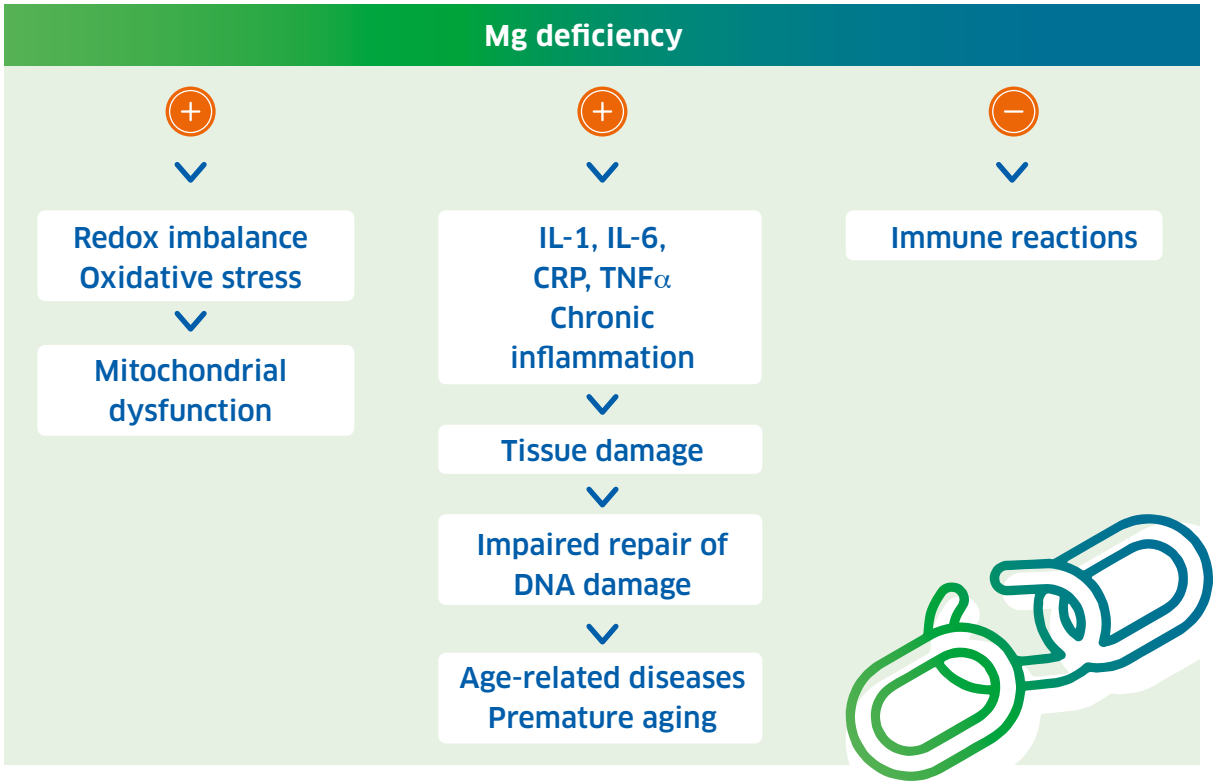




Typical mechanisms of development of Mg deficiency are enhanced in elderly:[10, 11]

- Mg intake with food decreases in line with decreased amount of food intake in general
- Intestinal absorption of Mg tends to fall with age
- Reduced kidney function is common in the elderly and leads to decreased Mg reabsorption
- Polypharmacotherapy often leads to drug-induced Mg deficiency

Mg deficiency contributes to the development of age-related diseases through various cellular mechanisms [9, 10, 12]



Daily requirements

The recommended daily Mg intake for adolescents, adult men and women and pregnant women is 300 to 400 mg.[13]

Recommended Dietary Allowances (RDAs) for Mg				
Age	**Male**	**Female**	**Pregnancy**	**Lactation**
Birth to 6 months	30 mg*	30 mg*		
7–12 months	75 mg*	75 mg*		
1–3 years	80 mg	80 mg		
4–8 years	130 mg	130 mg		
9–13 years	240 mg	240 mg		
14–18 years	410 mg	360 mg	400 mg	400 mg
19–30 years	400 mg	310 mg	350 mg	310 mg
31–50 years	420 mg	320 mg	360 mg	320 mg
51+ years	420 mg	320 mg		

*Adequate Intake (AI)

Note: Scientists warn that the recommended intakes were calculated respectively to mean body weight, which increased over time. They therefore **recommend increasing Mg intake to as much as 500-700 mg/day.[14]**

Hypomagnesemia: definition and prevalence

Hypomagnesemia is defined as **a low level of Mg in the body**. Most often it is determined by measuring serum or plasma Mg, but measurements of ionized Mg, intracellular Mg or urine Mg retention are also used.

Although in some studies and guidelines only patients with serum Mg <0.6 or <0.75 mmol/l are considered hypomagnesemic, these values are too low and are based on very old data. Typically, hypomagnesemia should be defined as **serum Mg <0.85 mmol/l.**[15,16]

One in ten people in the general population suffers from hypomagnesemia, while in certain groups, the prevalence of hypomagnesemia can reach:

50-65%	in diabetics[17]
44%	in patients with depression[18]
16-79%	in pregnant women[19, 20]
55%	in women with hormone-related conditions[20]
20-30%	in PPI users[21, 22]
29%	in elderly patients attending a tertiary care centre[23]
42%	in apparently healthy students[24]

Diagnosis of magnesium deficiency

CLINICAL signs and symptoms[1, 25, 26]

- Neuromuscular hyperexcitability
- Spasms, muscle tension
- Arrhythmias
- Sleep problems
- Fatigue
- etc.

PATIENT HISTORY to assess the risk of Mg deficiency[1, 25-27]

- Heart failure
- Coronary heart disease
- Hypertension
- Diabetes
- Malabsorption syndrome
- Pregnancy
- Medication use
- Elevated consumption of alcohol

LABORATORY measurement of serum Mg concentration[16]

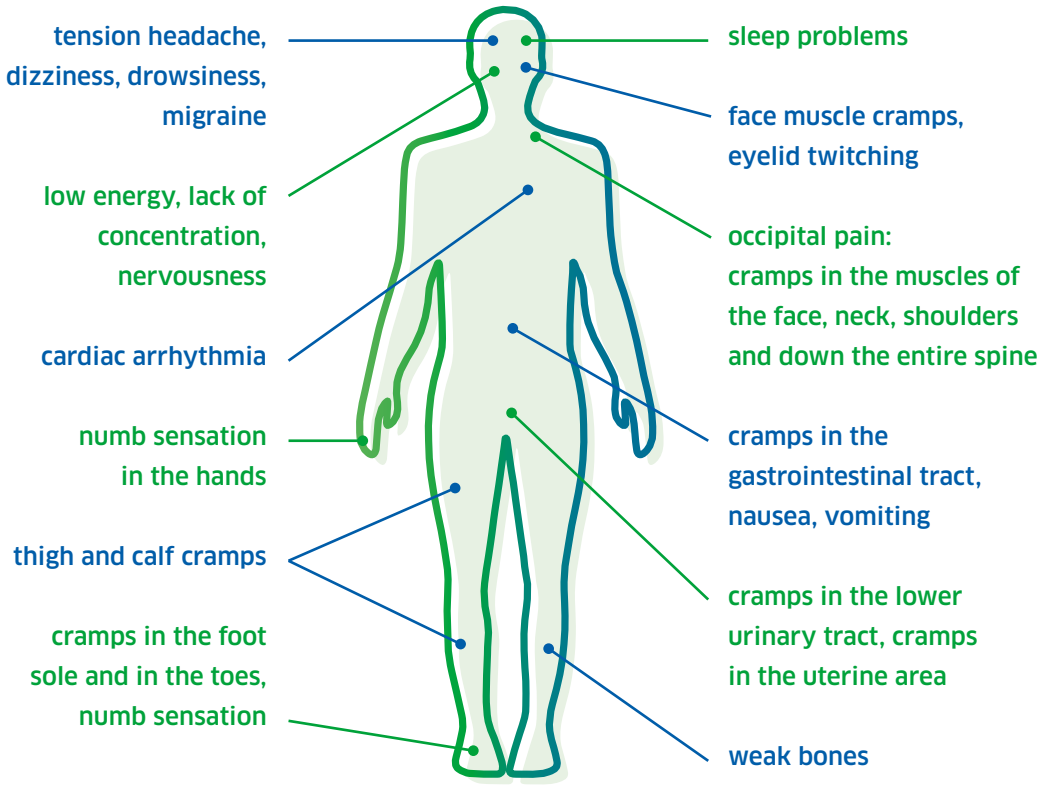
In cases of possible Mg deficiency or for follow-up

Hypomagnesemia is often associated with other electrolyte disorders

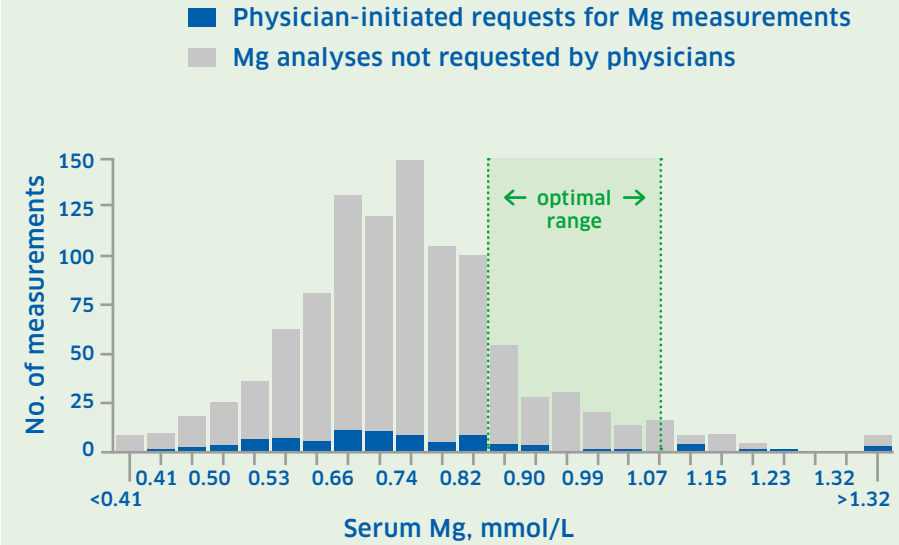
When evaluating **clinical symptoms**, one should be aware that milder symptoms such as cramps occur even at slightly decreased levels of serum Mg, while severe problems like seizures or tetany usually appear when serum Mg drops below 0.4 mmol/l.[1, 26]

Diagnosis of magnesium deficiency

It is essential to include typical symptoms and case history information in the evaluation of Mg status, since Mg deficiency may also be present in patients with normal serum Mg concentrations.[25] This happens because the body tries to balance serum Mg and redistributes Mg from bones to serum.



Serum Mg levels as measured at a primary care hospital[28]



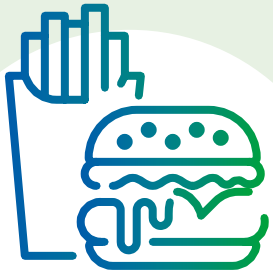
As serum Mg is rarely measured, the prevalence of Mg deficiency is often underestimated. A survey of 1,033 serum specimens for electrolyte analysis at a primary care hospital has shown that many cases of decreased Mg level are overlooked.[28]

Causes of hypomagnesemia

The main causes of hypomagnesemia are:[1, 26, 27]

Reduced intake

- Unbalanced diet
- "Nutrient-depleted" food
- Low-caloric diet



Impaired absorption (malabsorption)

- Genetic defects
- Gastrointestinal diseases
- Medication (PPI)

Increased excretion

- Genetic defects
- Diseases (diabetes)
- Abuse of alcohol, laxatives
- Medication (diuretics, cyclosporine, cisplatin)

Drug-induced hypomagnesemia

Many pharmaceuticals can induce or enhance Mg deficiency

Drugs that cause Mg deficiency[1, 27, 29]	
DIURETICS Loop diuretics (furosemide) Thiazide diuretics (chlorothiazide, indapamide)	**CYTOSTATICS** Cisplatin Carboplatinum
EGFR MODULATORS Cetuximab Erlotinib	**CALCINEURIN INHIBITORS** Cyclosporine A FK506 Tacrolimus
PPI Omeprazole Pantoprazole Lansoprazole Rabeprazole	**ANTIMICROBIOTICS** Aminoglycosides Pentamidine Rapamycin Amphotericin B Foscarnet
CARDIAC GLYCOSIDES Digoxin	**LAXATIVES**

Treatment of drug-induced hypomagnesemia:[1, 29]

- Withdrawal of drugs involved in the development of hypomagnesemia, if possible, or use of analogues (e.g. switch to K and Mg-sparing diuretics such as amiloride; cetuximab users may switch to erlotinib; PPI users may try histamine H2 receptor antagonists)
- Administration of oral Mg salts in mild hypomagnesemia
- Administration of Mg sulphate intravenously in severe hypomagnesemia, as well as in patients with poor intestinal Mg absorption

Drug-induced hypomagnesemia

Proton pump inhibitors (PPI)

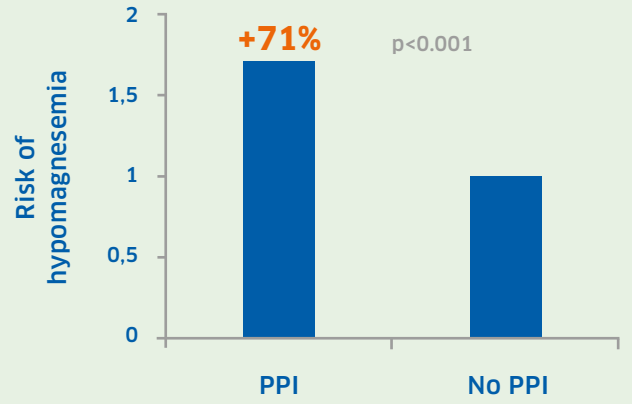
The PPI market is big and continues to grow, with an estimated increase of USD 3.45 billion from 2021 to 2025. The trend of shifting from prescription PPIs to OTC PPIs will continue.[30]

The long-term use of PPIs is associated with Mg malabsorption, which leads to severe Mg deficiency and resulting disorders.[29, 31] **About 20-30% of PPI users develop hypomagnesemia**[21, 22] evident due to the appearance of clinical symptoms and decreased serum Mg. In numerous case studies, patients with PPI-associated hypomagnesemia showed **critically low Mg levels** ranging between 0.03 and 0.71 mmol/L, with a median of 0.21 mmol/L.[32]

Meta-analysis of 16 studies revealed that PPI use increases the risk of hypomagnesemia 1.7-fold ($p<0.001$).[33] High-dose PPIs lead to 2.13-fold higher increase of hypomagnesemia risk compared to low-dose PPIs.[33]

PPI-induced hypomagnesemia typically occurs in elderly people on long-term treatment. In critically ill patients, even short-term PPI use may cause hypomagnesemia.[29] Mg deficiency in patients taking PPIs should be treated with organic Mg salts because they are absorbed independent of gastric acid.

PPI-induced hypomagnesemia[33]



Magnesium in therapy and research

REGULATION OF NEUROTRANSMITTERS AND HORMONES

- Catecholamines (adrenaline etc.)
- Hydrocortisone
- Energy and glucose metabolism
- Glutamate
- PTH
- Calcitonin
- Vitamin D

BRAIN

- Stress
- Sleep
- Migraine and headache
- Depression
- Epilepsy
- Craniocerebral trauma
- Parkinson‘s, Alzheimer‘s, dementia
- Schizophrenia

MUSCULOSKELETAL SYSTEM

- Muscle cramps
- Tetanic syndrome
- Fibromyalgia
- Pain
- Bone density and fragility
- Osteoporosis

CARDIOVASCULAR

- Coronary heart disease
- Myocardial infarction
- Cardiac arrhythmia
- Hypertension
- Stroke
- Atherosclerosis

LUNGS

- Asthma
- COPD

GERIATRICS

- Neurodegeneration
- Oxidative stress

PEDIATRICS

- ADHD

MAGNESIUM DEFICIENCY CAUSED BY …

… INCREASED REQUIREMENT

- During pregnancy and lactation
- During exercise

… INCREASED EXCRETION OF MAGNESIUM

- Alcoholism
- Malabsorption, eating disorders

GYNECOLOGY

- Premature labour
- Pre-eclampsia
- Gestational hypertension
- Gestational diabetes
- Dysmenorrhea and PMS

INTERACTION WITH OTHER MEDICINES

- PPI
- Diuretics
- Antibiotics

DIABETES

- Insulin resistance
- Dyslipidemia
- Metabolic syndrome
- Diabetic retinopathy, neuropathy and nephropathy

Magnesium and neuromuscular hyperexcitability – an overview

Muscle cramps

- Muscle cramps is a common health problem
- Up to 40% of the general population regularly suffers from muscle cramps
- Acute Mg deficiency is one of the most prevalent reasons behind muscle cramps

Restless legs syndrome (RLS)

- Prevalence of RLS in general population is up to 10%
- RLS markedly decreases the quality of sleep and therefore the quality of life
- Mg supplementations improves symptoms of RLS

Magnesium and neuromuscular hyperexcitability

Muscle cramps

Acute Mg deficiency is one of the most prevalent reasons behind muscle cramps.[34, 35] Mg deficiency leads to:[36]

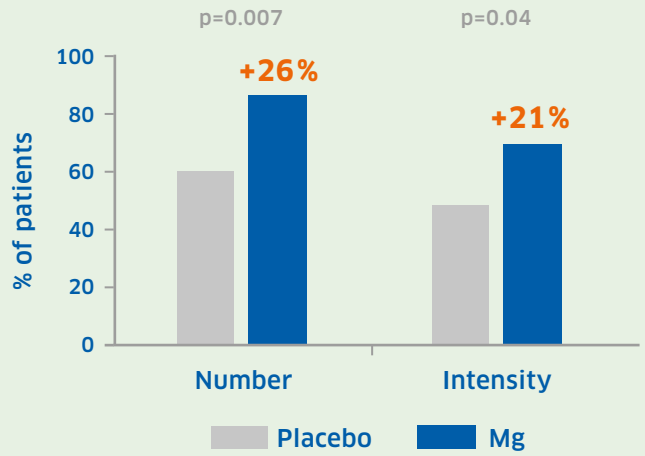
- Depolarisation of muscle cell membranes, which lowers the threshold for nerve stimulation and neurotransmitter release. Therefore, muscle cells have a greater chance of being triggered by various stimuli (neuromuscular hyperexcitability), which leads to involuntary muscle contractions and cramping.
- Reduced activity of Ca channels in muscle cells that causes excessive ATP and oxygen consumption and is linked to increased skeletal muscle excitability.

Muscle cramps in the calves usually occur at night most likely due to a circadian rhythm-dependent decrease in Mg concentration.[37]

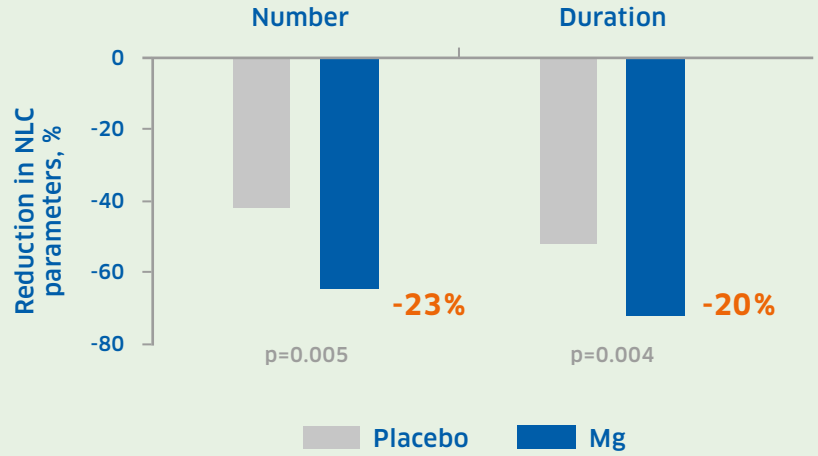
Pregnant women with higher serum Mg levels have lower prevalence of leg cramps[19]; Mg supplementation significantly improves pregnancy-related leg cramps.[38, 39]

Mg supplementation was also effective against muscle cramps in **elderly patients**[40] and in patients suffering from **nocturnal leg cramps (NLC).**[41]

50% reduction in parameters of leg cramps[39]



Reduction of NLC parameters[41]



Magnesium and neuromuscular hyperexcitability

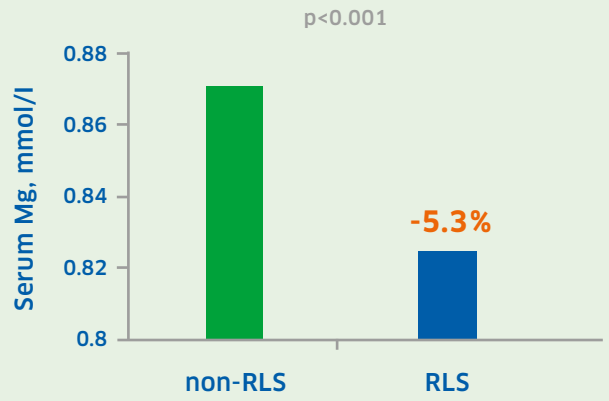
Restless legs syndrome

Restless legs syndrome (RLS) is a multifactorial movement disorder, in which patients have the urge to move their legs due to unpleasant sensations, and this urge to move further increases during rest. RLS significantly decreases quality of sleep and quality of life.
The prevalence of RLS in the general population is 2-10%.

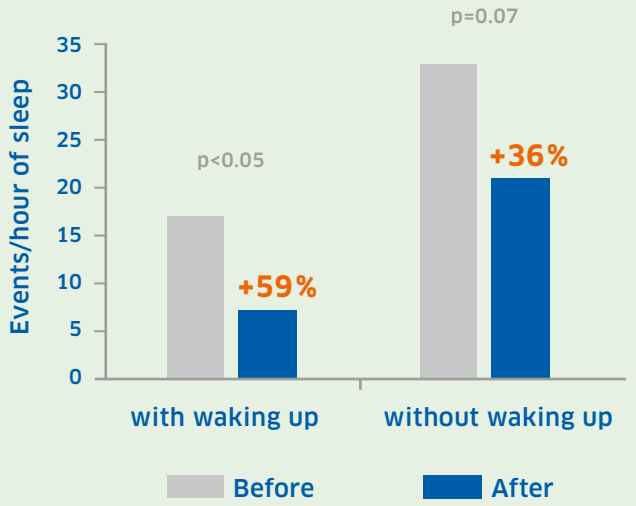
Pregnant women with RLS have significantly **lower serum Mg levels**[42]

In people with RLS, **Mg supplementation improves** periodic limb movements during sleep[43]

Serum Mg in pregnant women[42]



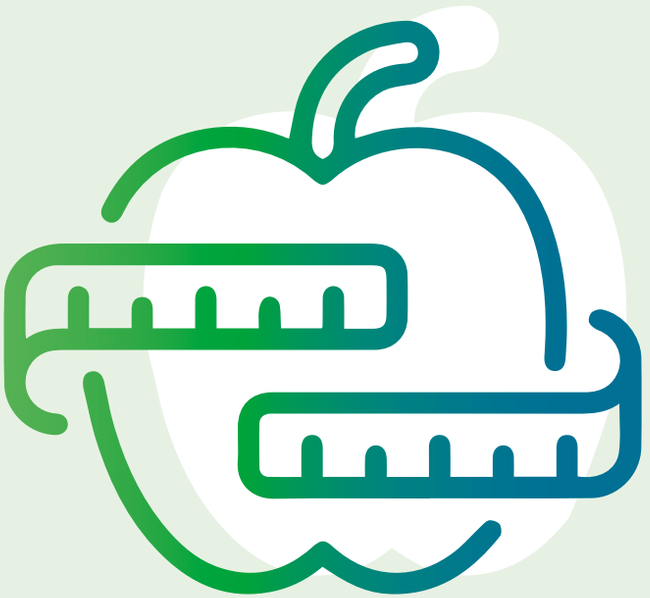
Periodic limb movements during sleep[43]



Magnesium and metabolic syndrome – an overview

Mg is involved in pathogenesis and progression of metabolic syndrom (MetS)

- Patients with metabolic syndrome have significantly lower Mg levels
- Mg intake reduces the risk for MetS
- Parameters of MetS (blood pressure, insulin resistance, triglyceride levels) are improved by Mg supplementation



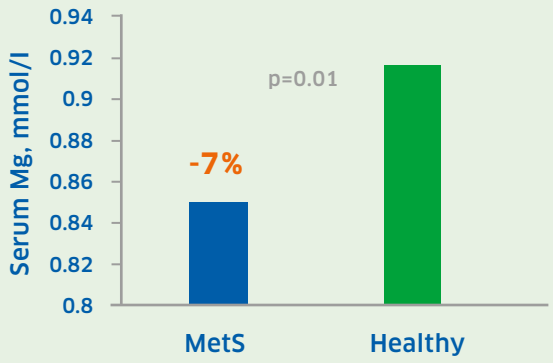
Magnesium and metabolic syndrome

Metabolic syndrome (MetS) is a pathological condition characterised by a set of metabolic impairments: insulin resistance, obesity, atherogenic dyslipidemia (high plasma triglycerides levels and/or low high-density lipoprotein cholesterol levels), and hypertension.[44, 45] MetS is a serious health problem as it increases the risk of various diseases.

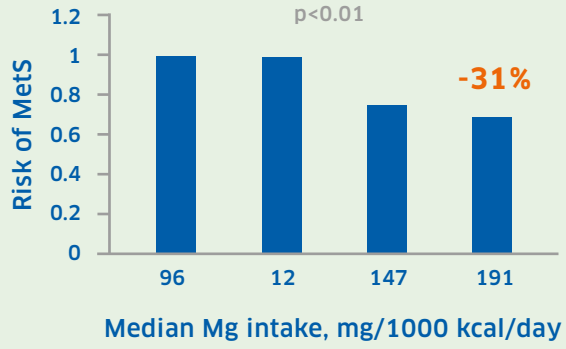
Mg deficiency is involved in MetS pathogenesis:

- Patients with MetS have significantly lower Mg levels compared to healthy people[46-48], and low Mg levels are associated with a 44-56% higher risk of MetS.[49, 50]
- Only 25-30% of non-diabetic individuals with MetS met the RDA (recommended dietary allowance) for dietary Mg intake[51], and an inverse association was found between dietary Mg intake and the prevalence of the MetS [52-54] as well as with the severity of MetS parameters.[51, 53]
- A meta-analysis of five studies has shown that for every 100 mg/day increment in Mg intake, the overall risk of having MetS was lowered by 17%.[55]

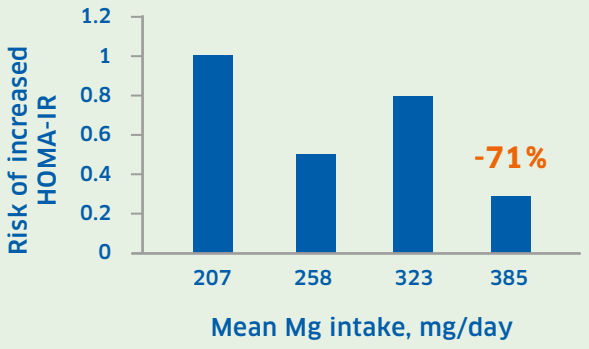
MetS patients have lower serum Mg[47]



Decrease in risk of MetS[53]



Insulin resistance in MetS patients [51]

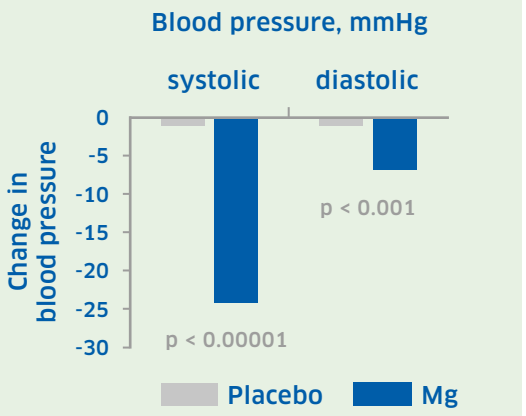


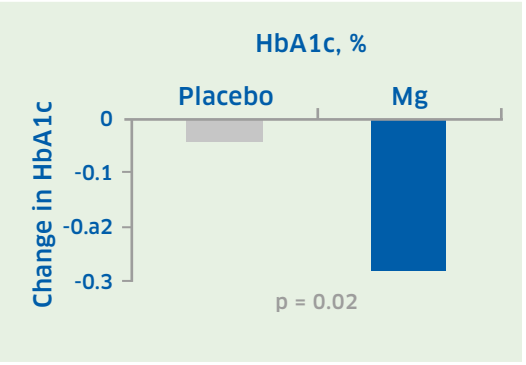
Magnesium and metabolic syndrome

Mg supplementation significantly improves MetS parameters:

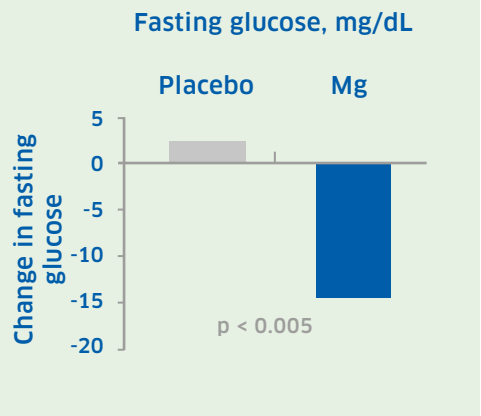
- In normomagnesemic individuals with MetS, supplementation with Mg citrate (Magnesium-Diasporal®) significantly reduced HbA1c and both systolic and diastolic blood pressure.[56]
- Mg supplementation significantly reduced systolic and diastolic blood pressure values, insulin resistance, fasting glucose and triglyceride levels in metabolically obese, normal-weight individuals[57] and in MetS patients.[58]
- In non-diabetic subjects with insulin resistance, Mg supplementation significantly improved fasting glucose and fasting insulin, HOMA-IR index and the lipid profile.[59]

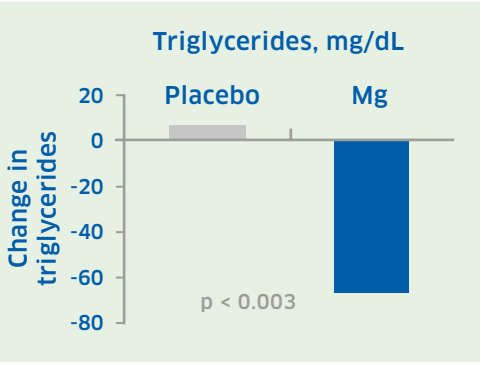
Decrease in MetS parameters[56]



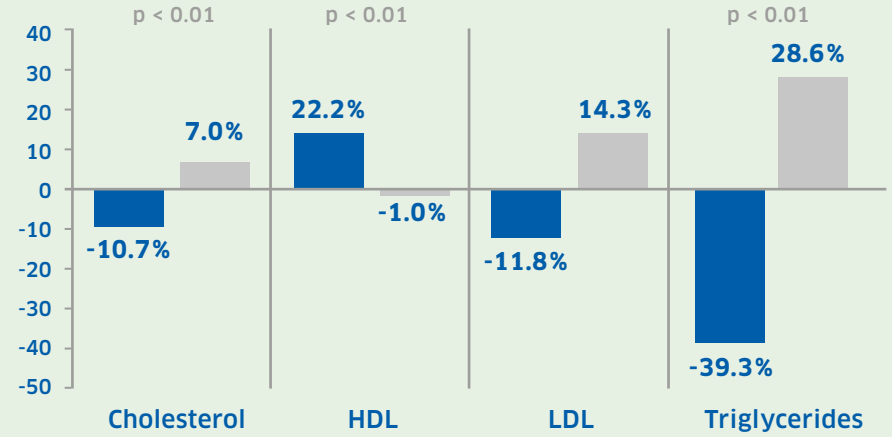


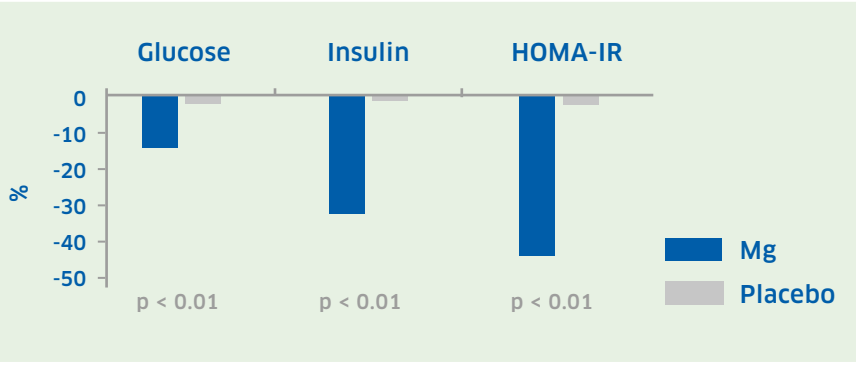
Reduction in MetS parameters[58]





Improvement in MetS parameters[59]





Magnesium and diabetes – an overview

Mg deficiency is involved in pathogenesis and progression of diabetes

- Prevalence of Mg deficiency in diabetics is 50-65%
- Mg deficiency as well as inadequate Mg intake are risk factors for the development of type 2 diabetes
- Mg supplementation improves parameters of diabetes: Hb1Ac, fasting glucose, insulin levels and insulin resistance (HOMA-IR)
- Hypomagnesemia is also common in patients with diabetes complications: nephropathy, neuropathy, and retinopathy

Magnesium and diabetes

Diabetes mellitus is a complex chronic disease characterised by hyperglycemia:

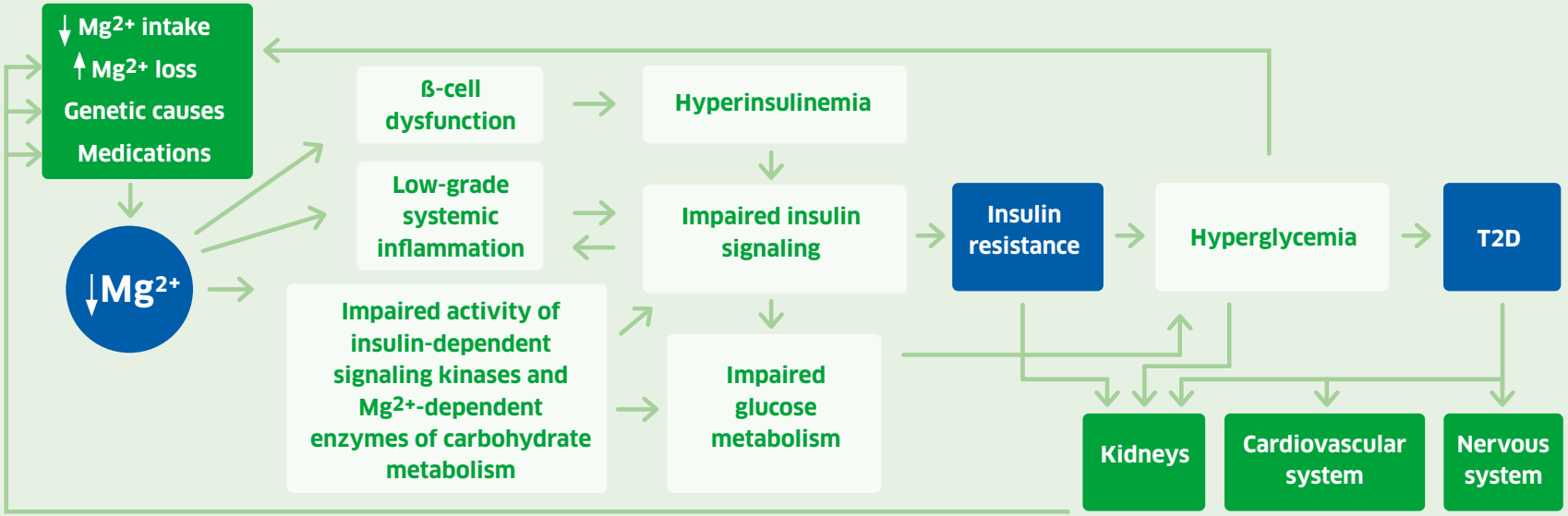
- Type 1 is caused by the loss of the insulin-producing beta cells in pancreas, leading to insulin deficiency.
- Type 2 is characterised by insulin resistance that develops primarily due to lifestyle factors and genetics. Type 2 diabetes (T2D) makes up about 90% of all diabetes cases[60].

In 2019, an estimated 463 million people worldwide had diabetes **(9.3% of the population)**, rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.[61] Diabetes at least doubles a person's risk of early death and is the 7th leading cause of death globally.

Mg deficiency is involved in diabetes pathogenesis[62]:

- Mg is required for the activation of the insulin receptor, an important step in transmitting the insulin signal into cells[63]
- Low Mg levels alter cellular glucose transport and decrease cellular glucose utilization[64]

Mg and type 2 diabetes[64]

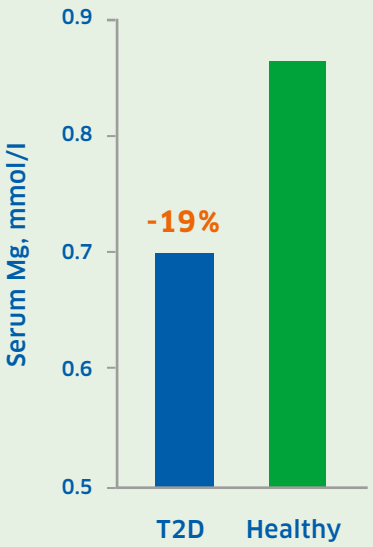


Magnesium and diabetes

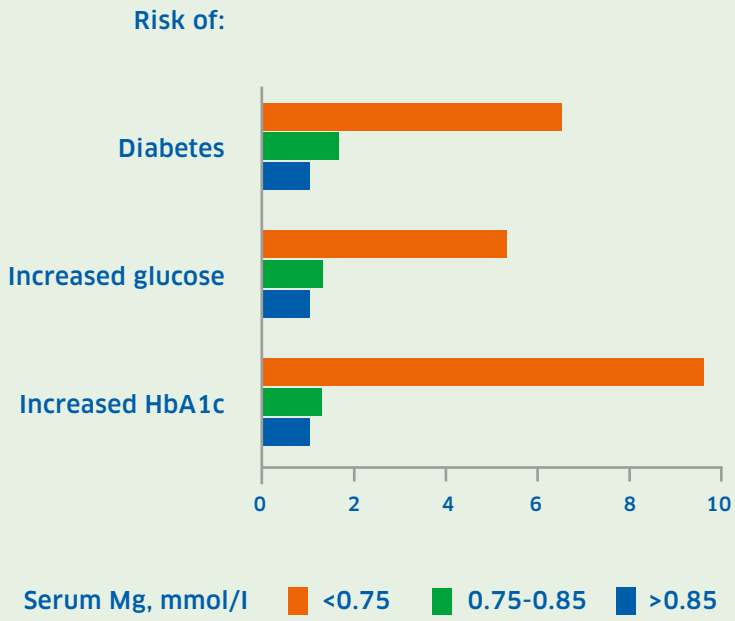
Patients with T2D have significantly lower Mg levels than healthy people[65-67]

- The prevalence of hypomagnesemia in diabetics reaches 50-65%[17]
- Serum Mg concentration negatively correlates with HbA1c, serum glucose and insulin concentrations[68] as well as with diabetes severity and duration[17]
- Decreased Mg levels increase the risk of T2D[69, 70] and its parameters such as increased glucose levels, HbA1c[66, 69] and insulin resistance[70]
- According to a meta-analysis of 26 studies, a higher Mg intake was associated with a 22% lower risk for T2D; the risk was reduced by 6% for each 100 mg increment of daily Mg intake[71]

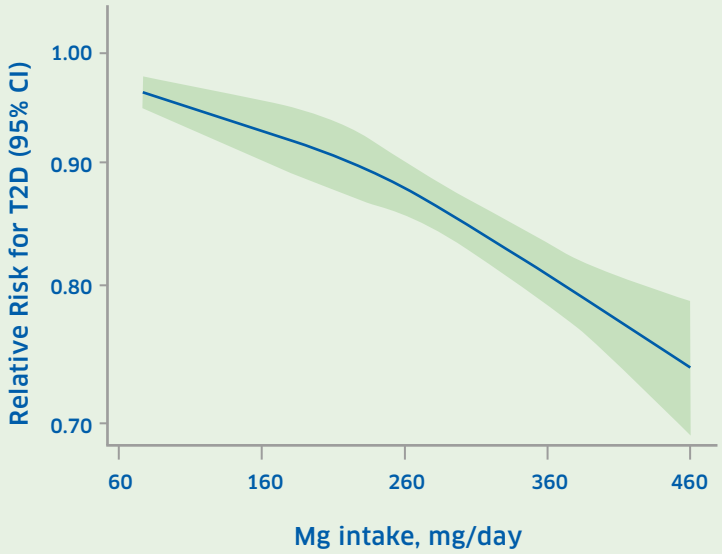
Lower serum Mg in T2D[67]



Risk of diabetes and its parameters[69]



Mg Intake and risk of T2D[71]

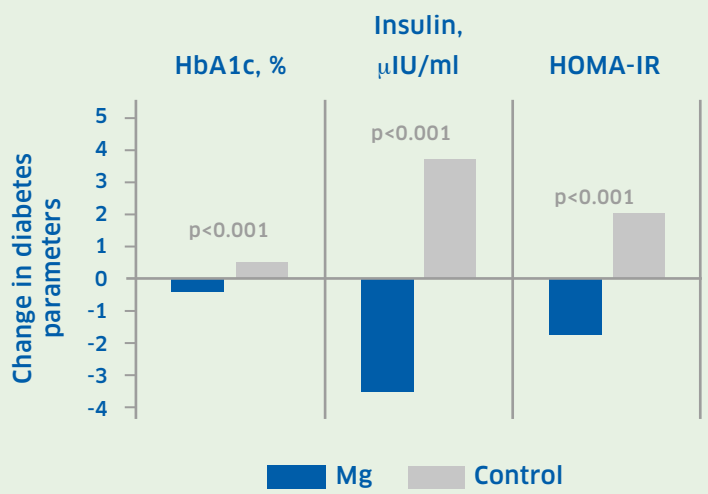


Magnesium and diabetes

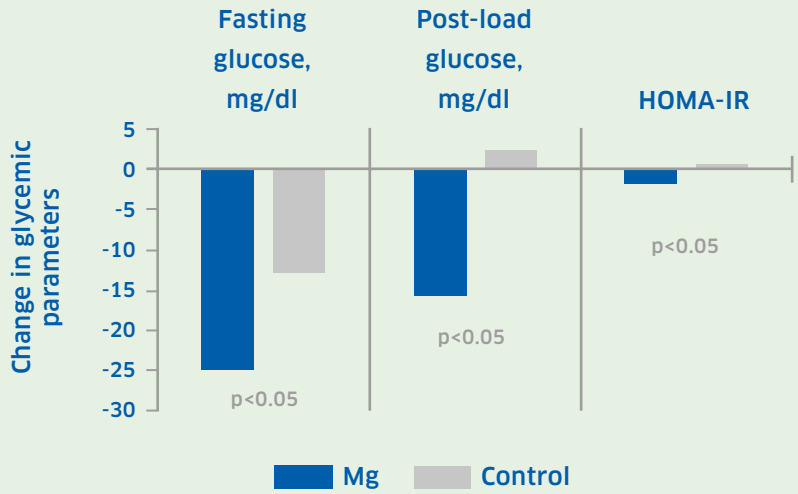
Mg supplementation significantly improves diabetes parameters:

- Mg supplementation significantly improved HbA1c, insulin levels and HOMA-IR in T2D patients and in prediabetics[72-74]
- Mg supplementation in T2D patients with CKD led to significant decrease in HbA1c, insulin resistance, fasting insulin and waist circumference[75]
- The effects of Mg supplementation on diabetes parameters are more pronounced in hypomagnesemic patients[76] and if duration of supplementation exceeds 4 months[77]

Effects of Mg supplemenation on T2D[72]



Mg supplemenation in prediabetes[74]

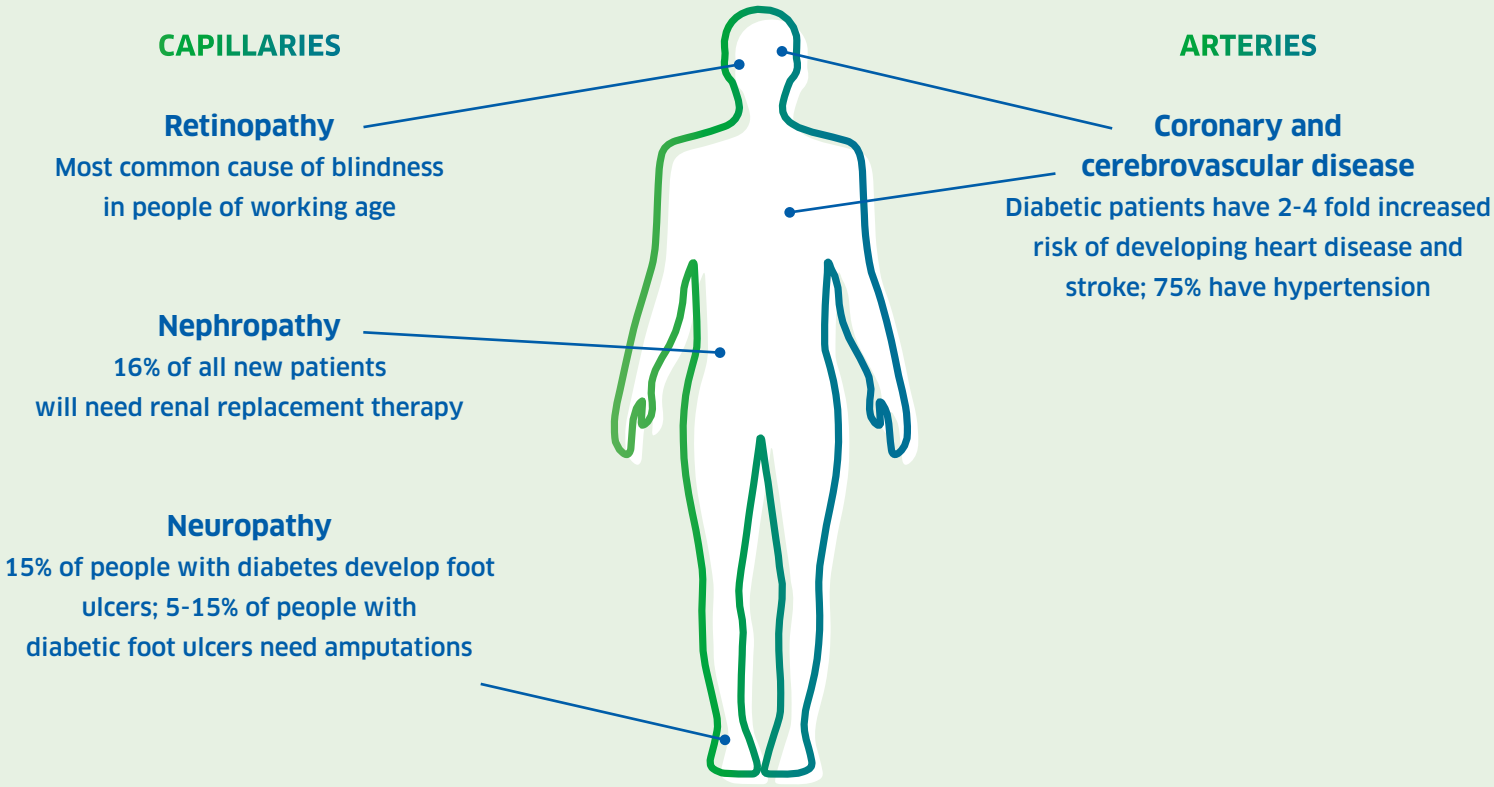


Magnesium and diabetes

Diabetes complications

- Diabetes is associated with an increased risk of developing vascular complications that contribute to **morbidity and mortality** of patients
- Poor glycemic and blood pressure control lead to vascular complications that affect large (macrovascular), small (microvascular) vessels, or both[60, 78]
- The macrovascular complications may lead to a 2 to 4-fold higher incidence of cerebrovascular stroke, coronary heart disease and peripheral vascular disease
- Microvascular complications contribute to diabetic **neuropathy** (nerve damage), **nephropathy** (kidney disease) and **retinopathy** (eye disease)

Macrovascular and microvascular complications of diabetes[78]



Magnesium and diabetes

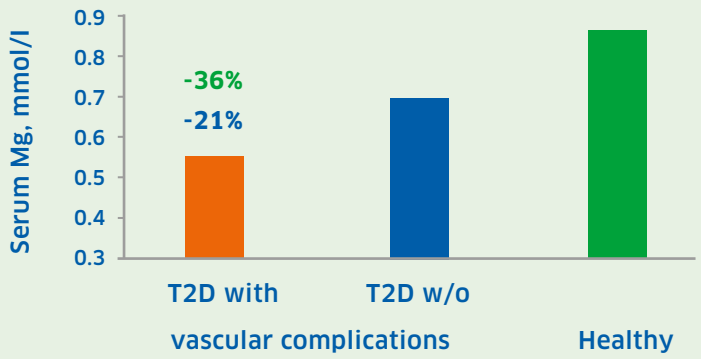
Mg deficiency is associated with the development and progression of T2D complications:

- Diabetics with microvascular and macrovascular **complications** (retinopathy, peripheral vascular disease and coronary heart disease) have lower serum Mg than diabetics without complications and than healthy people[67]; this is also true for patients with diabetic nephropathy[79, 80]
- Hypomagnesemia is associated with progression of diabetic **nephropathy**[81], and patients with serum Mg <0.75 mmol/l have 2.12-fold higher risk of developing end-stage renal disease than patients with serum Mg >0.75 mmol/l (p = 0.004)[82]
- Hypomagnesemia is more prevalent in patients with diabetic **retinopathy**[83] and leads to almost 4-fold increase in the risk of diabetic retinopathy[84]. Serum Mg correlates with severity of retinopathy[85, 86]: each 0.1 mmol/L increase in serum Mg decreases the risk of sight-threatening diabetic retinopathy by 23%[86]
- Serum Mg is also significantly lower in patients with diabetic **neuropathy** (foot ulcer)[87-89]; low serum Mg increases the risk of foot ulcer almost 3-fold[87]

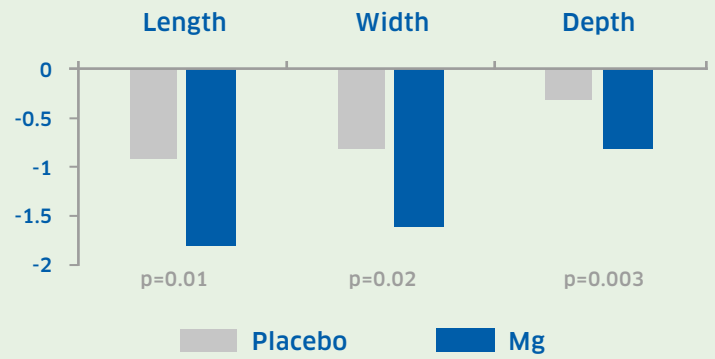
Mg supplementation is beneficial for patients with diabetes complications:

- Mg supplementation in patients with diabetic neuropathy (diabetic foot ulcer) led to significant decrease in ulcer parameters as well as to significant improvement of fasting plasma glucose, serum insulin and HbA1c[90]
- Co-supplementation of Mg and vitamin E led to similar results: decrease of ulcer length, width and depth and improved glycemic control[91]

Serum Mg in T2D complications[67]



Improvement in diabetic foot ulcer parameters, cm[90]



Magnesium and cardiovascular diseases – an overview

Mg deficiency is associated with the development of cardiovascular diseases (CVD) and Mg intake has positive effects on cardiac function

- Mg deficiency has a negative effect on functioning of blood vessels and myocardial contractility
- Low Mg levels increase the risk of various CVD, such as heart failure, stroke, hypertension etc.
- Higher Mg intake significantly reduces the risk and fatality of coronary heart disease
- Mg supplementation is effective in improvement of hypertension, cardiac function and heart rate

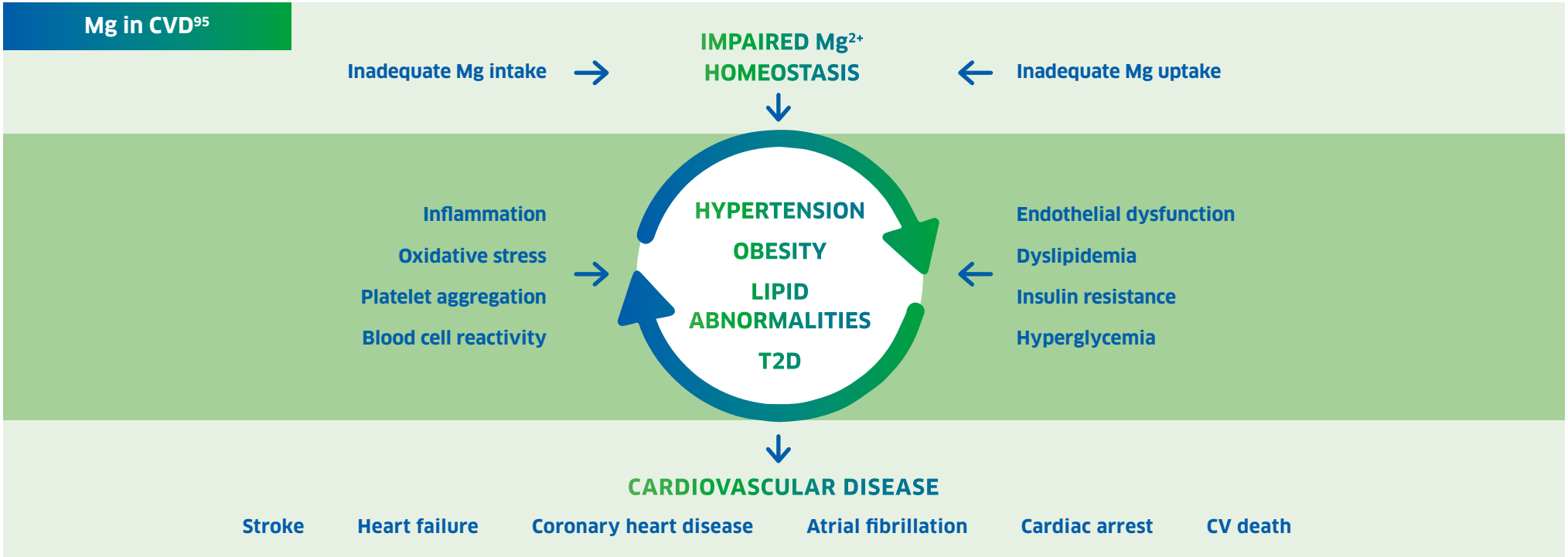
Magnesium and cardiovascular diseases

Mg has beneficial effects on the cardiovascular system:[1, 3]

- Mg is required for the proper functioning of cardiomyocytes as it regulates activity of ion channels and myocardial contractility
- Mg improves lipid metabolism, reduces inflammation, and inhibits platelet function
- Mg has a vasodilatory effect

Mg deficiency is involved in CVD:[92]

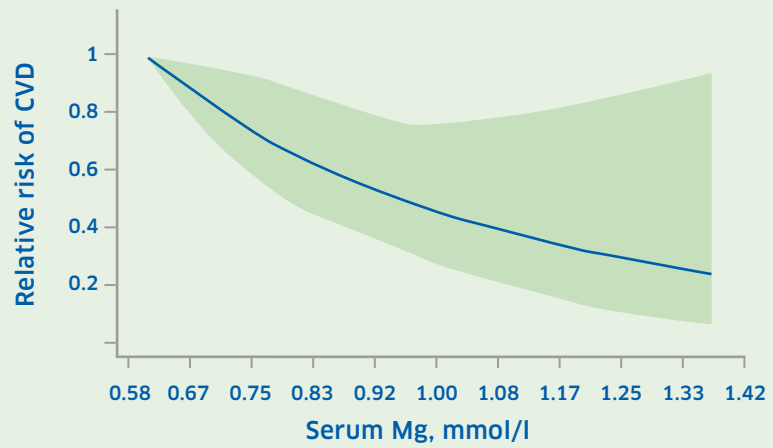
- Hypomagnesemia induces oxidative stress, mitochondrial dysfunction and inflammation, which are among the common mechanisms of CVD[93]
- Mg deficiency is associated with heart failure, heart rhythm abnormalities and atrial fibrillation, hypertension, vascular calcification and coronary artery disease[94, 95] and Mg supplementation was shown to improve the symptoms and outcomes[93]



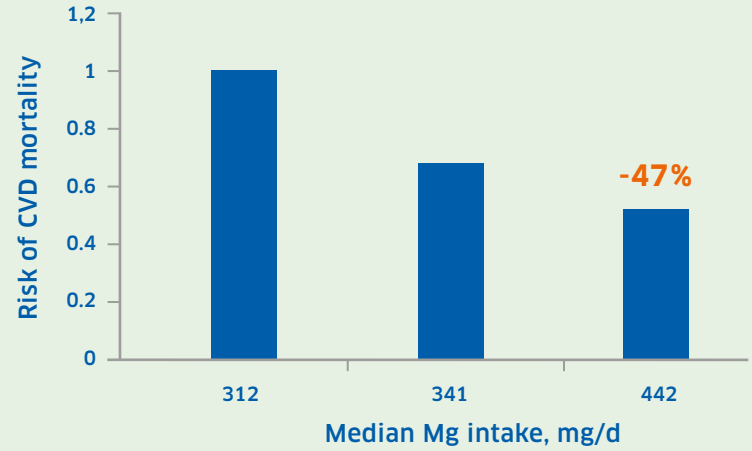
Magnesium and cardiovascular diseases

- A meta-analysis of 18 studies showed that each 0.04 mmol/l increase in serum Mg decreases the risk of CVD by 7%, and increase of dietary Mg by 100 mg/day decreases the risk of CVD by 10%[96]
- Higher dietary Mg intake led to a 34% lower risk of CVD and a 38% lower risk of atherosclerotic CVD[97]; it also decreased the risk of CVD mortality by 47% and the risk of all-cause mortality by 37%[98]
- For prevention and treatment of CVD, the Israel Heart Society and the Israel Dietetic Association recommend to increase consumption of Mg-rich food, and for those not getting enough Mg with food, **supplementation up to 600 mg/day** should be considered[92]
- Mg citrate supplementation in overweight and obese patients significantly reduced arterial stiffness (a predictor of ischemic heart disease, CVD risk and CVD mortality)[99]

Serum Mg and CVD risk[96]



Risk of CVD mortality[98]



Magnesium and cardiovascular diseases

Hypertension

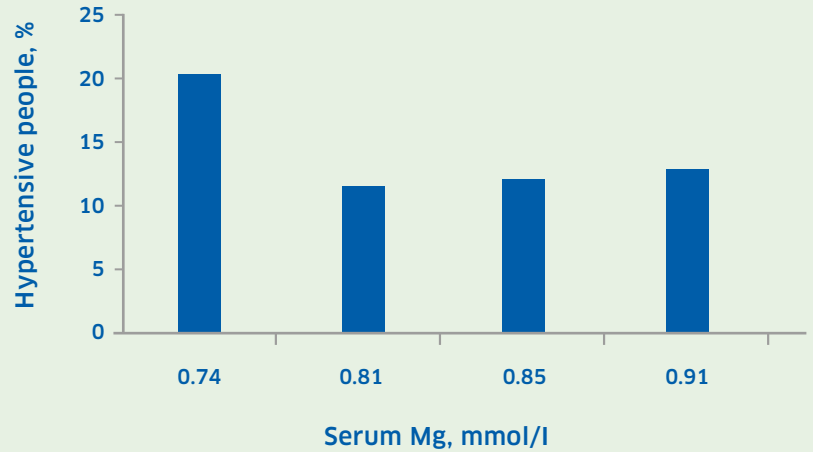
Mg regulates blood pressure (BP):[11, 100]

- Mg decreases Ca concentration in vascular muscle cells and therefore leads to vasodilatation
- Mg enhances production of such vasodilators as NO and prostaglandins
- Mg decreases secretion of the stress hormone adrenaline

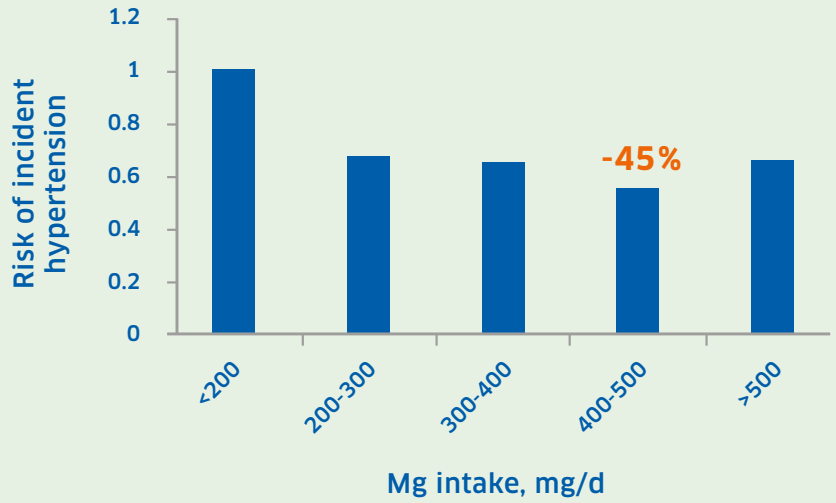
Mg deficiency is associated with hypertension:

- There is an inverse correlation between serum Mg concentration and hypertension[70, 101]
- Dietary Mg intake of people with hypertension is 23% lower, and of people with prehypertension – 12% lower than that of normotensive people[102]
- Higher dietary Mg intake decreases the risk of incident hypertension by 45%[103]

Serum Mg and prevalence of hypertension[70]



Mg intake and risk of hypertension[103]



Magnesium and cardiovascular diseases

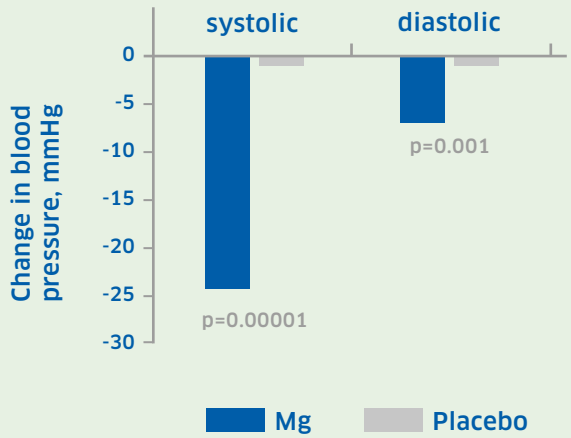
Hypertension

European Society of Hypertension claims that Mg supplementation could improve BP[104]

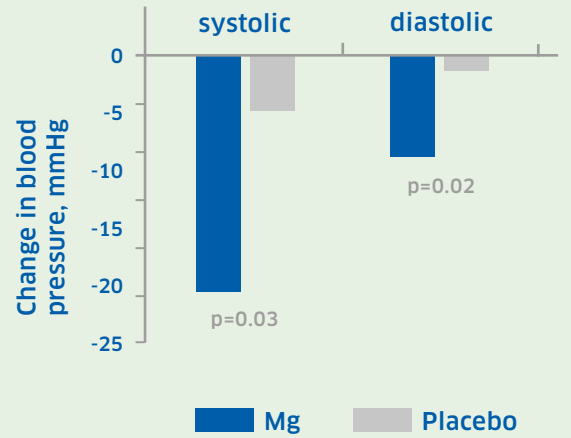
Mg supplementation is effective in BP reduction:

- Several meta-analyses confirmed that Mg supplementation leads to a significant decrease in systolic and diastolic BP[105-107]
- Mg significantly reduced both systolic and diastolic BP in MetS patients[56, 58], in metabolically obese, normal-weight individuals[57], and in T2D patients with hypertension[108]
- Mg led to a significant reduction of systolic BP (8.97 ± 2.01 mmHg), diastolic BP (5.87 ± 1.49 mmHg) and mean arterial pressure (8.06 ± 1.67mmHg), as well as a decrease in systemic vascular resistance and left cardiac work[109]
- Mg may lead to a reduction of antihypertensive medication[110]

Mg decreases BP in MetS patients[56]



Mg decreases BP in T2D patients[108]

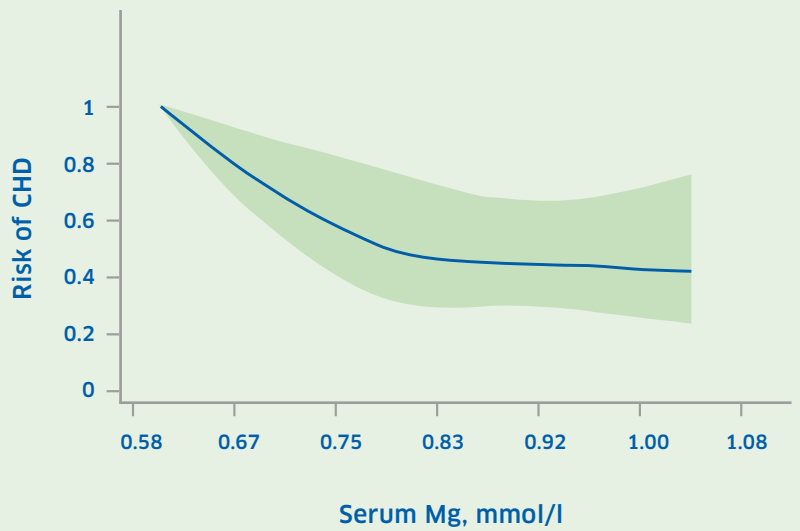


Magnesium and cardiovascular diseases

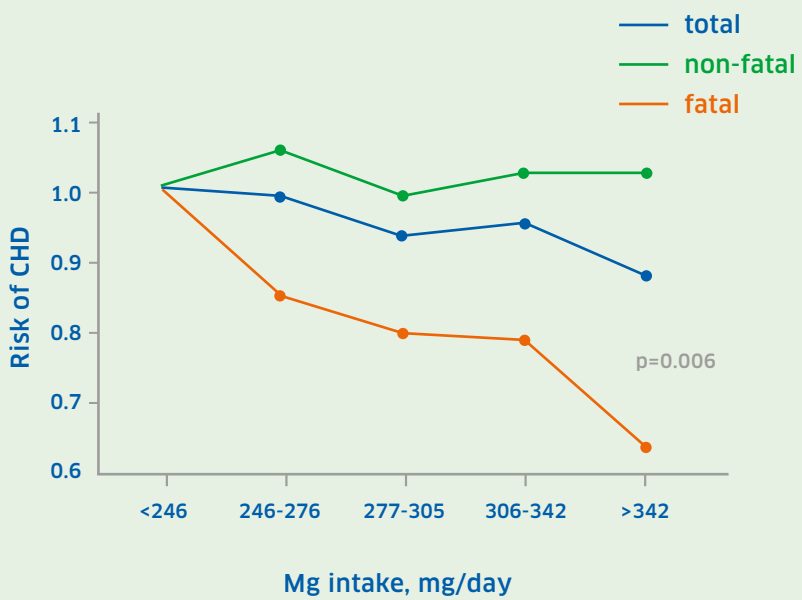
Cardiac function and coronary heart disease

- Meta-analysis of 18 studies showed that each 0.04 mmol/l increase in serum Mg decreases the risk of coronary heart disease (CHD) by 10%[96]
- Low serum Mg (≤0.80 mmol/L) increased the risk of CHD mortality by 36% and of sudden cardiac death by 54%[111]
- Higher dietary intake of Mg decreased the risk of CHD by 34-60%[96, 112, 113] and the fatality of CHD by 36%[114]

Serum Mg and risk of CHD[96]



CHD fatality[114]



Magnesium and cardiovascular diseases

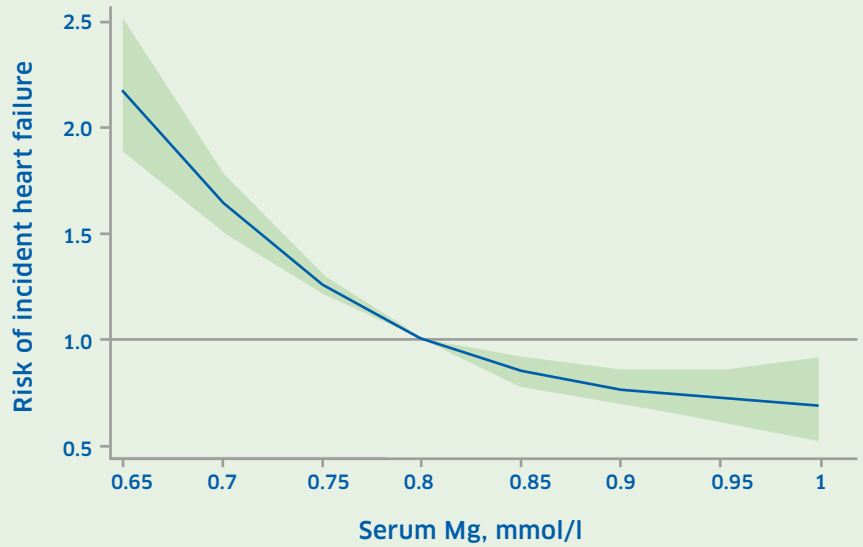
Cardiac function and coronary heart disease

- Low serum Mg increases the risk of incident heart failure by 71%[115]
- Meta-analysis of 40 studies showed that 100 mg/day increase in dietary Mg intake led to a 22% reduction in the risk of heart failure[116]

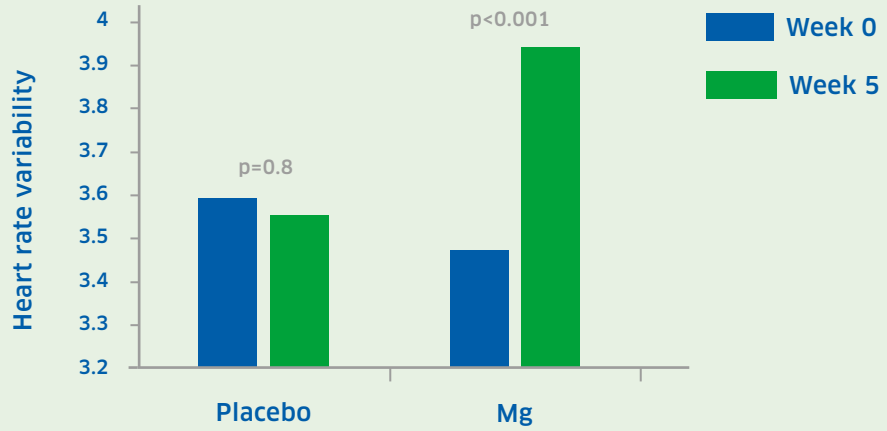
Mg supplementation improves cardiac function:

- Mg significantly improves heart rate variability (Magnesium-Diasporal®)[118], increases the survival rate and improves clinical symptoms[119] and improves endothelial function[120] in patients with heart failure
- Mg significantly improves myocardial function and heart rate[121] as well as endothelial function[122] in patients with coronary artery disease

Serum Mg and risk of heart failure[115]



Mg improves heart rate variability[118]



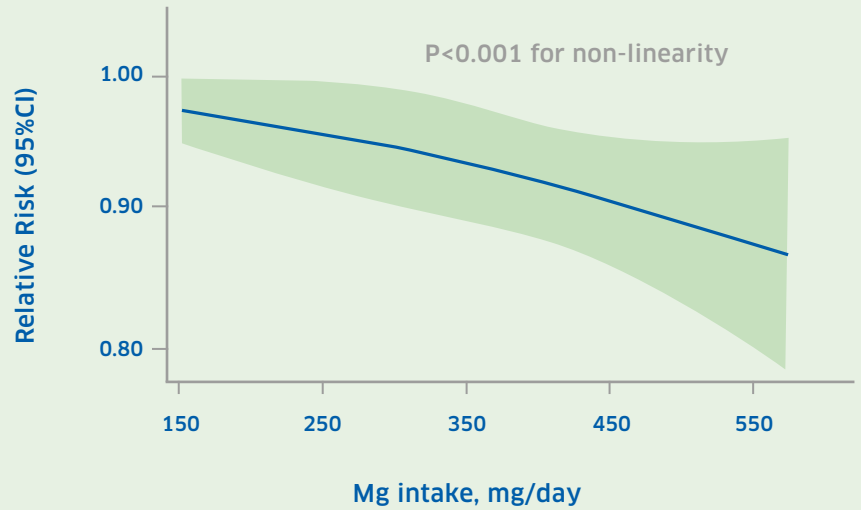
The German Society for Magnesium Research recommends oral Mg supplementation as single agent or as an adjunct to other therapeutic actions in the prevention and treatment of cardiac arrhythmias[117]

Magnesium and cardiovascular diseases

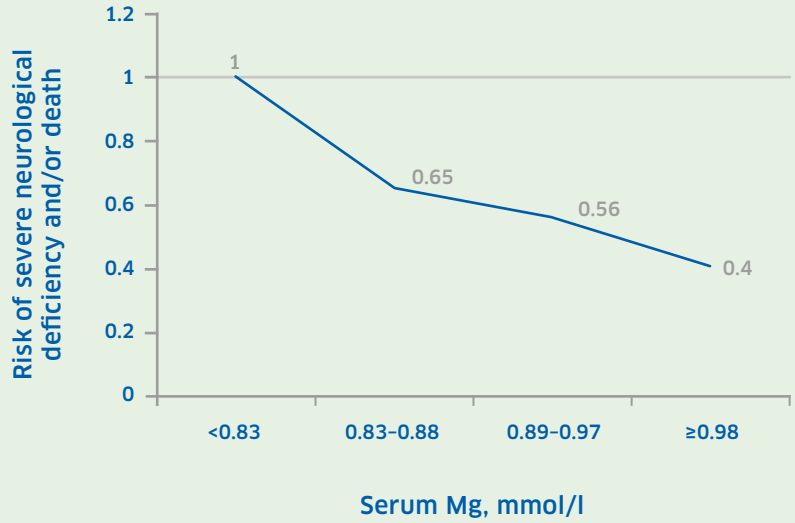
Stroke

- Lower dietary Mg intake increases the risk of total and ischemic, but not hemorrhagic stroke[123, 124]
- Meta-analyses (40 and 41 studies, respectively) showed that 100 mg/day increase in dietary Mg intake led to a 2-7% reduction in the risk of stroke[116, 124]
- Serum Mg is decreased after stroke[125, 126] and correlates with stroke severity[126] and development of post-stroke depression[125]
- Higher serum Mg decreases the risk of ischemic stroke[127] and leads to a 60% lower risk of severe neurological deficiency and/or death after acute ischemic stroke[128]

Decreased risk of stroke[116]



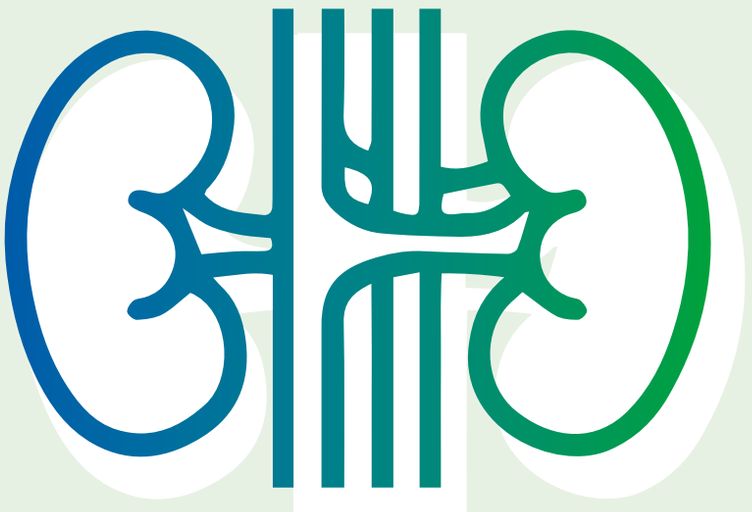
Serum Mg and risk of stroke outcomes[128]



Magnesium and chronic kidney disease – an overview

Chronic kidney disease (CKD) enhances Mg deficiency and hypomagnesemia is involved in progression of CKD

- Both low serum Mg levels and low Mg intake lead to a faster decline in renal function
- Hypomagnesemia increases the risk of all-cause mortality in CKD patients



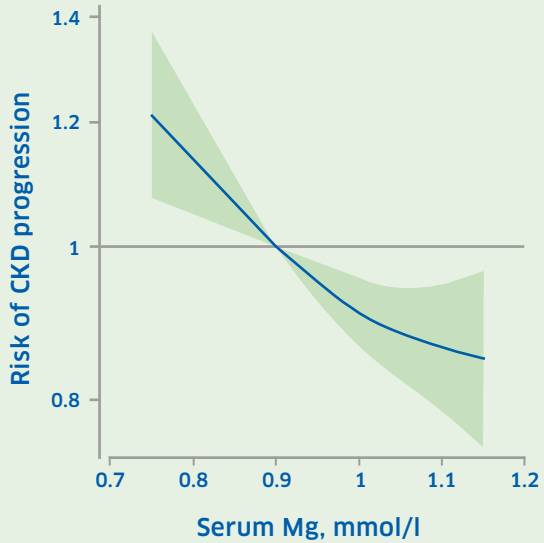
Magnesium and chronic kidney disease

Chronic kidney disease (CKD) is characterised by a gradual loss of kidney function. The global estimated prevalence of CKD is 13.4%.[129]

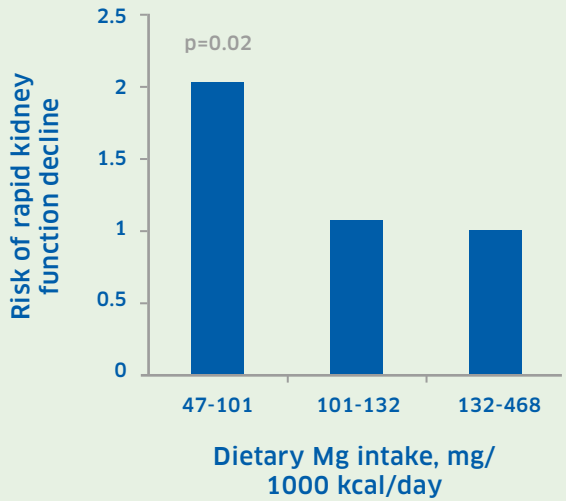
During CKD, tubular dysfunction/interstitial fibrosis impairs tubular Mg reabsorption and therefore enhances Mg deficiency. Hypomagnesemia is in turn involved in the progression of CKD by increasing tubular cell death and inflammation induced by phosphate load.[130]

- Low serum Mg leads to faster decline in renal function[131] (–0.23 mL/min/1.73m² per year per each 0.08 mmol/l decrease) and increases the risk of CKD progression[132] (32% for each 0.5 mmol/l increase in serum Mg)
- Lower dietary Mg intake led to a 2-fold increase in the risk of rapid kidney function decline (>3% eGFR decline per year)[133]
- Hypomagnesemia increases the risk of all-cause mortality 2-fold (meta-analysis of 31 studies)[134], and each 0.1 mmol/l increase in serum Mg decreases the risk by 10% (meta-analysis of 22 studies)[135]
- Other studies, however, suggest U-shaped dependence, with increased risk of all-cause mortality at serum Mg < 0,79 mmol/L and >0,88 mmol/L[136]

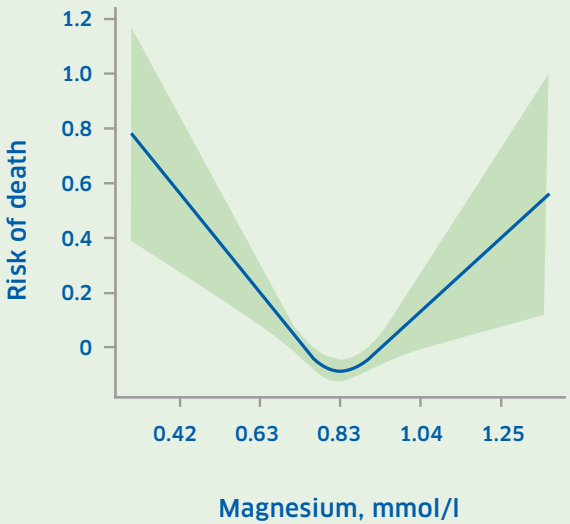
Serum Mg and risk of CKD progression[132]



Mg intake and rapid kidney function decline[133]



Serum Mg and mortality in CKD[136]



Magnesium and mental health – an overview

Mg is essential for the function of the nervous system. Mg deficiency is involved in the development of various mental diseases

- Mg is required for good brain health in older people
- Mg is involved in answer to stress
- Low Mg levels and insufficient Mg intake increase the risk of mental diseases such as depression, hyperactivity, and anxiety
- Mg supplementation decreases the severity of depression and anxiety and improves the quality of sleep

Magnesium and mental health

Mg plays an important role in the proper functioning of nervous system:[1,137-139]

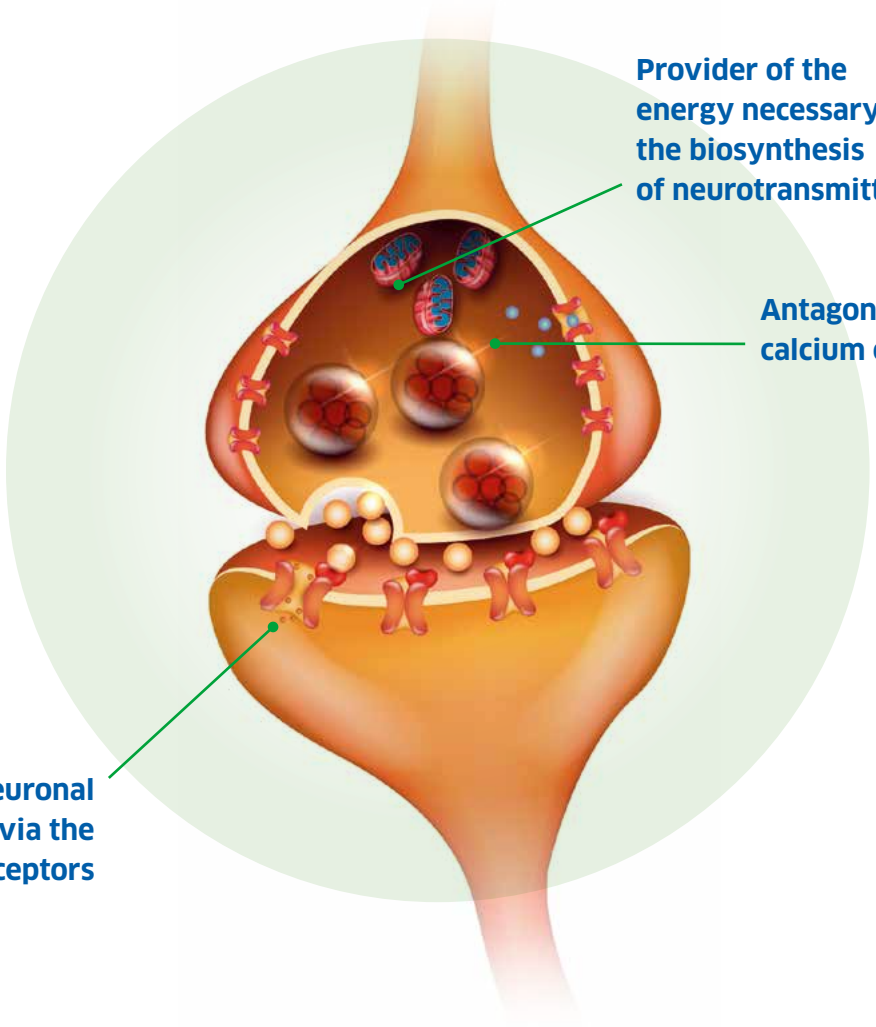
- Mg supports neuronal development
- Mg is required for neuronal activity and synaptic transmission
- Mg regulates glutamate signalling in the brain

Mg deficiency is involved in development of depression, anxiety, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder, and other disorders[139, 140]

Moreover, Mg is required for brain health in older age:

- Serum Mg >0.75 mmol/l[141] as well as higher intake of total Mg[142] were associated with better cognition in older adults
- Serum Mg <0,58 mmol/l increased the risk of incident dementia by 24%[143]
- A meta-analysis of 18 studies showed that people suffering from Alzheimer's disease have significantly lower serum and plasma Mg than healthy controls[144]

MAGNESIUM IS MANDATORY FOR THE FUNCTION OF SYNAPSES[1]



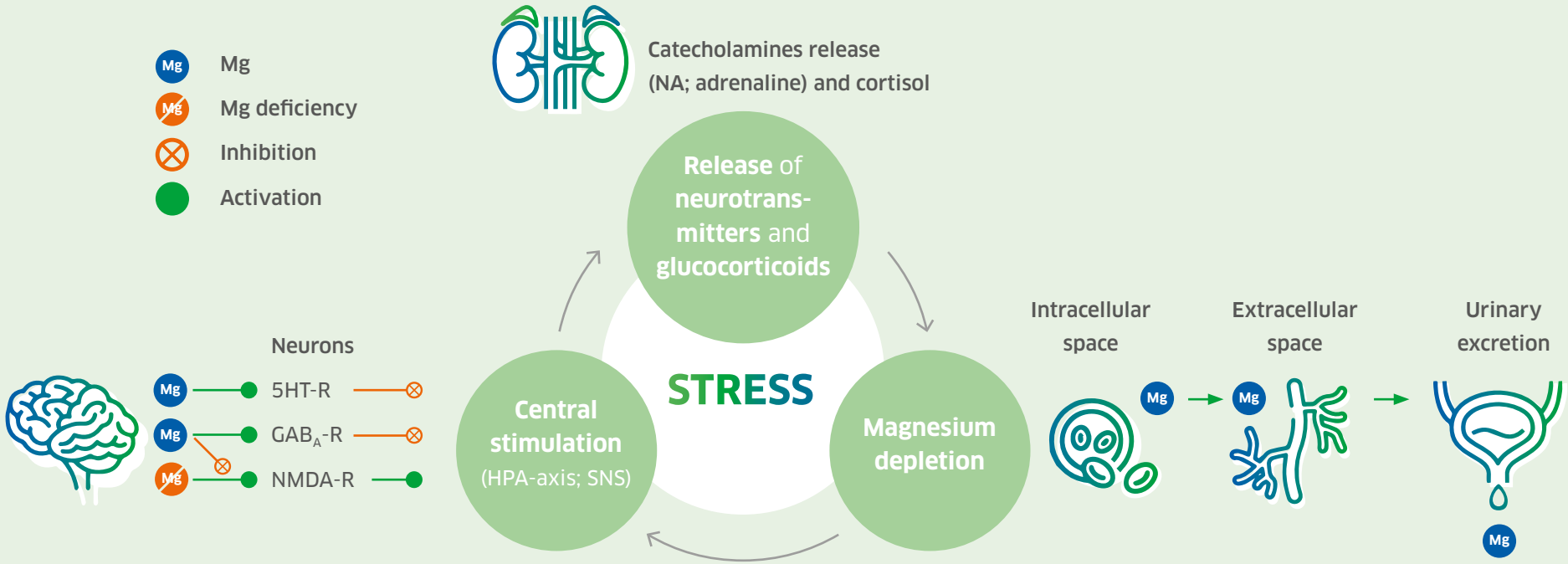
Magnesium and mental health

Stress and depression

Mg is involved in the response to stressful stimuli:[145]

- Mg is required for the transmission of serotoninergic, GABAergic and glutamatergic (NMDA) signals
- Mg has a neuroprotective function and decreases oxidative stress
- Mg regulates the release of stress hormones such as adrenaline, noradrenaline and hydrocortisone
- Symptoms of Mg deficiency and of stress are very similar, the most common being fatigue, irritability, and mild anxiety

Mg and stress[145]



GABAA-R, γ-aminobutyric acid-A receptor; NMDA-R, N-methyl-D-aspartate receptor; NA, noradrenaline; SNS, sympathetic nervous system, 5HT-R, 5-hydroxytryptamine (serotonin) receptor; HPA, hypothalamic–pituitary–adrenal axis

Magnesium and mental health

Stress and depression

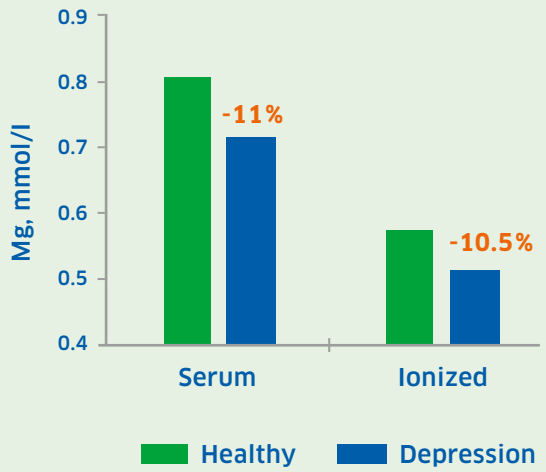
Mg deficiency plays a role in depression:

- Patients with major depression have significantly lower serum and ionized Mg than healthy people[146]; serum Mg <0.83 mmol/l increases the risk of depression 2.1-fold1[47]
- People with depression consume 9% less Mg than healthy ones[148]; higher dietary intake of Mg decreases the risk of depression by 47-53%[149, 150]

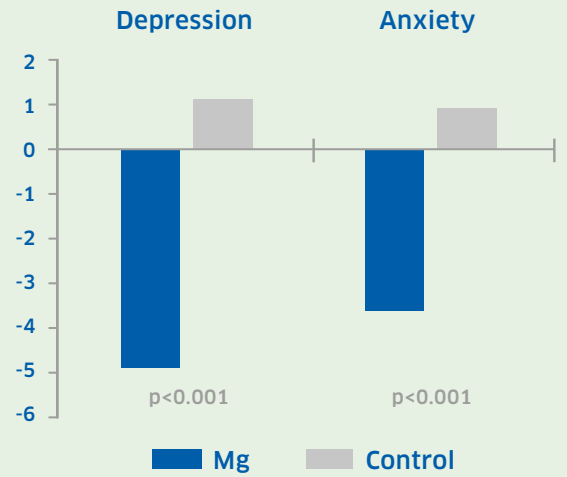
Mg supplementation is effective against anxiety and depression:

- Mg supplementation led to a significant decrease in depression (PHQ-9 score) and anxiety (GAD-7 score)[151]
- Mg supplementation significantly decreased anxiety and depression measured by DASS-42 score[152, 153] and depression measured by Beck's score[154]

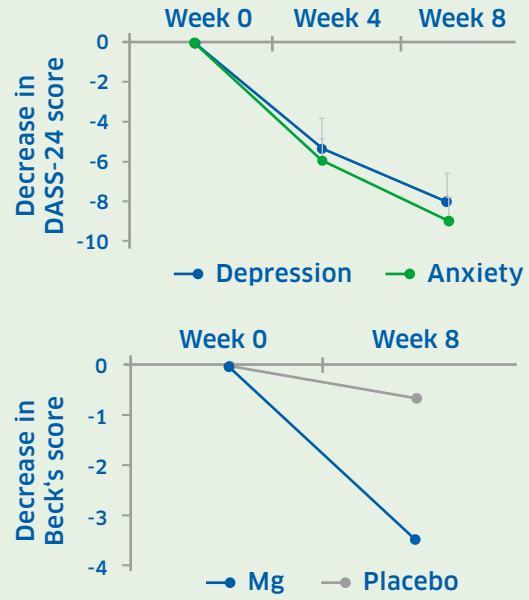
Mg decrease in patients with depression[146]



Effects of Mg supplementation on anxiety and depression[151]



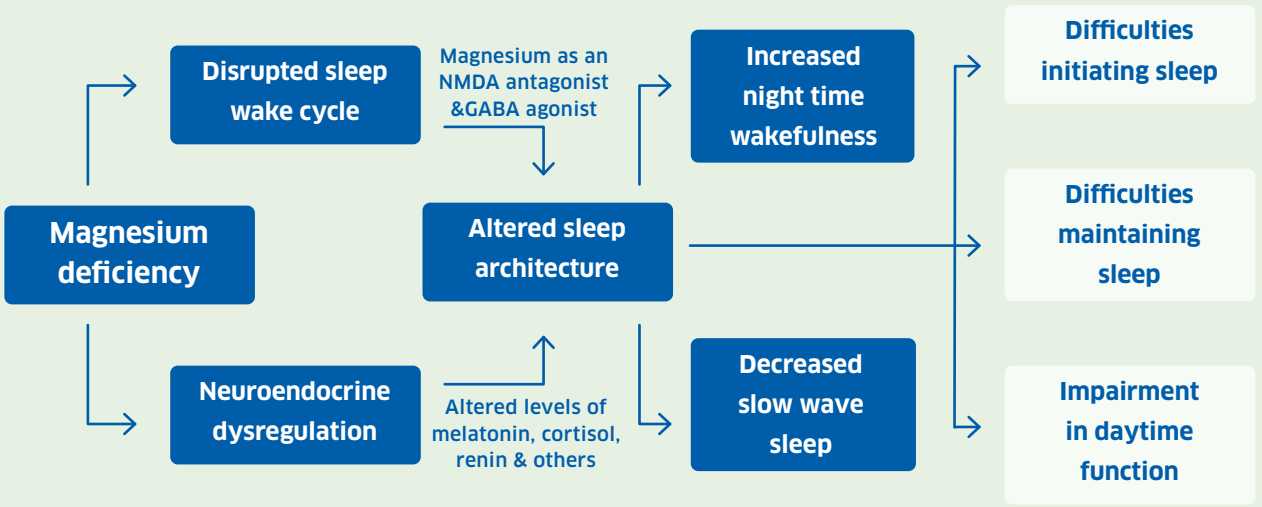
Mg improves depression[152, 154]



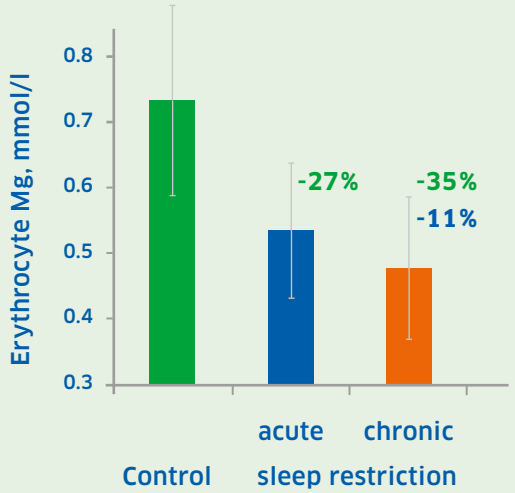
Magnesium and mental health

Sleep

Mg deficiency and insomnia[155]



Mg in sleep restriction[156]



- Both acute and chronic sleep restriction lead to significant decrease in intracellular Mg levels[156, 157]
- People with low sleep efficiency[158] and with short sleep duration[159] consume 16% and 7% less Mg, respectively, than people with normal sleep
- Higher Mg intake decreases the risk of short sleep (<7h) by 36%[160], and also decreases the likelihood of falling asleep during the day and self-reported sleep disorder symptoms in women[161]

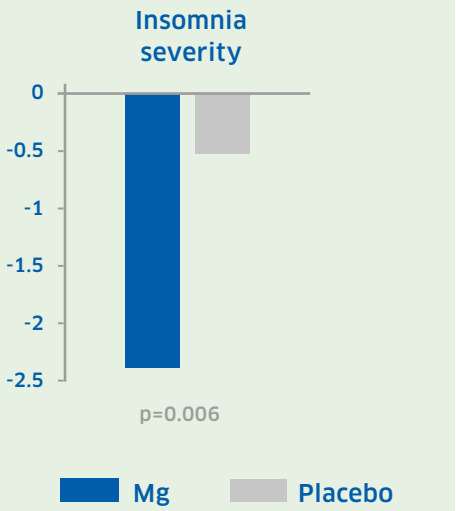
Magnesium and mental health

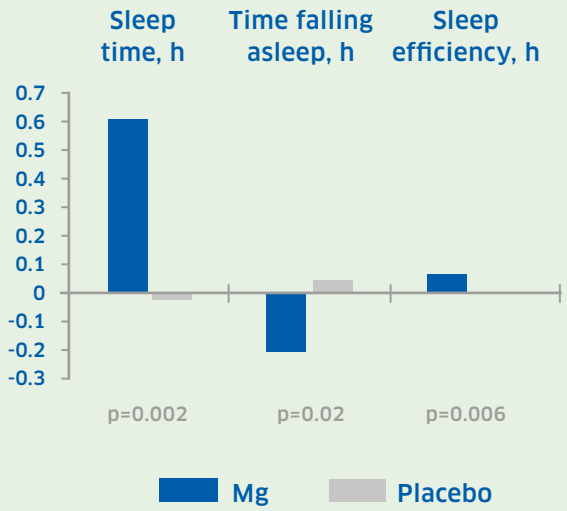
Sleep

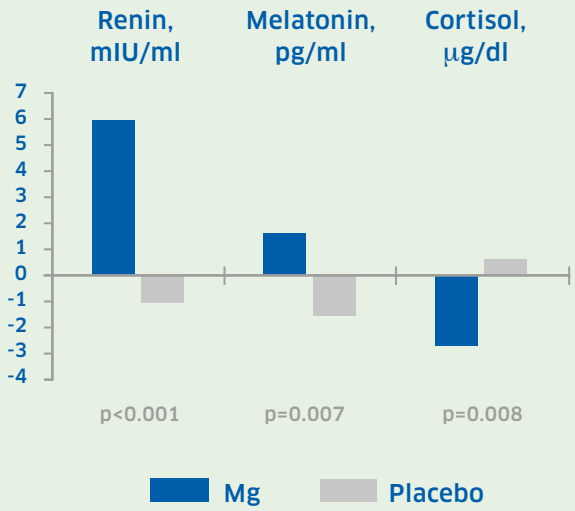
Mg supplementation markedly improves sleep:

- Mg supplementation improved sleep quality as well as serum markers of circadian cycle (renin, melatonin, cortisol) in the elderly[162]
- Co-supplementation with Mg, melatonin and zinc[163] as well as Mg plus melatonin plus vitamin B complex[164] significantly improved sleep quality

Mg supplementation improves insomnia parameters and biochemical markers[162]







Magnesium and ADHD – an overview

Attention-deficit hyperactivity disorder (ADHD) affects about 5% children. Mg deficiency is involved in development of ADHD

- Children with ADHD consume less Mg and have lower Mg levels
- Mg levels inversely correlate with the severity of ADHD traits
- Mg supplementation reduces hyperactivity and emotional problems as well as improves cognitive function in children with ADHD

Magnesium and ADHD

Attention-deficit hyperactivity disorder (ADHD) is a common childhood behavioural disorder characterised by hyperactivity, inattention, and impulsivity that affects about 5% of children worldwide.[165]

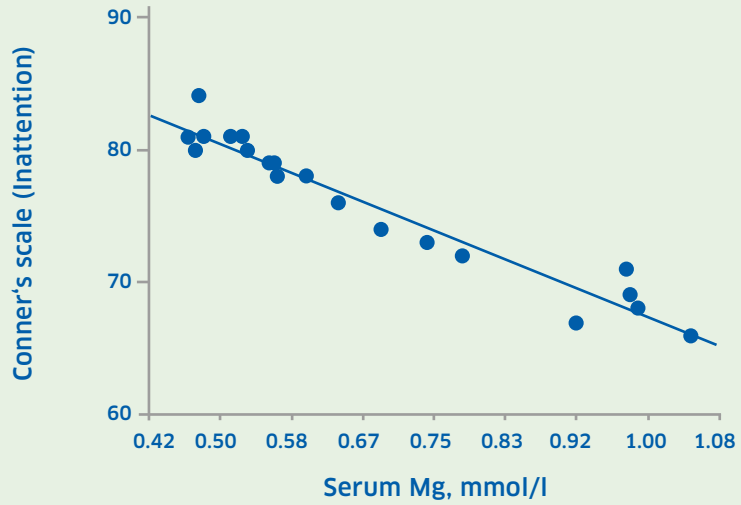
Magnesium deficiency most likely plays a role in ADHD:

- Children with ADHD have significantly lower levels of Mg in serum and hair[166,167]; meta-analysis of 7 studies suggested a difference of 0.105 mmol/l in serum Mg between ADHD and healthy children[168]
- Serum and hair Mg levels negatively correlate with inattention, impulsivity and hyperactivity in ADHD children[167]
- Children with ADHD (mean age 11.3 years) have a lower dietary intake of Mg (223 vs 291 mg/day)[169]

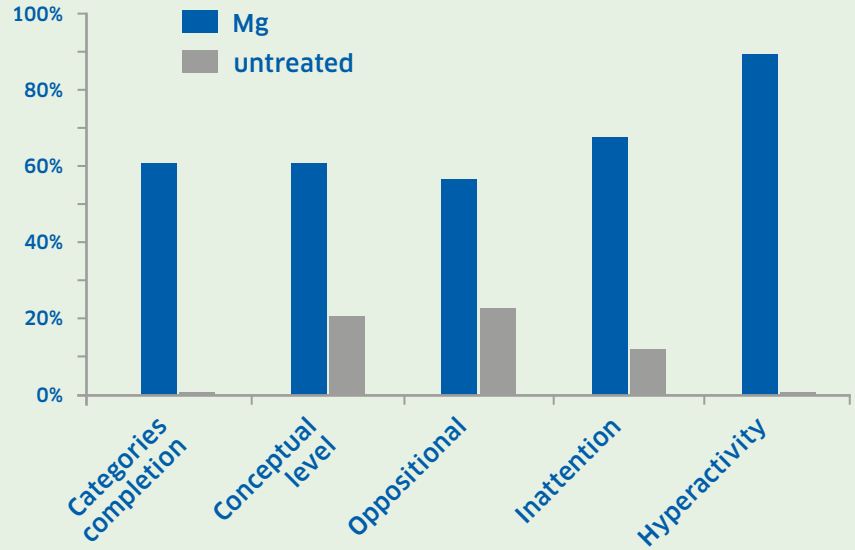
Mg supplementation could be used as an adjuvant therapy for ADHD:

- Mg supplementation significantly reduced hyperactivity[170] and improved cognitive function in ADHD children[171]
- Co-supplementation with Mg and vitamin B6 significantly reduced hyper-activity and hyperemotivity/aggressiveness and improved school attention[172] while also significantly improving physical and emotional symptoms in ADHD children[173]
- Co-supplementation with Mg and vitamin D led to a significant reduction in emotional problems, conduct problems, peer problems, prosocial score, total difficulties, externalising and internalising score compared to placebo[174]

Serum Mg and inattention[167]



Improvements in ADHD children [171]



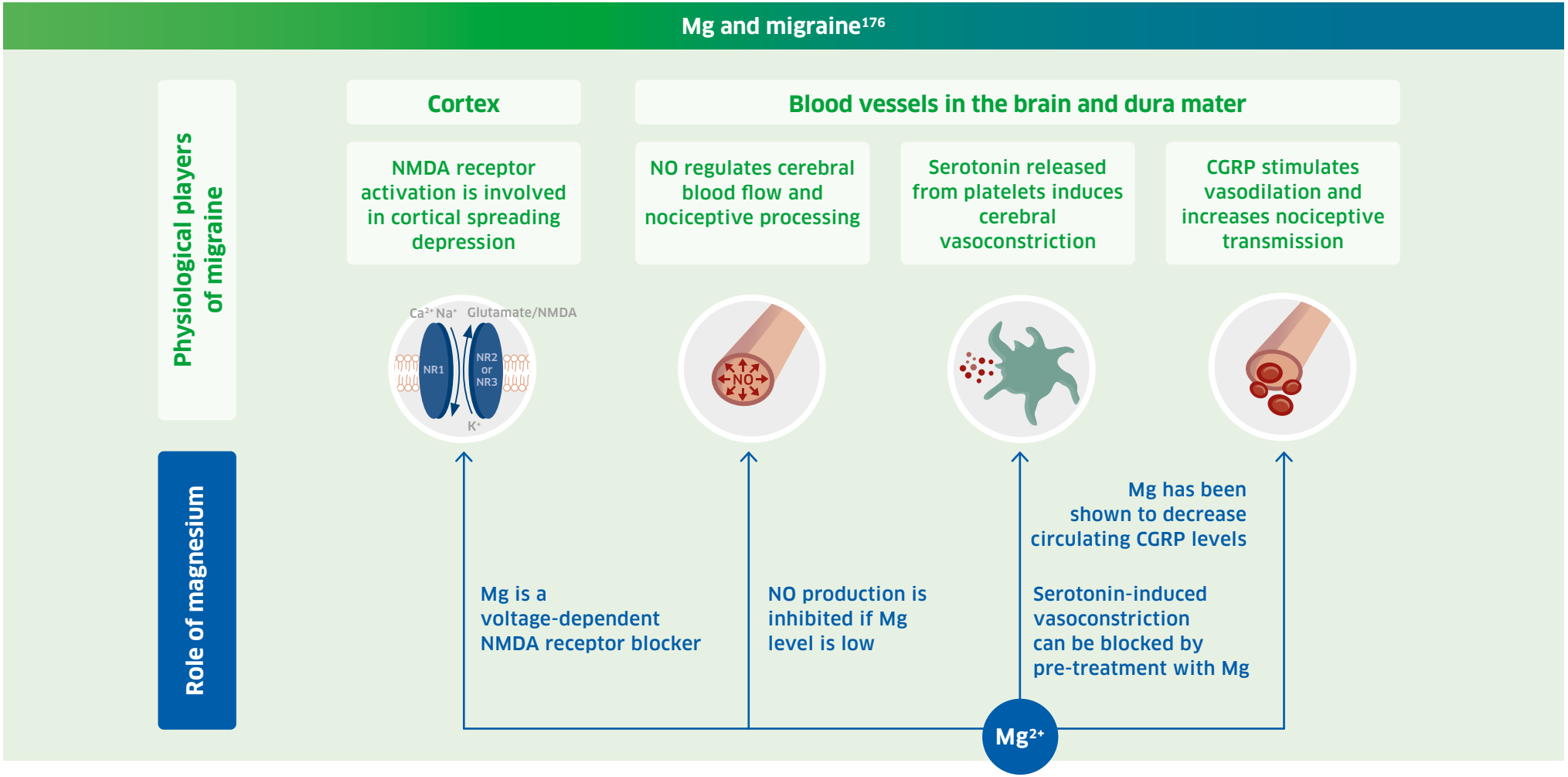
Magnesium and migraine – an overview

Mg deficiency is involved in migraine pathogenesis by affecting neurotransmission and blood vessels.

- Mg levels negatively correlate with the migraine severity and are especially low during the migraine attacks
- Higher Mg intake decreases the risk of migraines
- Mg supplementation reduces frequency and intensity of migraine attacks and allows to reduce other medication.
  Mg was shown to be as efficient as other anti-migraine drugs and to enhance their action

Magnesium and migraine

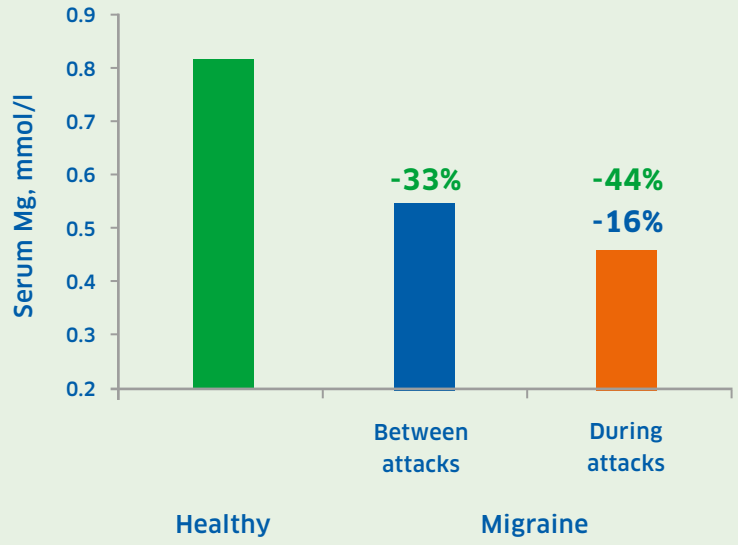
Migraine is a neurological disease characterised by severe attacks of headache with hypersensitivity to light and sound, often accompanied by nausea and vomiting. Mg deficiency is known to play a role in migraine pathogenesis through the induction of cortical depression and of abnormal glutamatergic neurotransmission, as well as through affecting blood vessels:[175, 176]



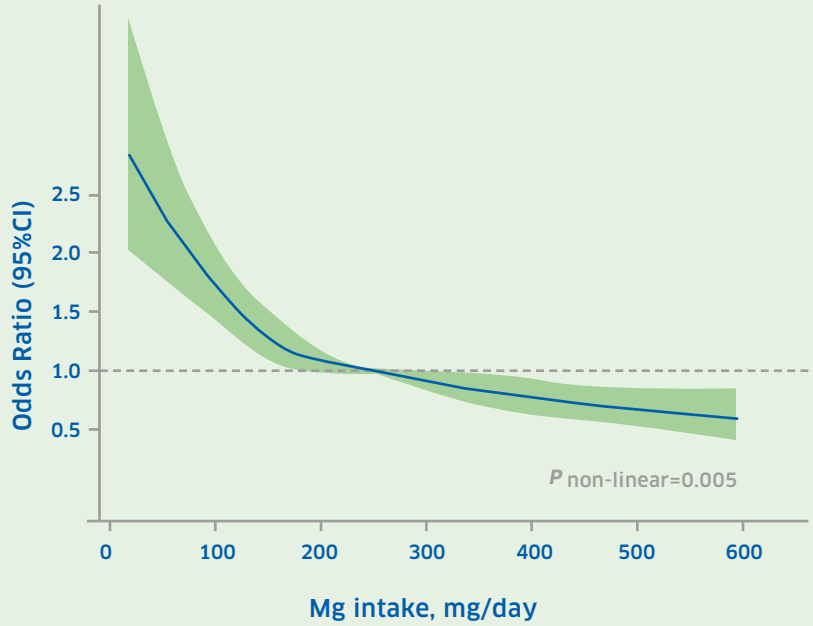
Magnesium and migraine

- People with migraines have lower serum Mg[177-179]
- Mg level negatively correlates with migraine severity[177] and further decreases during attacks[178]
- People suffering from migraines consume 7-11% less Mg than healthy people[180, 181]
- Higher dietary Mg intake leads to a 24-31% decrease in migraine risk[180, 181]

Mg levels in migraine patients [178]



Risk of migraine [181]



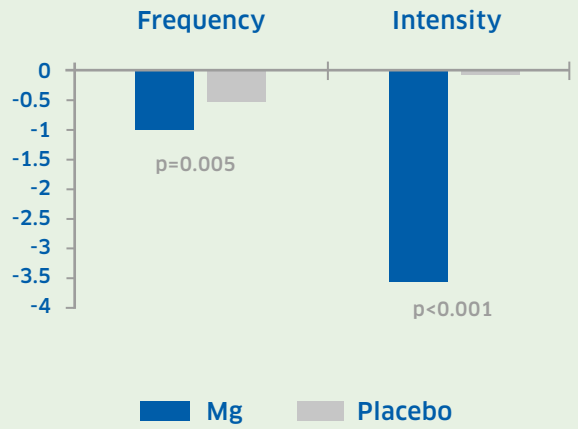
Several guidelines in the EU and other countries recommend Mg for the prophylaxis of migraine.[182-184]

Magnesium and migraine

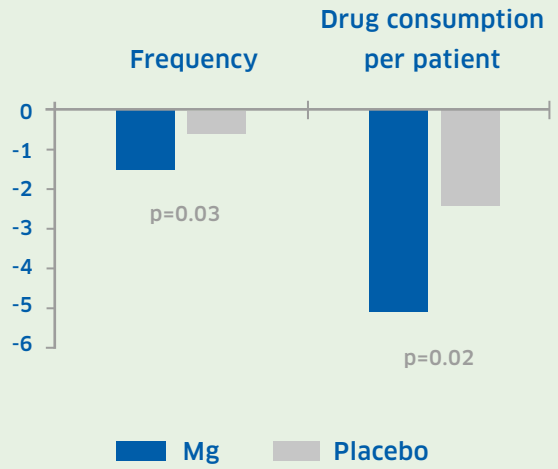
Supplementation studies confirm the effectiveness of Mg against migraines:

- An analysis of 10 studies shows that oral Mg led to a significant reduction in the frequency (OR=0.20) and duration (OR=0.27) of migraines[185]
- Mg citrate supplementation (Magnesium-Diasporal®) significantly reduced the frequency and intensity of migraine attacks[186] as well as the number of days with migraine, frequency of attacks and drug consumption by patients[187]
- Mg was as effective against migraine as sodium valproate (an antiepileptic agent used for prophylaxis and treatment of acute migraine)[188]. Moreover, Mg enhanced valproate action when administered together, reducing such migraine parameters as duration, severity, number of attacks and consumption of painkillers[189]
- Mg supplementation in children (mean age 13.4 years) decreased headache days by 69.9% and analgesic consumption by 65.4%[190]

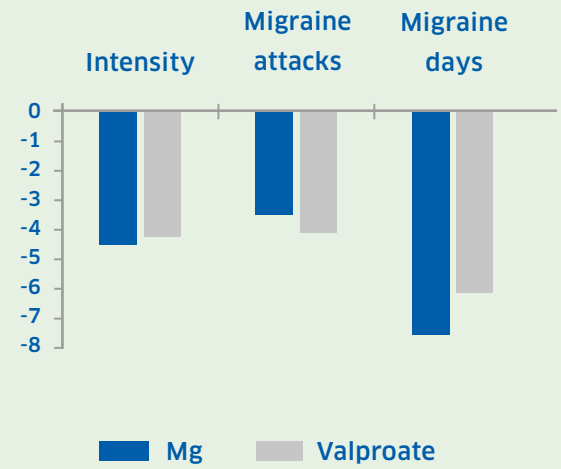
Mg improves migraine parameters[186]



Mg improves migraine parameters[187]



Improvement of migraine parameters[188]



Magnesium in women's health – an overview

Mg supports women's health and is particularly important during pregnancy

- Mg levels change during the menstrual cycle
- Mg supplementation improves physiological and emotional symptoms of premenstrual syndrome
- Although Mg is required for proper course of pregnancy (including fetal development), up to 80% of pregnant women are hypomagnesemic – this may lead to a poor health of a child in the future
- Hypomagnesemia is significantly correlated with the occurrence of pre-eclampsia, gestational diabetes, leg cramps, and preterm birth
- Mg supplementation significantly improves blood sugar values as well as blood pressure

Magnesium in women's health

- 54.8% women with hormone-related conditions have hypomagnesemia[20]
- Mg plays an important role in the prevention and the treatment of a number of conditions relevant for women's health[191]

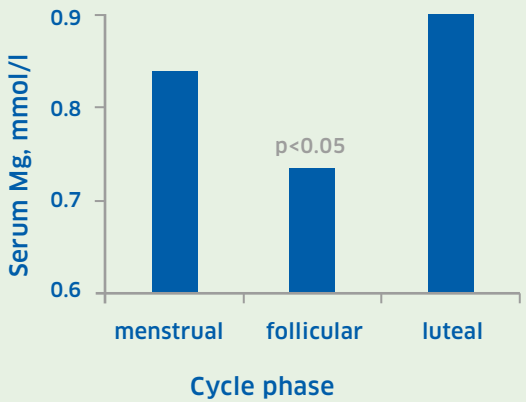
Dysmenorrhea and premenstrual syndrome (PMS)

- 80-90% of women experience the symptoms of PMS in reproductive age, among whom the symptoms are severe in 3-8%[192]
- Serum Mg levels change significantly during the menstrual cycle in healthy women[193]
- PMS patients often show a decrease in Mg levels, which is associated with an increased risk of PMS[194]

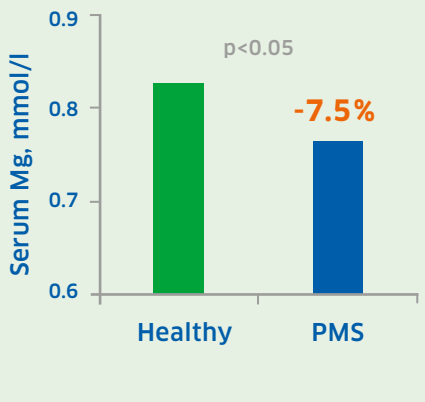
Mg supplementation:

- significantly reduced menstrual pain intensity[195] and severity of dysmenorrhea[196]
- decreased the menstrual distress score during PMS; the decrease correlated with the increase in intracellular Mg levels[197]
- significantly reduced PMS symptoms[192, 198]

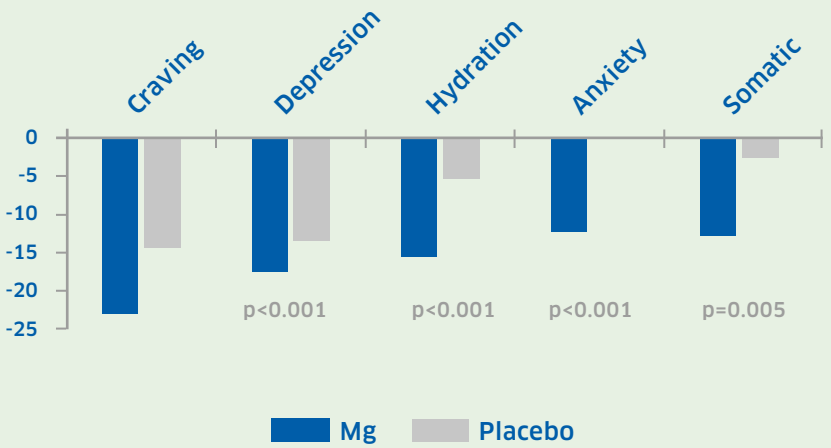
Mg in menstrual cycle[193]



Mg in women with PMS[194]



Improvement in PMS parameters[192]



Magnesium in women's health

Pregnancy

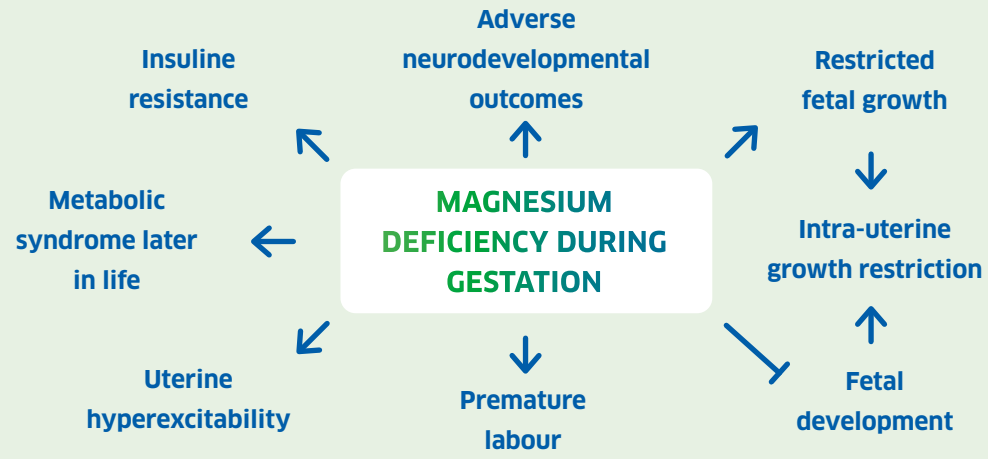
Pregnant women have an increased Mg requirement:[199]

- Mg status is important for fetal development during gestation and for the newborn growth during the perinatal period
- Serum Mg concentration decreases, and renal loss of Mg increases during pregnancy
- Pregnant women need more Mg due to changes in the body

Mg in pregnancy:

- 16 to 79% of pregnant women have low serum Mg levels[19, 20, 200]; more women develop hypomagnesemia already during pregnancy[19]
- Hypomagnesemia is significantly correlated with the occurrence of pre-eclampsia, leg cramps, and preterm birth[19]
- Higher Mg intake is associated with better well-being of pregnant women[201]
- Inadequate intake of Mg during pregnancy is associated with 3.7-fold higher risk of allergic reaction (wheezing) in the offspring at age of two years[202]

Mg deficiency in pregnancy[203]



The German Society for Magnesium Research recommends that all pregnant women should be supplemented with 240-480 mg Mg daily[199]

Magnesium in women's health

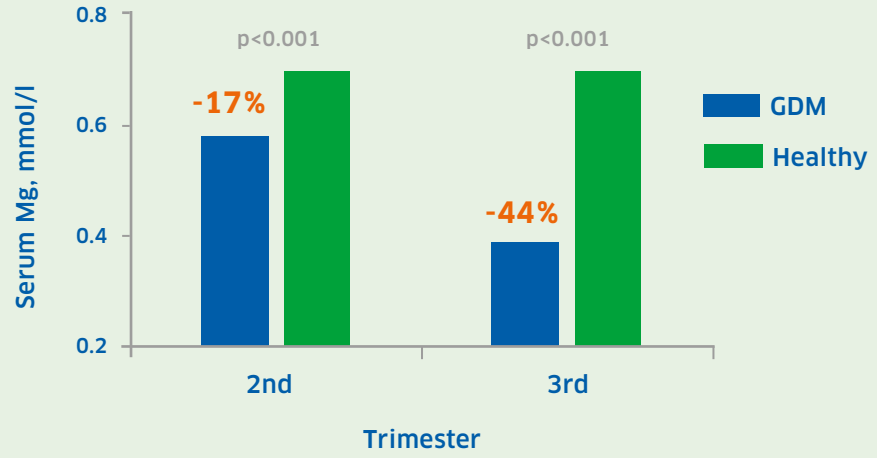
Gestational diabetes

- The prevalence of gestational diabetes mellitus (GDM) in Europe is approximately 5.8% (range 1.8–22.3%), while in other regions it may reach 25%; GDM prevalence is rising worldwide parallel to the increase in the prevalence of obesity and T2DM[204, 205]
- Unlike T2D, GDM only appears during pregnancy and disappears afterwards; nevertheless, it still leads to future health problems in both mother and offspring
- Women with GDM have significantly lower Mg levels[206-208]
- Low serum Mg in women with GDM is a predictor of developing prediabetes and T2D later in life [209]

Mg supplementation has pronounced positive effects in women with GDM:

- Mg supplementation compared to placebo significantly decreased fasting plasma glucose and affected the expression of genes related to insulin and lipid metabolism[210]
- Mg supplementation decreased the expression of genes related to inflammation and significantly decreased newborn hospitalisation (11.1% versus 44.4%, p = 0.02) compared to placebo[211]
- Co-supplementation with Mg and vitamin E significantly decreased fasting plasma glucose, insulin levels and HOMA-IR and improved lipid profiles[212]

Serum Mg in GDM[206]



Magnesium in women's health

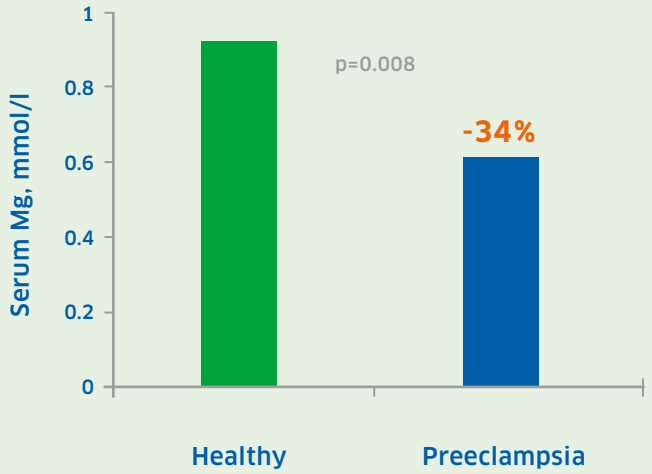
Pregnancy hypertension and preeclampsia/eclampsia

Preeclampsia is a pregnancy complication that affects 3–5% of all pregnancies; it is characterised by hypertension and endothelial dysfunction, and/or maternal organ dysfunction, and/or uteroplacental dysfunction. Preeclampsia increases maternal mortality as well as risk of various diseases later in life in both mother and offspring.[213]

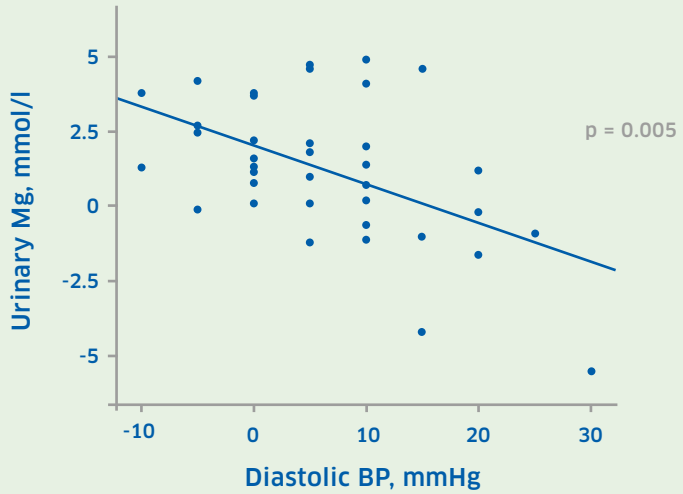
Mg deficiency is considered a key factor in the pathogenesis of pre-eclampsia[214]

- Pregnant women with pre-eclampsia have significantly lower Mg levels than women with a normal course of pregnancy[215, 216]
- Decrease in urinary Mg excretion (suggesting a Mg deficiency) correlates with the BP increase at weeks 12-37[217]

Serum Mg in pre-eclampsia[215]

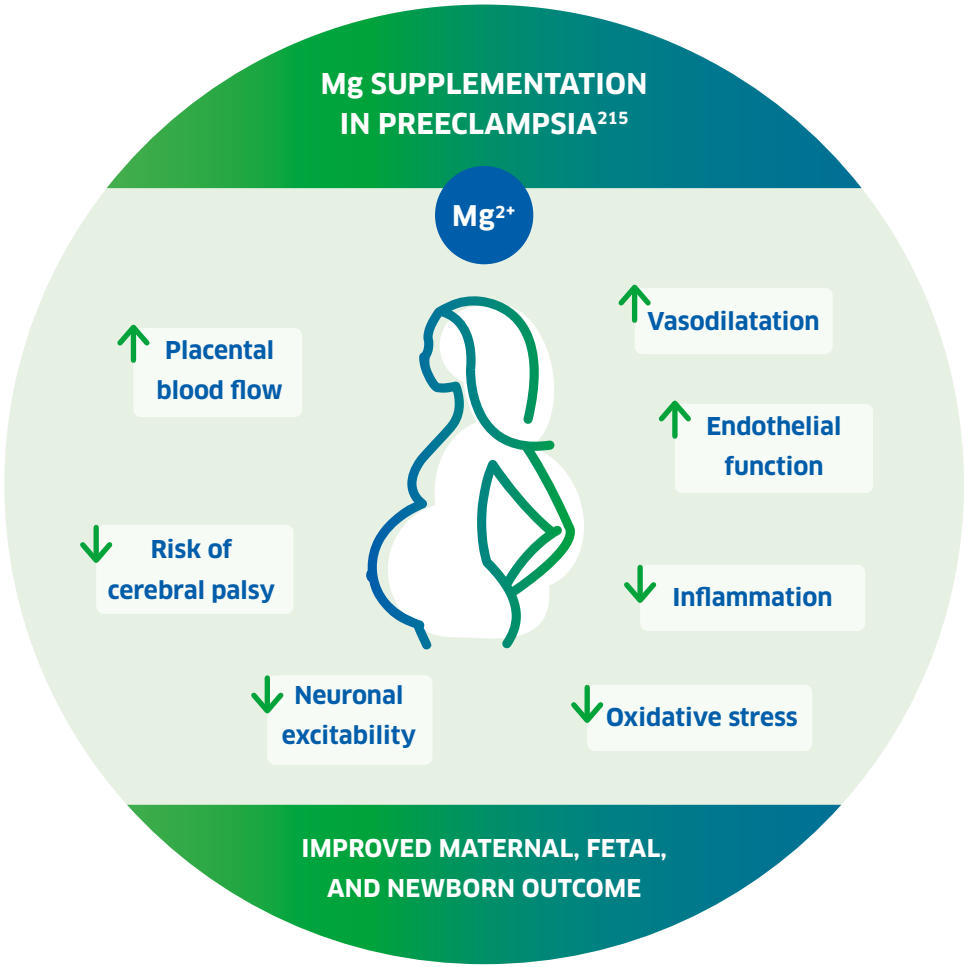


Change in Mg excretion and BP from week 12 to 37 of pregnancy[217]



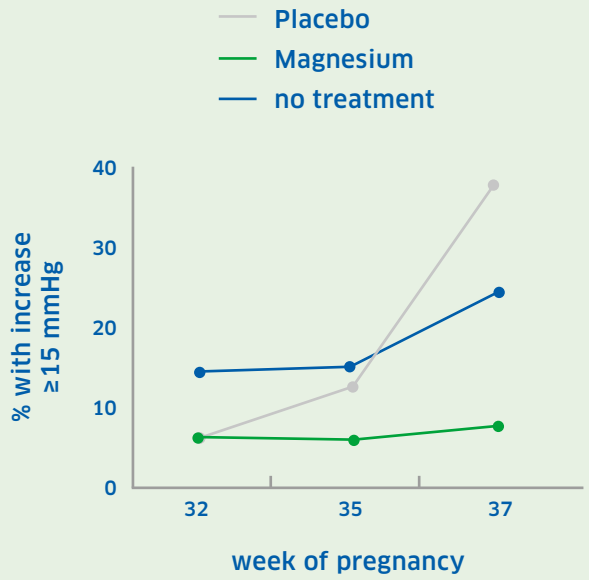
Magnesium in women's health

Pregnancy hypertension and preeclampsia/eclampsia



- Mg supplementation significantly decreased the percentage of pregnant women with elevations of diastolic BP ≥15 mmHg[217]
- A meta-analysis of 7 studies showed that oral Mg supplementation decreases the risk of pre-eclampsia in high-risk pregnant women by 46%[218]

BP elevation in pregnant women[217]



Magnesium and osteoporosis – an overview

Bones are the largest store of Mg in the body, and Mg content correlates with bone strength. Mg deficiency is a risk factor for osteoporosis

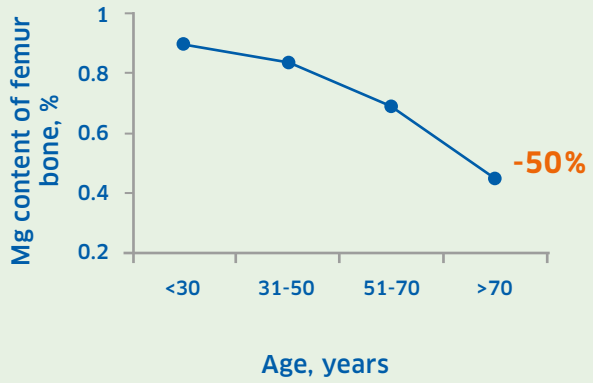
- Mg content in bone decreases with age
- Higher Mg intake increases bone mineral density
- Lower Mg levels and dietary intake increase the risk of bone fractures
- Mg supplementation improves bone turnover markers

Magnesium and osteoporosis

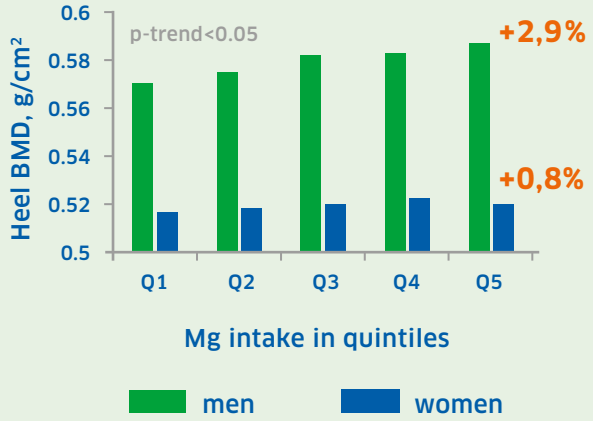
Mg plays an important role in bone health:

- Bone tissue is the largest Mg store in the human body:[219]
  - 50-60% of total body Mg is located in bone
  - 30% of bone Mg is located at the surface and, unlike Mg that is located deep in the bone, is available for ionic exchange. It functions as a pool to stabilise serum Mg concentration
- The level of Mg in bone varies depending on the type of bone and the geographical region[220]
- Mg content in bone decreases markedly with age[221]
- Bone strength strongly correlates with bone Mg content.[221] Higher Mg intake increases BMD (bone mineral density) in men[222] and women[222, 223]
- Consequently, the risk of bone fractures is drastically decreased in people with higher Mg intake[224] and with higher serum Mg levels[225-227]

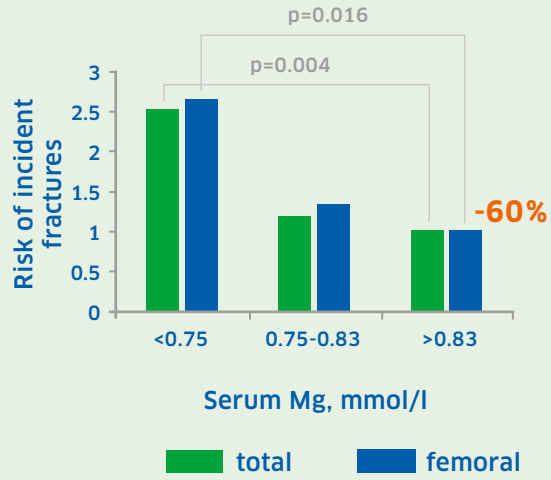
Mg in bone[221]



Mg intake and BMD[222]



Risk of incident fractures according to serum Mg[225]

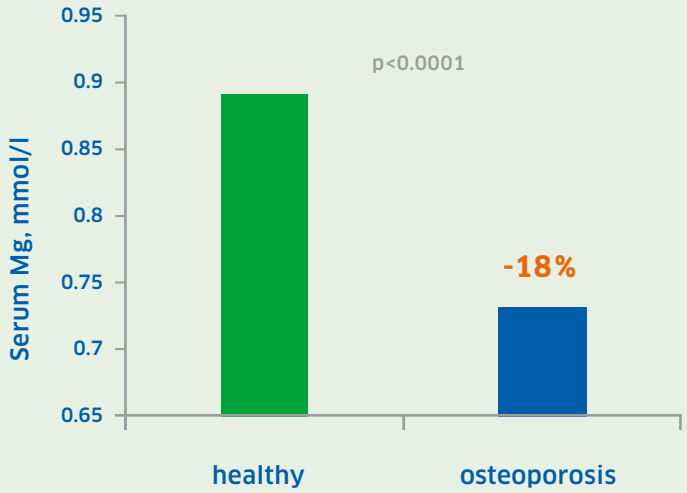


Magnesium and osteoporosis

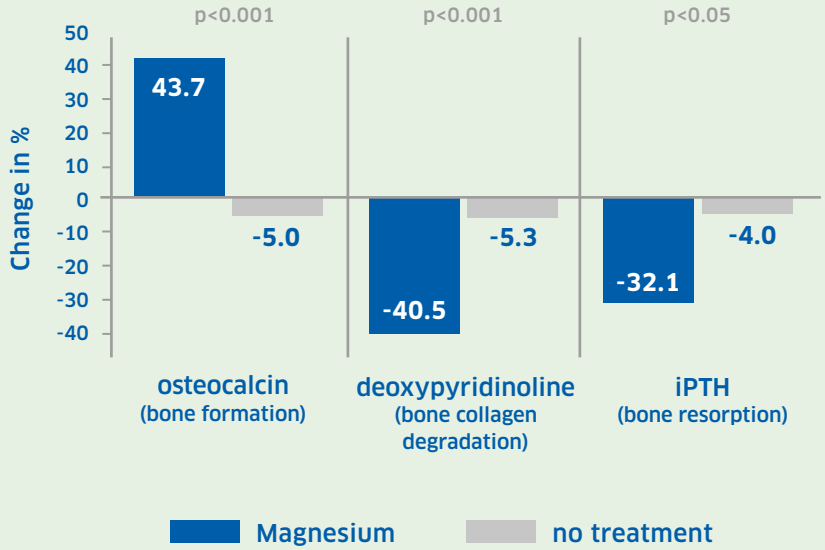
Mg depletion is a risk factor for osteoporosis[228]

- Women with postmenopausal osteoporosis have significantly lower serum Mg[229-231], which in turn is significantly associated with BMD[229]
- In postmenopausal women with osteoporosis, supplementation with Mg citrate (Magnesium-Diasporal®) significantly alters bone turnover markers that indicates reduced bone loss[232]

Serum Mg in osteoporosis[229]



Mg improves bone turnover markers[232]



Magnesium and pain – an overview

Mg affects pain transduction and is efficient against both acute and chronic pain

- Higher Mg intake reduces the risk of chronic pain
- Patients with fibromyalgia have significantly lower Mg levels than healthy people
- Mg supplementation improves fibromyalgia severity
- Higher Mg levels are associated with the decreased risk and severity of osteoarthritis
- Patients taking Mg supplements have lower osteoarthritis severity

Magnesium and pain

Mg reduces pain:

- It acts as an antagonist of NMDA receptors involved in pain transduction[233]
- Mg was shown to be effective against acute as well as chronic pain[233-235]
- Numerous studies confirm the efficacy of intravenous Mg in reducing postoperative pain intensity and decreasing the amounts of analgesics consumption[234]
- Oral Mg citrate (Magnesium-Diasporal® Lozenges) decreased the incidence of sore throat and severity of pain after orthopedic surgery[236]
- Oral Mg before hysterectomy surgery significantly decreased the severity of postoperative pain compared to painkillers[237]
- People suffering from chronic pain consume less Mg on average than healthy people. The odds of having chronic pain decrease by 8% for each mg of Mg intake per kg per day[238]

Magnesium and pain

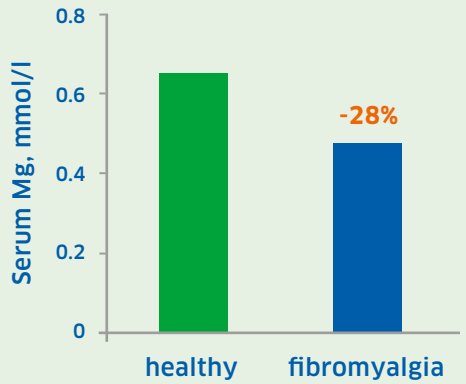
Fibromyalgia

- A chronic disease manifesting as general pain in the muscles and connective tissue, fatigue, sleep disturbance, and increased pain in response to light pressure (especially in so-called tender points)
- Only symptomatic treatment (anticonvulsants, painkillers, antidepressants), no known cure
- **Mg** has always been considered one of the **most promising non-pharmacological supplements** for fibromyalgia
- Several fibromyalgia manifestations such as fatigue, muscle weakness, irritable bowel and paresthesia are similar to symptoms of Mg deficiency
- Patients with fibromyalgia have **significantly lower Mg levels**[239-242]

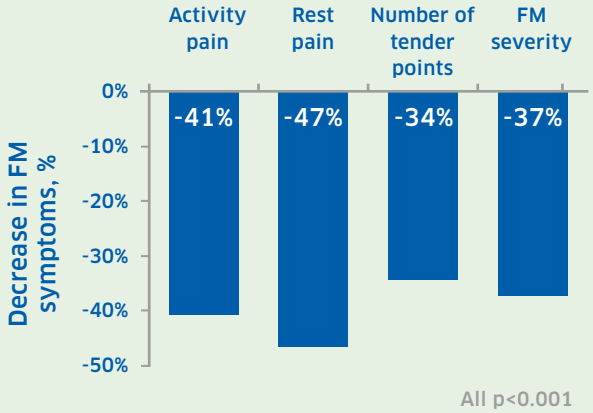
Mg supplementation in fibromyalgia:

- Mg citrate significantly reduces the disease severity (including the degree of pain and number of tender points)[240, 243] as well as depressive symptoms (measured with the Beck Depression Inventory)[240]

Mg in fibromyalgia[242]



Magnesium-Diasporal® reduces the symptoms of fibromyalgia[243]

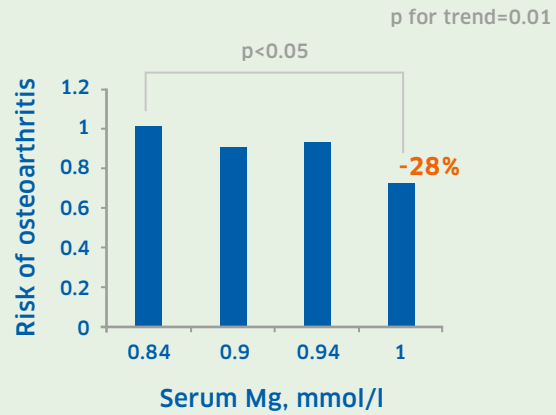


Magnesium and pain

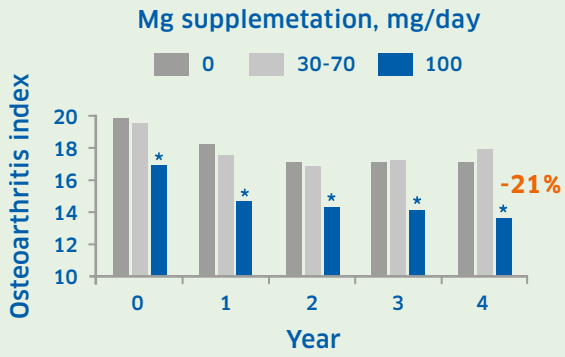
Osteoarthritis

- Chronic degenerative joint disease, characterised by the loss of articular cartilage, which cushions the joint during movement, and bone damage. It leads to joint pain, stiffness and limited mobility
- Osteoarthritis (degenerative joint disease) should not be confused with rheumatoid arthritis (autoimmune disease)
- **Mg could be a potent therapeutic option** for osteoarthritis patients, as Mg promotes the proliferation and differentiation of osteoblasts, chondrocytes and bone marrow mesenchymal stem cells; it protects the cartilaginous matrix and reduces pain and inflammation[244]
- Higher serum Mg is significantly associated with a lower risk of osteoarthritis[245] and with a lower disease severity[245, 246]
- Higher dietary Mg intake is significantly associated with a better knee cartilage architecture (mean cartilage thickness and cartilage volume)[247] and significantly decreases the risk of osteoarthritis[248]
- Higher Mg intake reduces severity of osteoarthritis and pain score. Moreover, osteoarthritis patients taking at least 100 mg/day Mg supplements have significantly lower osteoarthritis severity compared to those who do not take any Mg[249]

Serum Mg and risk of osteoarthritis[245]



Mg supplementation decreases osteoarthritis severity[249]



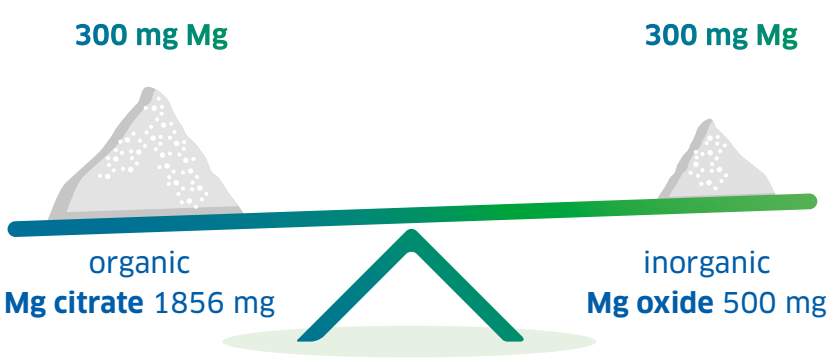
* p<0.001 relative to 0 mg/day Mg

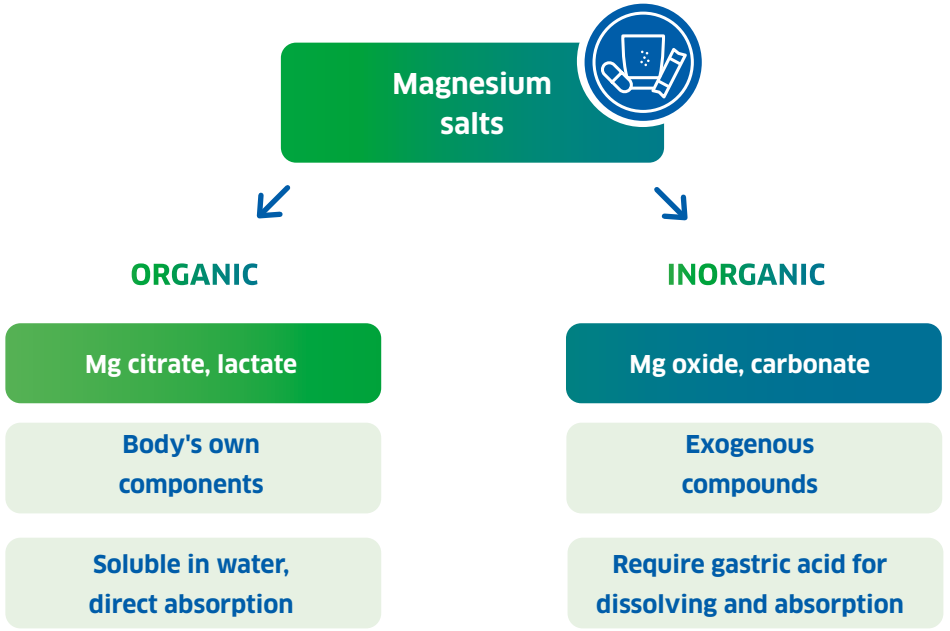
Magnesium bioavailability

All Mg salts could be divided into organic (citrate, lactate, aspartate etc.) and inorganic (oxide, carbonate, sulphate etc.). Their main difference is the solubility, which determines the bioavailability, but the question of price/volume is also important.

Mg oxide is an inorganic salt, which can be produced at **low cost.** Because of its **low volume**, it is used in the industry to form tablets and capsules of the lowest possible size. Mg citrate is much more voluminous due to the size of citrate anion.

Comparison of the size of Mg oxide and citrate



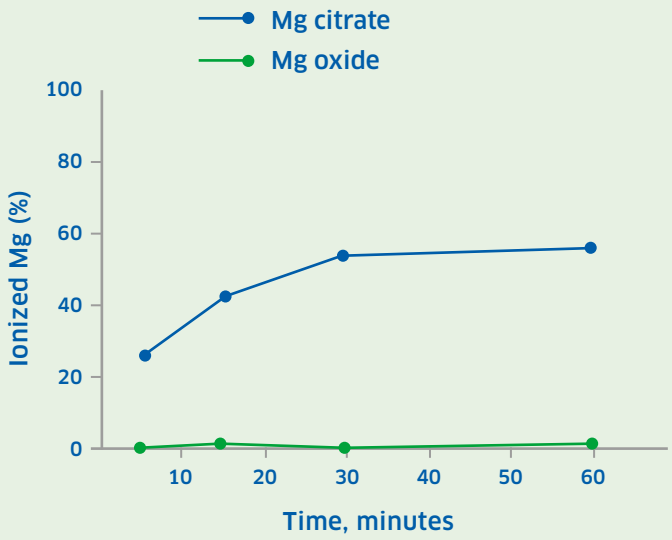


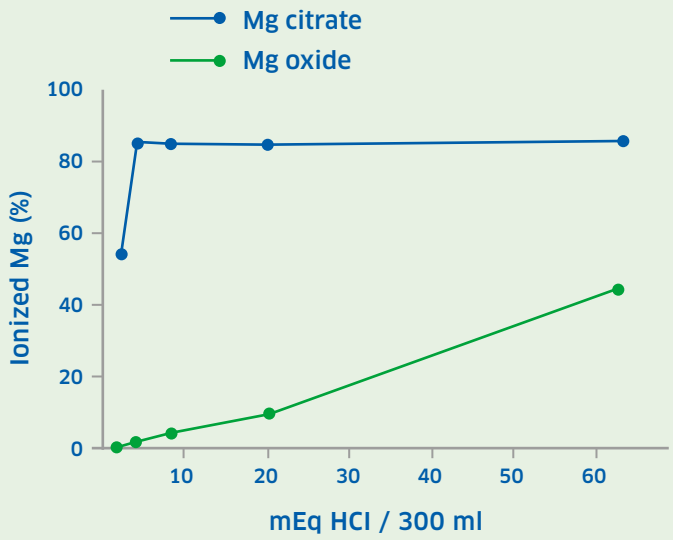
Magnesium bioavailability

The **solubility** of Mg oxide is poor especially compared to citrate:

- Mg oxide does not dissolve in an aqueous solution of neutral pH, whereas Mg citrate dissolves very well under the same conditions within 60 minutes[250]
- In an acid environment (equivalent to the pH of gastric acid), up to 43% of Mg oxide dissolves after 60 minutes, whereas Mg citrate will have dissolved almost completely after this period[250]
- The solubility of Mg oxide is reduced in a basic environment. Its bioavailability is particularly poor in persons taking PPIs and pure oxide (without any acid excipients)

Comparison of the solubilities of Mg citrate and Mg oxide in water and in increasing concentrations of hydrochloric acid after 60 minutes[250]





Therefore, Mg citrate can be taken regardless of meals, while Mg oxide must be taken about 30 minutes before eating, when the concentration of gastric acid is the highest. Otherwise most of it will not be dissolved and absorbed.

Magnesium bioavailability

Water solubility determines good **bioavailability** of Mg salts.[251] **Organic Mg compounds usually have better bioavailability than inorganic.**[251, 252]

This is confirmed by numerous studies:

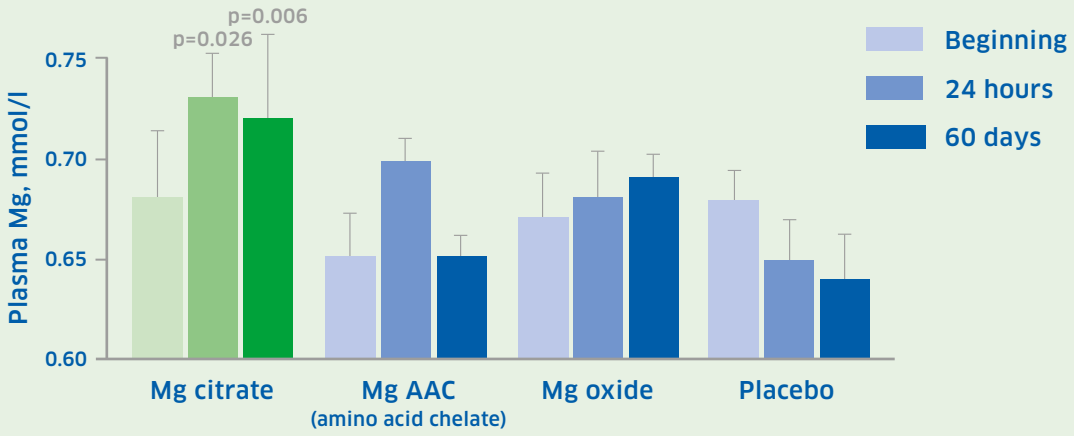
- Mg citrate supplementation of 300 mg for 1 and 60 days increased plasma Mg concentration better than oxide, while both were more effective than placebo and oxide as efficient as amino acid chelate[253]
- 400 mg Mg as citrate led to a higher increase in both plasma and urine Mg after 24 h than oxide[254]
- 300 mg Mg as citrate led to a higher increase in serum Mg values than Mg oxide[255]
- 300 mg Mg as citrate leads to a higher increase in the leukocyte Mg levels than Mg oxide[256]
- Increase in plasma Mg levels after administration of 300 mg Mg as citrate occurs as fast as 30 min[257]

An analysis of 38 studies on Mg bioavailability claims that:[258]

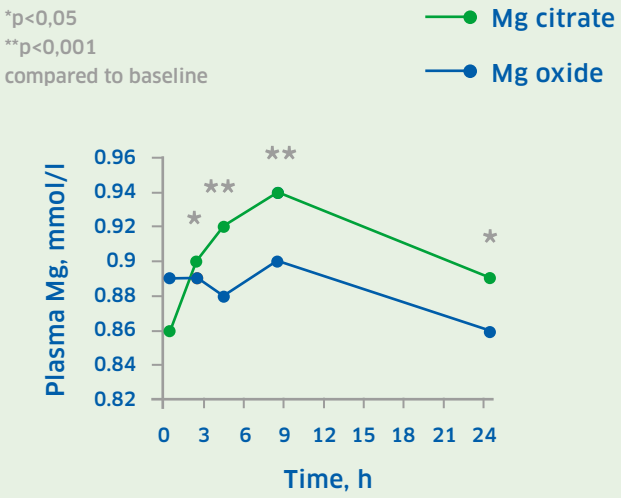
- Mg supplementation significantly elevates circulating Mg and 24-h urine Mg excretion compared to placebo
- Circulating Mg concentrations and 24-h urine Mg excretion respond to Mg supplementation in a dose and time-dependent manner, gradually reaching a steady state at doses of **300 mg/d and 400 mg/d**, or after ~20 wk and 40 wk, respectively
- The higher the circulating Mg concentration at baseline, the lower the responsiveness of circulating Mg to supplementation, and the higher the urinary excretion

Magnesium bioavailability

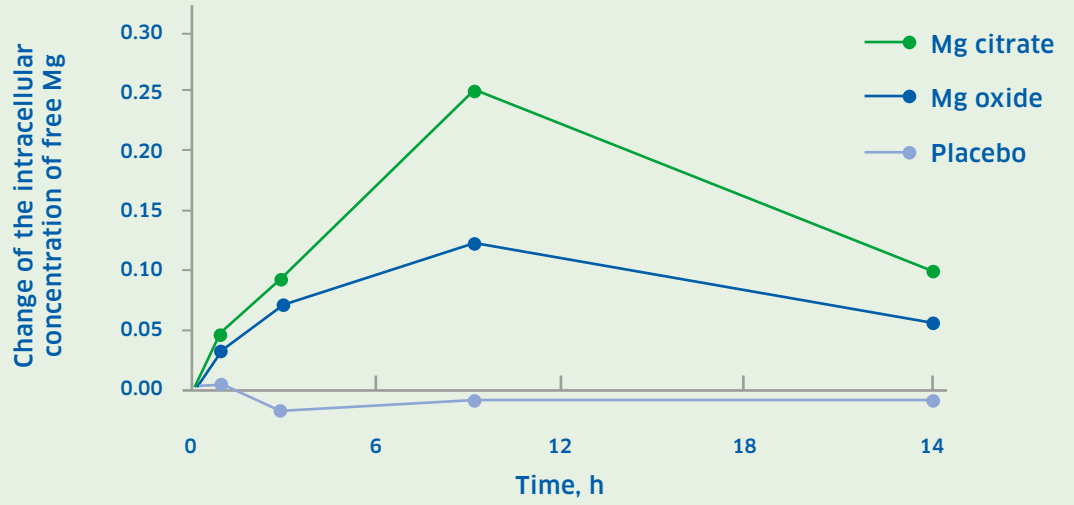
Comparison of Mg salts[253]

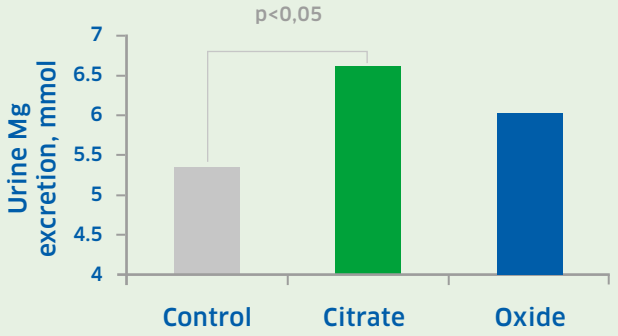


Mg citrate vs oxide[254]



Mg citrate vs oxide[256]





Expert advice on taking magnesium

TIMING

- Simultaneous intake of high-dose Mg and Ca (e.g. 300 mg Mg and 1000 mg Ca) alters absorption of both minerals. It is recommended to have a 2-3 h interval between the intakes
- For prevention and therapy of night cramps intake of Mg is recommended in the evening before sleep

SIDE EFFECTS (LOOSE STOOLS, DIARRHEA)

- Harmless and transitory
- Stop intake and resume after several days, optionally at a lower dose

CONTRAINDICATIONS

- Hypersensitivity to Mg or to any of the excipients
- Severe renal impairment (glomerular filtration rate < 30 ml/min)
- Cardiac conduction disorders that cause slow heartbeat (bradycardia)

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