Cellular Physiology and Biochemistry

Cell Physiol Biochem 2023;57(S1):1-23
DOI: 10.33594/000000603
Published online: 1 February, 2023

Accepted: 5 January, 2023

Review

Magnesium (Mg^{2+}) Deficiency, Not Well-Recognized Non-Infectious Pandemic: Origin and Consequence of Chronic Inflammatory and Oxidative Stress-Associated Diseases

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Key Words
Magnesium deficiency • Oxidative stress • Inflammation • Diabetes • Sudden death • Cardiovascular diseases

Abstract
Magnesium (Mg^{2+}) is an essential mineral nutrient, necessary for many biochemical reactions in the human body, including energy metabolism, protein and DNA synthesis, maintenance of the electrical potential of nervous and cardiac tissues, control of blood glucose, and regulation of blood pressure. However, currently, the world population suffers from a severe problem because the consumption of Mg^{2+} in the diet is deficient and generalized in the populations. Mg^{2+} deficiency causes oxidative stress (OS) due to the increase in reactive oxygen species (ROS) that originate from mitochondrial dysfunction, activation of the renin-angiotensin-aldosterone system (RAAS), and abnormal regulation of calcium homeostasis. In addition, Mg^{2+} deficiency also causes inflammation by increasing the production of proinflammatory molecules such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α), which in turn can exacerbate the production of ROS. The combination of inflammation and OS induced by Mg^{2+} deficiency increases the risk of developing chronic diseases. This review describes Mg^{2+} deficiency, its complications, and its relationship with OS and chronic inflammatory diseases. In addition, the importance of increasing the intake of Mg^{2+} throughout the world is highlighted.

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Introduction

Crucial micronutrients such as magnesium (Mg^{2+}) are essential for correct body function. Its deficiency is associated with the development of comorbidities such as diabetes, obesity, and cardiovascular diseases (CVD, i.e., heart failure, arrhythmias, atherosclerosis, stroke, and hypertension) [1–6]. These comorbidities are frequently associated with an increase in inflammatory markers and oxidative stress (OS), in which Mg^{2+} deficiency may play an important role [2, 7,8]. Subclinical Mg^{2+} deficiency is widespread worldwide, mainly due to insufficient dietary intake [6, 9–16]. Unfortunately, this deficiency is difficult to detect but stimulates the production of cytokines in cells, causing chronic inflammation and, consequently, OS [17, 18].

This narrative review focuses on Mg^{2+} deficiency, its complications, and its relationship with OS and chronic inflammatory diseases. We highlight the potential importance of increasing Mg^{2+} intake worldwide to attenuate manifestations and symptoms derivate from Mg^{2+} deficiency. Our exhaustive review of the scientific literature was conducted in the "PubMed databases". Search keyword terms included all possible combinations, abbreviations, and synonyms between "magnesium", "magnesium deficiency", "magnesium supplementation", "cardiovascular diseases", "Diabetes", "oxidative stress", and "inflammation." We also considered the publication date from 1957 to 2022.

Mg^{2+} body functions

Mg^{2+} is the fourth most abundant intracellular ion in the human body [18, 19]. Mg^{2+} is essential to cellular processes, including energetic metabolism, protein and amino acid synthesis, and maintenance of the electrical potential of nerve tissues and cell membranes [18, 20]. Many enzymes that are vital for life require Mg^{2+}. It is estimated that Mg^{2+} acts as a cofactor for over 600 enzymes and an activator in other 200 enzymes [21]. Fundamentally, Mg^{2+} participates as a cofactor in several complex electron transport chain subunits, including methylenetetrahydrofolate dehydrogenase 2 and pyruvate dehydrogenase phosphatase [22]. In this respect, Mg^{2+} is needed to feed the electron transport chain with nicotinamide adenine dinucleotide reduced (NADH) and flavine-adenine dinucleotide reduced ($FADH_2$) due to acetyl coenzyme A (acetyl-CoA) requires Mg^{2+} to enter the tricarboxylic acid cycle [23, 24]. Also, Mg^{2+} is fundamental to signal transduction processes requiring kinases because almost all transphosphorylation reactions require Mg^{2+} [25]. Mg^{2+} is needed for all the reactions in which ATP participates; binding sites of the substrate in kinases, ATPases, guanylyl cyclases, and adenylyl cyclases are specific to the Mg-ATP complex [21]. In this sense, 538 kinases have been identified that comprise the *human kinome*, and an example of them are glycolytic enzymes, i.e., hexokinase, phosphofructokinase, aldolase, phosphoglycerate kinase, and pyruvate kinase [21, 26]. Mg^{2+} is also necessary for the structure and activity of DNA and RNA polymerases. Mg^{2+} is required for the enzyme to make conformational changes during catalytic reactions [27]. Mg^{2+} also participates in muscle relaxation, neurotransmission, and stabilizing of the cellular membrane (reducing its fluidity and permeability indirectly by disturbances in lipid metabolism) [28–31]. Mg^{2+} is a key component in mediating protein synthesis through stabilizing the structure of ribosomes, stabilizing the secondary structure of ribosomal RNA (rRNA), and ribosomal binding proteins to rRNA [32]. Mg^{2+} binds to rRNA and ribosomal proteins alleviating electrostatic phosphates repulsion; they translate the genetic information encoded by mRNA [32, 33]. When Mg^{2+} concentration is low (e.g., 10 mM in 70S ribosomes from *Escherichia coli*), the ribosome dissociates with the release of ribosomal components, stopping polypeptide synthesis [33, 34].

Moreover, Mg^{2+} is also necessary to transport vitamin D and activate it [35, 36]. Vitamin D binding protein (VDBP) and vitamin D receptor (VDR) are Mg^{2+} dependent for binding

vitamin D [37]. Also, the enzymes responsible for vitamin D metabolism require Mg^{2+} as a cofactor for 25 hydroxylations of vitamin D in the liver and 1α hydroxylation in the kidneys [37]. Besides, Mg^{2+} may act as a second messenger in different cell signal pathways [38, 39]. For example, the Mg^{2+} cation has been described as a second signaling messenger in T cells [4, 21, 39]. Thus, Mg^{2+} has a closer relationship with adaptative immunity, mainly related to signaling and immunomodulatory pathways [20, 40, 41]. To summarize, Mg^{2+} has multiple functions, primarily associated with energy metabolism; its deficiency causes mitochondrial dysfunction and damage, increasing reactive oxygen species (ROS) production, which, in addition to the inflammatory response observed in Mg^{2+} deficiency, leads to chronic metabolic diseases [3, 17, 42, 43].

Mg^{2+} homeostasis

Mg^{2+} homeostasis is maintained by the intestine, bone, and kidneys [40]. In the small intestine, Mg^{2+} reabsorption is mediated by the passive paracellular pathway dependent on an electrochemical gradient. However, a small portion is absorbed by the large intestine mediated by transient receptor potential melastatin 6 and 7 channel (TRPM6 and TRPM7), which also involve calcium absorption [21, 40]. Proteins that transport Mg^{2+} are required to recognize the large, hydrated cation, remove its hydration layer, and deliver the dehydrated ion to the Mg^{2+} transporters for transcellular transport across the membrane [44]. It has been reported that in normal consumption of 370 mg, the intestine only absorbs between 30-50% of Mg^{2+}, and the not absorbed Mg^{2+} is eliminated in the feces [21].

Bone is the most important Mg^{2+} reservoir, containing around 65%, residing in the bone at hydroxyapatite crystals surface; 34% is intracellular, less than 1% is extracellular, and only 0.3% is found in serum. Bone surface Mg^{2+} or exchangeable Mg^{2+} pool is continuously exchanged with blood Mg^{2+}. During Mg^{2+} depletion, the Mg^{2+} concentration in bone exchangeable Mg^{2+} pool decreases to maintain blood Mg^{2+}, reducing bone formation [45]. Additionally, during Mg^{2+} deficiency, increased proinflammatory cytokines such as substance P, tumor necrosis factor-alpha (TNF-α), and interleukin (IL)1 promote osteoclastic bone resorption [46].

The kidney maintains the serum concentration of Mg^{2+}. Approximately 70% of the total serum Mg^{2+} is not protein bound, making it available for glomerular filtration. However, Mg^{2+} can be reabsorbed in the ascending limb of the loop of Henle (65-75%) and the proximal convoluted tubule (5-15%) using paracellular pathways. Also, the distal convoluted tubule reabsorbs 5-10% of Mg^{2+} through TRPM6/7 channels [47]. Under normal conditions, 96% of the filtered Mg^{2+} is reabsorbed, and the body's Mg^{2+} balance is delicately adjusted by urinary excretion [47].

To summarize, the intestine, bones, and kidneys maintain the serum Mg^{2+} concentration; kidneys play a central role because gastrointestinal absorption is balanced by renal excretion (Fig. 1).

Mg^{2+} intake

The primary source of Mg^{2+} is the diet [48]. Mg^{2+} intake recommendations are provided in the Dietary Reference Intakes (DRI), which are developed by the Food and Nutrition Board (FNB) at the National Academies Institute of Medicine (formerly the National Academy of Sciences) [49]. DRI is the set of reference values used to plan and assess the nutrient intake of healthy people. These values vary by age and gender and include a) the recommended dietary allowance (RDA), which refers to the average daily level of intake sufficient to meet the nutrient requirements of nearly all healthy people (97–98%); b) adequate intake (AI), which is the intake that guarantees nutritional adequacy; c) the estimated average requirement (EAR) which is equivalent to the average daily level of consumption estimated to meet the requirements of 50% of healthy individuals; and finally d) the tolerable upper

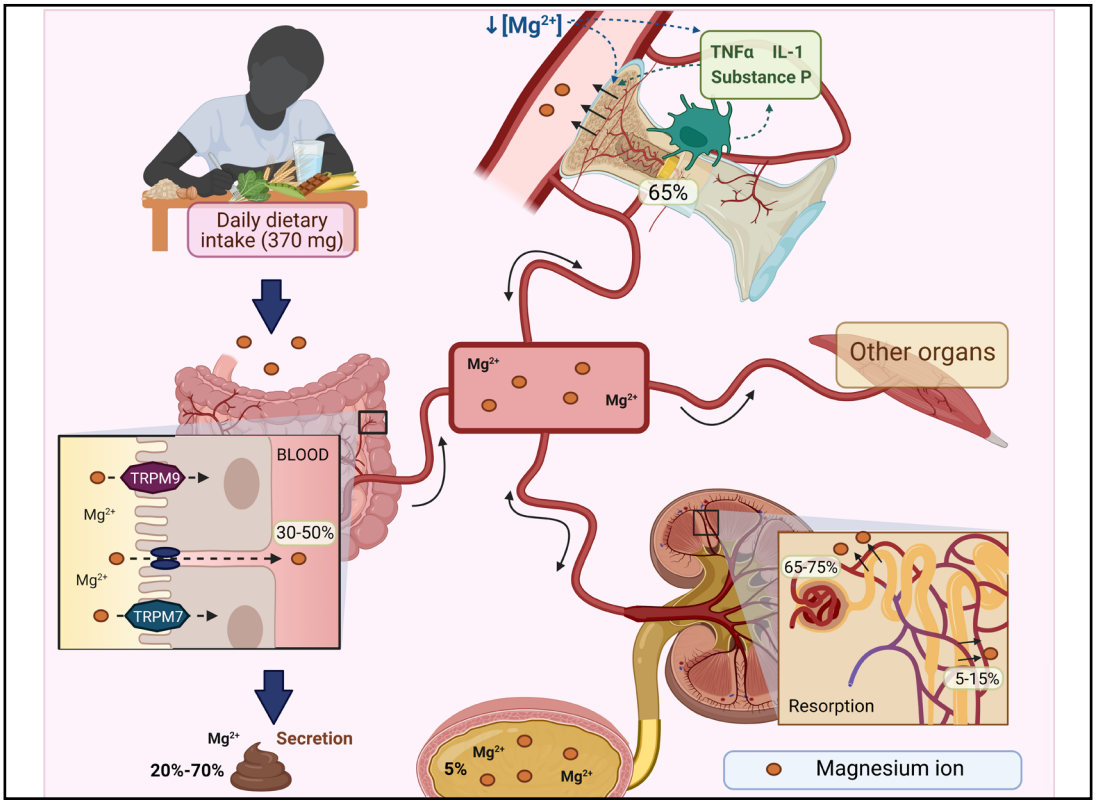

Fig. 1. Magnesium homeostasis (Mg^{2+}). The Mg^{2+} consumed through the diet is absorbed throughout the entire gastrointestinal tract and into the blood, while that not absorbed is excreted in the feces. Once in the blood, the Mg^{2+} passes quickly to the different tissues. The kidney is essential to Mg^{2+} homeostasis since the most significant amount is filtered here, and only about 5% is excreted in the urine. Under conditions of Mg^{2+} deficiency, the concentration of exchangeable Mg^{2+} in bone decreases to maintain Mg^{2+} in the blood, reducing bone formation. In addition, they increase proinflammatory cytokines that promote osteoclastic bone resorption. IL: interleukins, TNFα: tumor necrosis factor-α, TRPM: transient receptor potential melastatin. Created with biorender.com (published with permission from biorender.com).

intake level (UL), which refers to supplemented Mg^{2+}, that is, that which is not consumed in food because it is more for pharmacological use [49, 50]. Table 1 lists the different reference values for Mg^{2+} [49].

Whole grains are considered the best dietary source of Mg^{2+}. In fact, Mg^{2+} has been linked to most of the benefits of whole grain intake, including reduced risk of diabetes, coronary heart disease, stroke, and various types of cancer [51]. Also, leafy-green foods (e.g., chard, spinach, purslane), nuts, peas, and green lentils are good sources of Mg^{2+}. Other foods with high levels of Mg^{2+} are dark chocolate, black beans, avocados, and some other fruits, also seeds such as pumpkin and chia seeds [52–55].

Mineral water is another important source of Mg^{2+} in the diet [56, 57]. Due to the relatively frequent consumption of water for drinking and food preparation, mineral water as a source of Mg^{2+} may be an essential part of the daily Mg^{2+} intake. However, the quality of the water is essential since the available Mg^{2+} content depends on it. Using hard water (calcium and Mg^{2+} concentration of 100-200 mg/L) to boil food rich in Mg^{2+} may prevent its loss, while boiling this food in soft water (calcium and Mg^{2+} concentration less than 100 mg/L) may leach out it [58]. In this respect, many studies have found a relationship between drinking water mineral content and CVD risk [59–68]. Catling *et al.* [69] conclude with an extensive review of epidemiological studies that there was significant evidence of an inverse association between Mg^{2+} content in drinking water and cardiovascular mortality. Sabatier *et al.* [70] showed in a study with ten healthy white women (aged 25-45) that Mg^{2+} from Mg^{2+} rich mineral water (110 mg/L) is highly bioavailable, with a ≈50% Mg^{2+} absorption from mineral

water consumed, being even better when water was consumed with a light meal (may due the transit time of Mg^{2+} in the intestine). Thus, mineral Mg^{2+}-rich water is a calorie-free good source of Mg^{2+}. Mg^{2+} bioavailability is comparable for mineral waters with different mineralization levels or other food such as bread and dietary supplements [56].

However, most of the population does not consume these rich Mg^{2+} foods and water daily; therefore, it is insufficient to cover the dietary reference intake (DRI), leading to Mg^{2+} deficiency. Blache *et al.* [8] have shown in a preclinic study that a long-term moderate Mg^{2+} deficiency diet is closely related to increased mortality, blood pressure, inflammation, and lipid oxidation. Also, they demonstrated that these effects were mainly due to chronic impairment of redox status associated with inflammation, and these effects can be normalized or improved with Mg^{2+} supplementation. In addition, it has been seen that a high intake of processed foods provides low amounts of Mg^{2+}. Food processing, which can range from cooking to refining, causes a substantial loss of Mg^{2+} [71, 72]. Since a large part of the population has opted for refined cereals consumption, the intake of trace elements such as Mg^{2+}, which are found in the pericarp of cereal grains, has decreased notably [72]. For this reason, subclinical Mg^{2+} deficiency has been observed more frequently, mainly in populations that consume processed foods, such as the U.S. and countries with a Western diet [6, 10–15, 73, 74].

Table 1. Dietary Reference Intakes (DRI) for Magnesium Intake (Mg^{2+}). RDA: recommended dietary intake, EAR: estimated average requirement, UL: tolerable upper intake level, NE: not established. * Adequate Intake (AI)

Life Stage	RDA	EAR	UL
Birth to 6 months	30 mg*	NE	NE
Infants 7–12 months	75 mg*	NE	NE
Children 1–3 years	80 mg	65 mg	65 mg of Mg^{2+} supplemented
Children 1–3 years	130 mg	110 mg	110 mg of Mg^{2+} supplemented
Children 4–8 years	240 mg s	200 mg	
Children 9–13 years	410 mg	340 mg	
Teen boys 14–18 years	360 mg	300 mg	
Teen girls 14–18 years	400–420 mg	300-350 mg	
Men	310–320 mg	225-265 mg	350 mg of Mg^{2+} supplemented
Women	400 mg	335 mg	
Pregnant teens	350–360 mg	290-300 mg	
Pregnant women	360 mg	300 mg	
Breastfeeding teens	310–320 mg	255-265 mg	

Mg^{2+} deficiency

Mg^{2+} deficiency means body deficiency, including hypomagnesemia (specifically serum deficiency). Low levels of Mg^{2+} characterize Mg^{2+} deficiency and depends on its chronicity and status. For instance, Nielsen *et al.* [75] demonstrated a significant deprivation of red blood cell membrane Mg^{2+} in healthy postmenopausal women. They were on a restrictive diet of approximately 33% of the DRI of Mg^{2+} for 78 days. Thus, these authors concluded that Mg^{2+} deficiency is mainly associated with chronic inadequate Mg^{2+} intake [75].

Due to its facility and cost, total serum Mg^{2+} is the most used measure to diagnose Mg^{2+} deficiency clinically. The normal serum Mg^{2+} concentration is between 0.850 and 0.955 mmol/L [76]; if the serum Mg^{2+} concentration is below 0.7 mM, it is hypomagnesemia. According to Liu and Dudley Jr [3]., mild to moderate hypomagnesemia is when serum Mg^{2+} is between 0.5–0.69 mM, and severe hypomagnesemia is when serum Mg^{2+} is lower than 0.5 mM. Hypermagnesemia is characterized by high levels than normal serum concentrations of Mg^{2+} [3].

Unfortunately, even with a total serum Mg^{2+} level in the acceptable range, there may exist deficiency since approximately 55% of serum Mg^{2+} is in its bioactive form. At the same time, the rest is bound to proteins such as albumin or an anionic complex [77, 78]. Although Mg^{2+} serum concentrations are the main form to describe abnormalities in the Mg^{2+} status,

these are very unspecific, providing inaccurate body Mg^{2+} status data. For instance, body Mg^{2+} homeostasis in other tissues, including bone, the main reservoir, provides Mg^{2+} through bone resorption during Mg^{2+} deficiency or insufficient Mg^{2+} intake, but this is related to a lower bone mineral density [79–81]. Mg^{2+} deficiency has detrimental effects on skeletal health, contributing to osteoporosis [81]. Thus, normal serum Mg^{2+} concentrations could mask Mg^{2+} deficiency in other tissues like bone.

Also, some conditions affect circulating Mg^{2+} concentrations; an example of this is an abnormal state in the acid-base balance in the blood as slight acidosis. Defects can cause acidosis in renal tubules that facilities the reabsorption of bicarbonate or secretion of protons [82], also during a failure of respiratory ventilation due to carbon dioxide accumulation [83]. Acidosis generally occurs due to increased acid production, decreased acid excretion, acid ingestion, and bicarbonate losses [84]. That serum acid increase can release Mg^{2+} from the bone surface, artificially increasing the Mg^{2+} detected in serum that can mask hypomagnesemia [9]. In addition, the acidosis significantly increasing urine Mg^{2+} excretion [28, 85]. Thus, acidosis masks hypomagnesemia and induces Mg^{2+} excretion, harming Mg^{2+} homeostasis.

The positive correlation between hypomagnesemia, higher morbidity, and mortality in hospitalized patients in an intensive care unit (ICU) [86, 87] makes it fundamental to know the general Mg^{2+} status. Thus preventing increased risk parameters associated with mortality (i.e., high C-reactive protein (CRP) serum levels and electrolytic abnormalities) [86, 87]. Various methods of assessing Mg^{2+} status, from surveys to clinical concentration data, have been extensively reviewed [88–91]. Not all the methods are of clinical utility to diagnose hypomagnesemia, but these indicate clinical or subclinical Mg^{2+} deficiency. These are considered measures for the evaluation of the status of the nutrient [88, 91, 92]. To obtain a valid assessment of Mg^{2+} status, Costello and Nielsen [88] proposed the combined determination of the concentration of serum Mg^{2+}, the 24-hour urine Mg^{2+} excretion, and the intake diet. Due to difficulties in hypomagnesemia detection, it has proposed a sensible measurement of the bioactive form concentrations of whole blood from acute oral Mg^{2+} intake compared to serum and urine total Mg^{2+} [88].

Mg^{2+} deficiency can represent a potential risk to health [1, 4,93, 94]. An association between Mg^{2+} deficiency and sudden death has even been suggested [95]. In a preclinical study by Fiset *et al.* [96], rats assigned to an Mg^{2+}-free diet with consequent hypomagnesemia commonly died from episodes of sudden death after inadvertent startles. Because seizures preceded sudden death, the authors concluded that sudden cardiac death was probably due to a neurological trigger's interaction and ventricular repolarization dispersion [96]. Depending on the degree of Mg^{2+} deficiency and its chronicity, it can present from a mild clinical presentation, such as weakness or fatigue, and escalate to severe and life-threatening complications such as arrhythmias, heart failure, or electrolyte disorders (Table 2) [3, 9,17, 18, 21, 36, 40, 93, 94, 97].

Mg^{2+} deficiency can decrease the synthesis of proteins, carbohydrates, lipids, and genetic material [40]. It could also affect the functioning of the other micronutrients, such as reducing the number of VDRs available in vitamin D target cells [98, 99]. When Mg^{2+} deficiency is acute, muscle cramps help to its diagnosis [18]. However, in a chronic

Table 2. Mg^{2+} deficiency clinical presentation

Clinical presentation	
Gastrointestinal disorders	• Diarrhea • Queasiness • Vomit • Abdominal pain
Cardiovascular diseases	• Atrial and ventricular arrhythmias • Torsade de pointes • Prolonged QT interval • Heart failure • Hypertension
Humor changes	• Depression • Anxiety • Stress • Irritability • Lethargy • Psychosis • Migraine • Confusion • Decreased attention span
Electrolyte disorders	• Hypokalemia • Hypocalcemia • Decreased levels of parathyroid hormone (PTH) • Resistance to vitamin D
Muscular and Neuromuscular conditions	• Cramps • Paresthesia • Neuromuscular hyperexcitability • Tetany • Seizures • Muscular weakness

clinical deficiency, the symptoms are less severe, infrequent, and nonspecific, making its diagnosis difficult [18].

The causes of Mg^{2+} deficiency are many and very frequent

Abnormal Mg^{2+} levels during Mg^{2+} deficiency can be attributed to various factors. Intrinsic factors are insufficient intake or gastrointestinal insufficiency, decreased absorption due to injury to the intestinal epithelium (e.g., damage from alcoholism), kidney damage, and replacement therapies [17, 20, 100, 101]. At the same time, extrinsic factors may be diuretics that alter the renal tubule's reabsorption due to alterations in the electrochemical gradient. Loop diuretics decrease Mg^{2+} reabsorption, and thiazide diuretics reduce Mg^{2+} reabsorption and enhance its excretion [102, 103]. Also, some others are related to lower levels of Mg^{2+} in soil due to Mg^{2+} leaching, consequently affecting food levels [104]. An example is the decreased mineral concentration reported in wheat for the past several decades [105–107]. Fan *et al.* [106] showed a significant decrease of 27% in the concentration of Mg^{2+} in wheat from 1968. The authors conclude that significant changes were made that year in cultivars due to the "Green Revolution," with higher grain yields but a dilution effect on mineral concentration.

As in wheat, other comparative studies of ancient and modern times observed a historical depletion in the concentration of minerals in food [108–110]. Unfortunately, this decrease in the concentration of Mg^{2+} is observed in fruits, vegetables, and cereals, affecting other food groups such as their derivatives and animal origin [108]. The latter means that people need to eat more servings of food to obtain the same Mg^{2+} content as in the past, which is especially problematic due to metabolic syndrome problems in the current population [107].

In industrialized countries, clinical and subclinical Mg^{2+} deficiency is increasing, which can be associated with pathological states [1, 4,73, 74, 76, 93]. Multiple factors contribute to Mg^{2+} deficiency. For example, in people with diets high in phosphate (PO_4^{3-}), Mg^{2+} absorption may be decreased due to the ability of PO_4^{3-} to bind to Mg^{2+}, reducing its availability [9, 28, 93, 111]. In general, the main source of phosphorus comes from soda (phosphoric acid) and inorganic PO_4^{3-} contained in many ingredients used in processed foods (i.e., meat products). Dairy (especially cheese) also contributes to increasing Mg^{2+} requirements due to their phosphorus-magnesium-calcium ratio [93, 111]. Diets high in dietary fiber decrease the absorbed fraction of Mg^{2+}. Fiber phytate decreases Mg^{2+} absorption because Mg^{2+} binds to the PO_4^{3-} groups of phytic acid [28, 112]. In addition to the abovementioned cases, other factors contribute to Mg^{2+} deficiency, such as chronic diseases, gastrointestinal disorders, elderly age, and emotional stress [6, 9,17, 20, 93, 97, 100, 111]. The following list shows factors that contribute to Mg2+ deficiency:

- Diets with refined and processed foods
- Chronic diseases (kidney disease, cancer, insulin resistance, diabetes)
- Gastrointestinal disorders (intestinal lesions, Chhorn's disease, irritable bowel syndrome, celiac syndrome, celiac disease, gastroenteritis ulcerative colitis)
- Drugs (diuretics, insulin, proton pump inhibitors)
- Chronic stress
- Strenuous physical exercise
- Deficiency or excess of vitamin D (lack causes less absorption of Mg2+, the excess causes excessive absorption of Ca2+)
- Excessive supplementation or high levels content of other micronutrients in the diet such as Ca2+ and phosphorus
- Elderly age
- Alcoholism
- Intake of coffee and tea (caffeine)
- High saturated fat in the diet
- Excessive menstruation
- Emotional stress (overactivation of the sympathetic nervous system)
- Laxative abuse
- High intake of dietary fiber and phytic acid
- Metabolic acidosis

Subclinical Mg^{2+} deficiency is the most common in the population, especially in countries that consume refined or ultra-processed products [9, 73, 74, 93]. The 2013-2016 National Health and Nutrition Examination Survey (NHANES) conducted on the US population showed that approximately 48% of the general population over one year does not reach the adequate intake of Mg^{2+}. Moreover, in people older than 19 years (adult population), just over 50% of the population does not have consumption habits that cover the DRI [113].

According to an analysis of the 2006 national health and nutrition survey conducted on the Mexican population, 35% of adult men and women older than 20 have low serum concentrations of Mg^{2+} [10]. In addition, 64.2% of women and 25.2% of men presented a low ingestion of Mg^{2+} compared with the DRI [10]. Based on the same survey, Cruz-Góngora *et al.* [114] reported that in the 12 to 19-year-old population, the overall prevalence of low serum Mg^{2+} was 37.68%, and at least 50% of the analyzed population did not comply with the DRI [114]. In the case of the child population, Morales-Ruán *et al.* [11] reported that the nutritional status of Mg^{2+} in Mexican children from 1 to 11 years old is deficient, and the prevalence of low serum Mg^{2+} concentrations is 22.6% for this population. The lowest prevalence (9.1%) of low serum Mg^{2+} concentrations is in the population 1 to 2 years old [11]. The latter evidence shows the trend toward increasing Mg^{2+} deficiency prevalence with age.

At a global level, the consumption of Mg^{2+} in the diet is deficient and generalized in the populations (Table 3) [6, 9–16, 115]. Subclinical Mg^{2+} deficiency has been observed more frequently, mainly in populations consuming processed food, such as the US and countries with a Western diet [1, 4,9, 73, 74, 76, 93].

In addition to the countries mentioned above, DiNicolantonio *et al.* [93] included Japan and Ukraine as countries consuming insufficient amounts of Mg^{2+}. The latter derives from the results obtained in the National Nutrition Survey in Japan in 2002, where it was found that for people aged 15 to 49 years, the intake of Mg^{2+} was below the Japanese recommended daily dose. Moreover, in Kiev (Ukraine), men between the ages of 20 and 59 years (n= 780) consumed 10% less than the recommended Mg^{2+} intake.

Table 3. Mg^{2+} deficiency is global and general. Mg^{2+}: magnesium; mg/d: milligrams per day; mmol/d: millimole per day; DRI: Dietary Reference Intakes; RDA: Recommended Dietary Allowances; EAR: Estimated Average Requirement

Continent	Country	n	Population	Mg^{2+} Intake		Clinical Mg^{2+} levels	Ref.
				Men	Women		
Asia	Taiwan	1,911 (intake) 2,225 (plasma Mg^{2+})	Adults >65 years	250 ± 13 mg/d 69.4% of the DRI	216 ± 11mg/d 68.6% of the DRI	Prevalence of a plasma Mg^{2+} level <0.7 mM was 0.7-0.9% and <0.8 mM was 8.0-9.1%.	[6]
	India	283	Women >18 years pregnant (>28 weeks)	-	3.9% of the population consumes less than 50% of RDA	43.6% of the population had deficient serum Mg^{2+} concentration	[115]
Europe	Belgium	2,000	Healthy Belgium adult population in four sampling sites	271 ± 44 mg/d Below the RDA		-	[12]
	Spain	3,421 (intake) 354 (serum Mg^{2+})	Andalusia's population is aged 25 to 60 years	11.70 ± 3.02 mmol/d 32.31% had an intake of <2/3 RDA	11.76 ± 3.02 mmol/d	8.82% presented deficient serum Mg^{2+} concentration	[13]
	France	5,448	Adults 35 to 60 years	373 ± 169 mg/d 72% with intake below RDA	276 ± 126 mg/d 77% with intake below RDA	-	[14]
		2,373	French representative population aged 4 to 92 years	(4-9 years) prevalence of inadequate intake 5.7% (10-90 years) prevalence of inadequate intake (below the EAR) 71.7 %	(15-92 years) prevalence of insufficient intake (below the EAR) 82.5 %	-	[15]
America	Brazil	115	University students aged 19 to 29 years	217.6 ± 72.5 mg/d (below the EAR)	211.7 ± 77.7 mg/d (below the EAR)	42% had low Mg^{2+} in plasma or erythrocytes	[16]

Mg^{2+} deficiency is difficult to detect at an early stage since bone compensation of Mg^{2+} maintains normal serum Mg^{2+} levels; and the absence of signs or symptoms [45, 116]. Knowing the general body Mg^{2+} status is essential to avoid other related Mg^{2+} deficiency complications, such as chronic inflammation and excessive production of ROS. To properly diagnose and treat Mg^{2+} deficiency, it is necessary to carry out more than one measurement of the Mg^{2+} levels method. It is suggested that due to the compensation of the homeostasis of Mg^{2+}, the detection of low levels of $Mg^{2+}$with a single method cannot be a good indicator of deficiency

In summary, many factors could contribute to developing a chronic deficiency. It is clear that Mg^{2+} intake is inadequate worldwide, and Mg^{2+} deficiency is a potential public health problem; nevertheless, the consequences of this deficiency are more frequently reflected in older adults.

Relationship between Mg^{2+} deficiency with OS and inflammation

Mg^{2+} deficiency has been widely correlated to the development of OS [3, 117]. OS is defined as "an imbalance between the generation of oxidants (ROS and reactive nitrogen species) and their removal systems (antioxidants) in favor of oxidants, leading to disruption of redox signaling and control and/or molecular damage" [118]. Mitochondria are the primary source of ROS production, and mainly, when mitochondria suffer structural or functional damage, excessive ROS production is generated [119]. Studies have shown that Mg^{2+} deficiency causes mitochondrial dysfunction [43, 120]. Mitochondria are the main reservoirs of Mg^{2+} in most cells (with mitochondrial Mg^{2+} concentrations between 0.2 and 1.5 mM) [121]. However, intracellular Mg^{2+} deficiency inhibits Mg^{2+} transport to the mitochondria through mitochondrial RNA splicing protein 2 (MRS2) and promotes mitochondrial Mg^{2+} efflux via solute carrier family 41, member 3 (SLC41A3), leading to decreased mitochondrial Mg^{2+} [3]. Mitochondrial Mg^{2+} deficiency decreases the activity of the electron transport chain, which alters coupled respiration [122–124] and increases the production of mitochondrial ROS [125, 126]. In addition, the antioxidant defense system (such as superoxide dismutase (SOD), catalase, and glutathione) is suppressed, and ATP synthase (F0F1) is downregulated, causing a decrease in ATP concentration [127–129]. In turn, the decrease in ATP causes an increase in the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) [130].

Mg^{2+} deficiency also causes depolarization of the mitochondrial membrane potential ($\Delta\Psi m$) [131] by promoting the opening of the mitochondrial ATP-sensitive potassium (K) channel [132], the anion channel of the inner membrane (IMAC) [133] and the mitochondrial permeability transition pore (PTP) [134]. These effects exacerbate ROS production and lead to apoptosis, where Bcl-2-associated X (Bax) and the voltage-gated anion channel (VDAC) increase cytochrome C release, leading to apoptosome formation [135]. In addition, antiapoptotic proteins such as the Bcl-2 family are decreased, and proapoptotic proteins such as HIF-1α and p38/JNK are increased [136].

On the other hand, Mg^{2+} deficiency also increases the concentration of calcium (Ca) in the mitochondria through the mitochondrial Ca uniporter (MCU) [131, 137], which could alter $\Delta\Psi m$. In contrast, Ca leakage from mitochondria via VDAC increases with apoptosis induced by Mg^{2+} deficiency. Other mechanisms that explain the increase in intracellular calcium in situations of Mg^{2+} deficiency include the activation of N-methyl-D-aspartate (NMDA) receptors in neural cells and L-type calcium channels in adipose tissue [2, 138].

The excess of intracellular Ca results in the activation of Ca-dependent processes, such as the release of inflammatory cytokines and the activation of NOX by phosphorylation of protein kinase C (PKC), the activation of nitric oxide synthase (NOS) and the calcium-dependent calmodulin complex, which exacerbates ROS production [1]. Likewise, the increase in Ca stimulates the release of catecholamines, and it has been proven that catecholamines increase the production of ROS [139]. Furthermore, elevated levels of catecholamines, such

as epinephrine, cause Mg^{2+} deficiency to intensify, creating a vicious circle [140].

Likewise, Zheltova *et al.* [117] suggest that Mg^{2+} deficiency and Ca increase cause an increase in the number of available substrates for radical oxidation. A greater amount of Ca stimulates the activity of phospholipase A2 [141], an enzyme responsible for mobilizing unsaturated fatty acids (UFA) from phospholipids. UFAs, either free or bound to triglycerides and phospholipids, can be readily oxidized by ROS to form lipid hydroperoxides. In turn, hydroperoxides can decompose to form new radicals, thus initiating branching chain reactions that lead to self-sustaining peroxidation [142, 143].

OS can also be generated because the renin-angiotensin-aldosterone system (RAAS) is activated by Mg^{2+} deficiency [138, 144]. It is well established that angiotensin II activates NOX, monocytes, macrophages, and endothelial cells to produce ROS [145, 146]. In addition, RAAS has been shown to decrease the expression of TRPM6 and TRPM7, Mg^{2+} transporters, which further increases intracellular Mg^{2+} deficiency [147]. Fig. 2 shows the possible mechanisms by which Mg^{2+} deficiency increases ROS production.

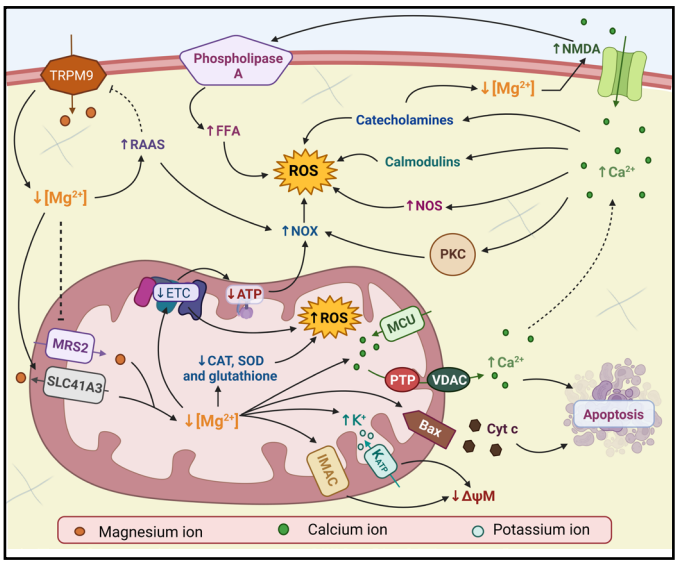

Fig. 2. Magnesium deficiency (Mg^{2+}) and oxidative stress (OS). Mg^{2+} deficiency in mitochondria leads to the inhibition of the electron transport chain (ETC) and the opening of different channels, decreasing the mitochondrial membrane potential ($\Delta\psi M$), Bax recruitment and calcium efflux (Ca^{2+}). These factors increase the production of reactive oxygen species (ROS) in mitochondria and induce apoptosis. Intracellular Mg^{2+} deficiency activates N-methyl-D-aspartate (NMDA) receptors, contributing to the increase in Ca^{2+}. High concentrations of Ca^{2+} they increase ROS through calmodulins, catecholamines, nitric oxide synthase (NOS), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX). NOX is also activated by decreased production of adenosine triphosphate (ATP) and the renin-angiotensin-aldosterone system (RAAS). NMDA also activates phospholipase A, increasing the concentration of free fatty acids (FFA) and ROS. Low concentrations of Mg^{2+} are enhanced by inhibition of mitochondrial RNA splicing protein 2 (MRS2), activation of solute transporter family 41 member 3 (SLC41A3), RAAS, and catecholamines. Bax: Bcl-2 associated X, CAT: catalase, Cyc c: cytochrome c, IMAC: inner membrane anion channel, K: potassium, MCU: mitochondrial Ca2+ uniporter, PKC: protein kinase C phosphorylation, PTP: pore permeability transition, SOD: superoxide dismutase, TRPM9: melastatin transient receptor potential, VDAC: voltage-gated anion channel. Created with biorender.com (published with permission from biorender.com).

On the other hand, inflammation is also a highly reported consequence in situations where the concentration of Mg^{2+} is insufficient [7, 148]. In addition, the OS generated by low concentrations of Mg^{2+} could have a strong relationship with inflammation [3, 149]. As mentioned above, Mg^{2+} deficiency causes excessive ROS production mainly due to mitochondrial dysfunction, abnormal calcium homeostasis, and RAAS activation. The increase in ROS activates transcription factors such as NF-κB [150]. For example, Mg^{2+} deficiency has been shown to induce lipid peroxidation and NF-κB activation in cultured canine cerebral vascular tissue [151]. NF-κB is inactive in the cytoplasm, and its activation generates the transcription of proinflammatory cytokines such as TNF-α and interleukins (IL-1 and 6) [150, 152]. Bussière *et al.* [153] showed that an early consequence of Mg^{2+} deficiency is the activation of polymorphonuclear leukocyte activity and elevated

circulating levels of IL-6. Likewise, Malpuech-Brugère *et al.* [154] observed macrophage activation and an elevation of IL-6 in rats after a few days of Mg^{2+} deficiency. Therefore, Mg^{2+} deficiency induces an acute phase inflammatory response that turns into chronic inflammation [7, 153].

In the brain, NF-κB can also be activated by substance P (SP), vascular cell adhesion molecule-1, and inhibitor of plasminogen activator-1, which is induced by NMDA activation and the increased intracellular calcium by decreasing the concentration of Mg^{2+} [155]. Indeed, in a mouse model of Mg^{2+} deficiency, immunochemistry revealed that substance P is increased by 230 and 200% in megakaryocytes and lymphocytes, respectively, after 1 day of Mg^{2+} depletion [46]. Furthermore, SP has a direct role in promoting the activation of neutrophils and endothelium and inducing nitric oxide (NO) production; these processes could participate in the OS that contributes to the depletion of blood glutathione [156].

Mg^{2+} deficiency also increases endothelin levels, an endothelial cell-derived cytokine [157]. Likewise, it has been reported that animals with Mg^{2+} deficiency present greater recruitment and activity of phagocytic cells [1, 158]. The origin of this phenomenon is not well understood, but it is probably also related to OS [1]. Finally, inflammation related to Mg^{2+} deficiency is also generated by reducing anti-inflammatory mediators such as NO, lipoxins, resolvins, and protectins [159, 160].

In summary, Mg^{2+} deficiency is strongly related to OS due to impaired calcium homeostasis, mitochondrial dysfunction, and RAAS activation. OS can cause inflammation, and inflammation, in turn, improves OS (Fig. 3). However, some aspects of this relationship are not yet fully elucidated. Therefore, more preclinical and clinical studies are needed to clarify the mechanisms involved in the relationship between Mg^{2+} deficiency with OS and inflammation.

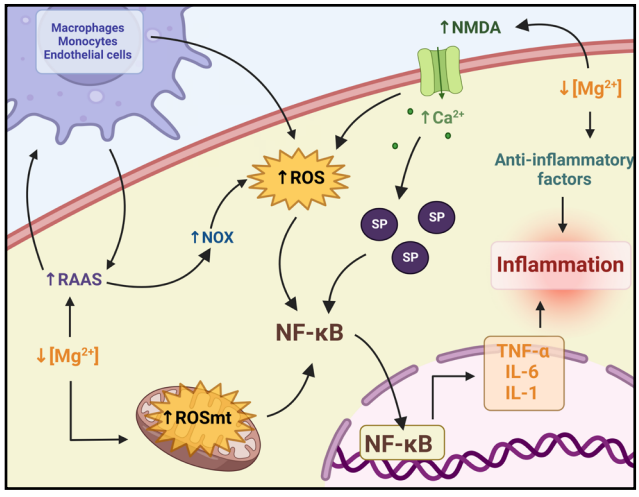

Fig. 3. Relationship between magnesium (Mg^{2+}) deficiency with oxidative stress (OS) and inflammation. Mg^{2+} deficiency causes an increase in reactive oxygen species (ROS) due to mitochondrial damage, an increase in N-methyl-D-aspartate (NMDA), and the activation of the renin-angiotensin-aldosterone system (RAAS). The latter also increases the recruitment of phagocytic cells, which exacerbates ROS. ROS activates the transcription factor nuclear transcription factor kappa B (NF-κB), which increases the transcription of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (1 and 6). This leads to inflammation. NF-κB is also activated by substance P (SP). Finally, Mg^{2+} deficiency causes a decrease in anti-inflammatory factors, exacerbating inflammation. Ca: calcium, mt: mitochondria, NOX: adenine dinucleotide phosphate (NADPH) oxidase. Created with biorender.com (published with permission from biorender.com).

Mg^{2+} deficiency, chronic inflammatory, and OS-associated diseases

Mg^{2+} deficient diets lead to low Mg^{2+} body concentrations, decreased antioxidants, and OS that progresses to oxidative damage, such as lipid peroxidation [2, 4,75, 161–163]. Also, there is evidence that low Mg^{2+} body concentrations are associated with increased OS and cytokine storm due to the alteration of antioxidant and immune defenses [111, 162, 164, 165]. Thus, Mg^{2+} deficiency is strongly associated with increased OS and metabolic syndrome mainly associated with low-grade systemic inflammation, such as obesity, diabetes, and CVD [2–4, 166]. These CVD includes heart failure, arrhythmias, atrial fibrillation, atherosclerosis, hypertension, and preeclampsia [3–5].

Mg^{2+} deficiency and cardiovascular diseases

Low serum Mg^{2+} levels have been associated with increased cardiovascular mortality by causing cardiovascular problems and exacerbating pre-existing ones [3, 5,8, 43, 75, 93, 120, 167–169]. In contrast, restoration of adequate Mg^{2+} levels or supplementation has been associated with improvements in CVD [3, 5,43, 75, 120, 169–171]. In a preclinical study with mice, Liu *et al.* [43] observed that a low Mg^{2+} diet for six weeks significantly decreased serum Mg^{2+} concentration. In addition, as a consequence, cardiac functions were affected with prolonged QTc intervals; mitochondrial dysfunction was observed in mouse cardiomyocytes with low cellular ATP production, overproduction of mitochondrial ROS, and mitochondrial membrane depolarization. Finally, normalizing these affectations with the replacement of Mg^{2+} [43]. In another study by Watanabe *et al.* [120], similar results were observed since an Mg^{2+} deficient diet for eight weeks significantly decreased plasma Mg^{2+} levels. In addition to increased systolic and diastolic blood pressure, left ventricular hypertrophy, macrocytic anemia, and impaired basal cardiac contractile activities. Similarly, observing that with the replacement of Mg^{2+}, the conditions described above were normalized [120].

One of the causes of these CVDs is that intracellular Mg^{2+} deficiency leads to inflammation and cardiovascular fibrosis. The latter was identified thanks to the anti-inflammatory and anti-fibrotic role of coenzyme TRPM7 mediated partly through Mg^{2+} dependent mechanisms since mice deficient in TRPM7 presented significant cardiac hypertrophy, fibrosis, and inflammation; Mg^{2+} treatment at a cellular level ameliorated effects [172]. Also, the electrophysiologic changes resulting from Mg^{2+} deficiency can increase the risk of malignant ventricular arrhythmias and sudden cardiac death [173, 174].

A higher incidence of sudden death in some geographic regions attracts attention, and researchers begin to relate them to geological environments such as drinking water due to their mineral content [62]. Residents in soft water areas presented higher sudden death rates due to an increased susceptibility to lethal arrhythmias [62, 63, 95]. Electrolyte disturbances are a frequent complication of chronic heart failure [175]. Patients with isolated hypomagnesemia (without other electrolyte disturbance) frequently present electrocardiogram disturbances with a P wave, corrected QT, and corrected T peak-to-end-interval duration prolonged, suggesting atrial depolarization and ventricular repolarization dispersion increased [176]. Even though the electrophysiologic action on cellular function is unclear, it suggests that these disturbances may have importance in the relationship between hypomagnesemia and sudden death [176]. Mg^{2+} deficiency has been implicated in sudden death, and it is suspected that the electrophysiological changes induced by calcium are involved [177, 178].

Mg^{2+} deficiency and diabetes

Mg^{2+} deficiency is widely associated with diabetes, mainly in type 2 diabetes [179–186]. Hypomagnesemia is frequently identified in diabetic patients and contributes to the progression of diabetes complications [187, 188]. Also, numerous studies have described a high prevalence of Mg^{2+} deficiency in diabetic patients [6, 180, 185, 189–192]. There has been evidence that Mg^{2+} deficiency alters calcium homeostasis by competitively inhibiting the voltage-dependent calcium channel, leading to lower insulin secretion [42, 193]. Mg^{2+} deficiency also may influence the insulin signaling pathway, modifying sensitivity to insulin, such as increasing the association between insulin receptor substrate-1 and p58 subunit of phosphatidyl-inositol 3 kinase or reducing the phosphorylation of protein kinase B (Akt), leading to a diminished response to insulin [194, 195]. As if that were not enough, it has been observed that Mg^{2+} excretion is more significant in diabetic patients than in healthy subjects due to type 2 diabetes frequently causing damage to the glomerular filtration barrier, altering Mg^{2+} reabsorption [196–198]. The latter indicates that Mg^{2+} deficiency is promoted by diabetes, and at the same time, Mg^{2+} lack exacerbates IR and impaired insulin secretion diabetes.

Also, as mentioned previously, inflammation and OS are related to the incidence of diabetes, a consequence of cellular signaling pathways interference [179, 199, 200]. The secretion of IL-1, IL-6, IL-8, IL-18, TNF-α, beta-adrenergic, and ROS in IR is enhanced in Mg^{2+} deficiency [42]. King *et al.* [201] observed that diabetic patients with elevated glycated hemoglobin levels present elevated CRP concentrations, indicating systemic inflammation. Han *et al.* [202] even suggest that inflammation is essential in diabetic pathogenesis and a high CRP level increases the risk of developing diabetes. Although the linking mechanisms of inflammation and IR are unclear, inflammation plays an important role via cytokines and molecular pathways [203].

Mg^{2+} supplementation to prevent diseases progression

Fortunately, Mg^{2+} replenishment in inflammatory pathologies associated with Mg^{2+} deficiency through supplementation is favorable. Clinic and pre-clinic studies showed decreased inflammatory biomarkers and disease improvement (Table 4) [8, 170, 171, 204–211]. These optimistic and encouraging results suggest using Mg^{2+} as an immunomodulatory agent, a regulator of inflammation and associated conditions, thus preventing the development of severe or chronic inflammation [3, 163, 205]. Mg^{2+} therapy decreases nuclear transcription factor kappa B (NF-κB), IL-6, TNF-α, and CRP and enhances vitamin D functionality [36, 99, 111, 212].

Also, Mg^{2+} supplementation has been observed to be effective as a treatment in diabetic rats due to increased insulin receptors and glucose transporter-4 improving glucose tolerance and lowering blood glucose levels almost to the normal range [215]. Even it has observed reduced oxidative damage and increased glutathione concentrations [215]. Liu *et al.* [216] also observed that Mg^{2+} supplementation positively affects insulin sensitivity by increasing insulin receptor expression. Additionally, Kamran *et al.* [217] observed that Mg^{2+} supplementation improved blood glucose levels and

Table 4. Diseases associated with Mg^{2+} deficiency and the effect of supplementation. BDSW: Balanced Deep Water, hs-CRP: High Sensitivity Serum C-Reactive Protein, IL-1: Interleukin 1, Mg^{2+}: Magnesium, OGTT: Oral Glucose Tolerance Test, PCO: Protein Carbonyl, TAC: plasma total antioxidant capacity, TNF-α: tumor necrosis factor-alpha, ICU: intensive care unit

Associated disease	Population or study model	Supplementation	Conclusions	Ref.
Hypertension (effective supplementation associated with a deficiency)	Uncomplicated hypertensive patients with normal renal function Age: 20 to 65 years	Oral magnesium aspartate hydrochloride (20 mmol elemental Mg^{2+}/day) for 3 months	There were no significant changes in systolic, diastolic, or mean blood pressure. It was concluded that supplementation with Mg^{2+} is only effective when there is a deficiency of Mg^{2+}.	[208]
Ventricular arrhythmias	Patients with stable congestive heart failure secondary to coronary artery disease Age: 42 to 73 years	Magnesium chloride (15.8 mmol of Mg^{2+}/day) for six weeks:	Oral intake of Mg^{2+} decreased the frequency of asymptomatic ventricular arrhythmias in patients with chronic congestive heart failure and lower mean arterial pressure.	[170]
Hypertension	Patients with mild to moderate primary hypertension without complications Age: 36 to 65 years	Magnesium oxide (600 mg Mg^{2+}/day, divided into 3 doses) for six weeks	Oral intake of Mg^{2+} reduced diastolic, systolic, and mean blood pressure, with an increase in intracellular Mg^{2+} and a decrease in intracellular Na^{+}.	[209]
Cardiovascular diseases	Patients with systolic heart failure	Magnesium citrate (300 mg/day) for 5 weeks	Increased intracellular magnesium and the correlation of heart rate variability	[213]
Preeclampsia	Women with severe nulliparous preeclampsia	Therapy with a loading dose of 4 g magnesium sulfate ($MgSO_4$) intravenously over 30 min followed by a maintenance dose of 1 g/h.	$MgSO_4$ showed a significant reduction in the level of lipid peroxidation and osmotic fragility of red blood cells.	[210]
Diabetes	Diabetic patients Age: ≥65 years	Magnesium pidolate (368mg Mg^{2+}/day) for one month	Magnesium pidolate resulted in significant improvement of brachial artery endothelial function	[171]
Polycystic ovary syndrome (PCOS)	Women with diagnosed PCOS according to the Rotterdam criteria Age: 18 to 40 years, treatment	Magnesium oxide (250 mg/ twice daily) + zinc sulfate (220 mg/ twice daily) for 12 weeks	Co-supplementation of magnesium and zinc may confer an advantageous therapeutic potential in PCOS patients by decreasing hs-CRP, PCO, IL-1, TNF-α, and increasing TAC.	[206]
COVID-19	Patients diagnosed with COVID-19 Age: ≥ 50 years	Vitamin D_3 (1000 IU/day) + magnesium oxide (150 mg Mg^{2+}/day) + vitamin B12 (500 µg/day) for ≤14 days	The combination of treatments was associated with a significantly lower probability of requiring oxygen therapy or going to the ICU.	[205]
Prediabetes	Adults with the following history: Age: 19 to 70 years old OGTT: 75g Fasting glucose levels: 100-125 mg/dL. Glycemia at 2 postprandial hours: 140–199 mg/dL.	BDSW water with magnesium and calcium (3:1) and a hardness of 4000 (440 ml/day) for eight weeks. Amount of Mg^{2+}: 350mg	BDSW improves insulin sensitivity parameters and lipid profiles	[211]
Metabolic syndrome	Adults with metabolic syndrome and	30 mL of 5% magnesium chloride solution, equivalent to	Blood pressure, hyperglycemia and hypertriglyceridemia were reduced	[214]

intraperitoneal glucose tolerance test of diabetic rats and improved Akt-2 and insulin receptor substrate-1 gene and protein expression, increasing glucose transportation in skeletal muscle. In summary, Mg^{2+} supplementation promotes the correct insulin signaling pathway increasing the expression of proteins involved in enhancing its activity.

Concluding remarks and future directions

Although it is still uncertain whether Mg^{2+} deficiency is the origin or consequence of diseases associated with OS and inflammation, there is clear evidence that it represents a greater risk for their development, in addition to the high prevalence of Mg^{2+} deficiency in these patients and that this leads to exacerbating clinical symptoms. So, maintaining optimal Mg^{2+} body concentration may be favorable in preventing of OS, inflammation, and, thus, chronic comorbidities. Furthermore, Mg^{2+} deficiency is directly associated with physiological mechanisms such as electrophysiology, insulin excretion, and sensitivity. Therefore, it is associated with an increased risk of developing or exacerbating diabetes and CVD. Although favorable results have been observed with Mg^{2+} supplementation in inflammatory markers, more specific studies are required to evaluate and understand the Mg^{2+} supplementation effect as a joint therapy in comorbidities and to prevent disease development. Also, assessing the impact of Mg^{2+} supplementation in healthy subjects as a preventive treatment is necessary.

Acknowledgements

This research was funded by Consejo Nacional de Ciencia y Tecnología (CONACYT) México, Grants Numbers A1-S-7495, by Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica (PAPIIT), Grant Numbers IN202219 and IN200922 of the Universidad Nacional Autónoma de México (UNAM), and by Programa de Apoyo a la Investigación y el Posgrado (PAIP), Grant Number 5000-9105. Estefani Yaquelin Hernández-Cruz is a doctoral student from Programa de Doctorado en Ciencias Biológicas from the National Autonomous University of Mexico (UNAM), and she received a fellowship from CONACYT (779741).

Disclosure Statement

The authors declare no conflicts of interest.

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