AGING: OXIDATIVE STRESS AND DIETARY ANTIOXIDANTS

Edited by

VICTOR R. PREEDY

King's College London,
London, UK

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CHAPTER

16

Magnesium, Oxidative Stress, and Aging Muscle

Mario Barbagallo, Ligia J. Dominguez

Geriatric Unit, Department of Internal Medicine DIBIMIS, University of Palermo, Italy

List of Abbreviations

ATP adenosine triphosphate
Ca calcium
cAMP cyclic adenosine monophosphate
CRP C-reactive protein
DNA deoxyribonucleic acid
IFN interferon
Ig immunoglobulin
IL interleukin
K potassium
MAPK mitogen-activated protein kinase
MDA malondialdehyde
Mg magnesium
MgT total serum Mg concentrations
NADPH nicotinamide adenine dinucleotide phosphate
NFκB activation of nuclear factor-kappaB
NHANES National Health and Nutrition
NMDA *N*-methyl-D-aspartate
PAI plasminogen activator inhibitor
PMN polymorphonuclear
PTH parathyroid hormone
RBCs red blood cells
RDA recommended dietary allowance
RNA ribonucleic acid
ROS reactive oxygen species
TNF tumor necrosis factor
VCAM vascular cell adhesion molecule

INTRODUCTION

In recent decades the clinical relevance and biologic significance of magnesium (Mg) have been extensively documented. However, the role of Mg in medicine started as far back as the 17th century covering a large span of the chemical and pharmacologic fields of knowledge. The recognition by Grew, in 1695, that magnesium sulfate is one of the essential constituents of Epsom salt, may be considered the entry of magnesium into medicine.[1]

The Mg ion, the second most abundant intracellular cation after potassium, plays essential roles in the structure and function of the human body; it is an essential cofactor in a wide variety of biologic processes, including protein synthesis, nucleic acid synthesis and stability, neuromuscular excitability and the conduction of neural impulses, stimulus–contraction coupling and muscle contraction.[2,3] In particular, it is now clear that the Mg ion, although not directly involved in the biochemical process of contraction, modulates vascular smooth muscle tone and contractility by affecting calcium ion concentrations and the availability of the calcium ion at critical sites. Magnesium serves to actively promote relaxation, offset calcium-related excitation–contraction coupling and decrease cellular responsiveness to depolarizing stimuli by different mechanisms: (i) stimulating Ca-dependent K channels; (ii) competitively inhibiting calcium (Ca) binding to calmodulin; (iii) stimulating both plasma membrane and sarcoplasmic reticulum Ca ATPases; and (iv) activating the membrane Na,K-ATPase pump.[2,4] Magnesium is a critical modulator of the tension with which the contractile apparatus of striated muscle responds to the prevailing ionized calcium concentration; the Mg complex with adenosine triphosphate (MgATP) is the substrate for the enzymatic reactions that underlie the sliding filament mechanism for myofibrillar contraction and relaxation. Magnesium also participates in many of the most vital oxidative, synthetic, and transport processes of the muscle cell. Consistent with the above, calcium-induced contraction in muscles is not only sensitive to changes in Mg concentration, but direct reduction of extracellular Mg raises smooth muscle Ca content, while conversely, elevations in Mg concentrations reciprocally lower calcium content in muscle.[5] Magnesium is an indispensable part of the activated MgATP complex, and it is required for adenosine triphosphate (ATP) synthesis in the mitochondria.[2,3] Cell signaling requires MgATP for the phosphorylation of proteins and the synthesis and activation of the cell-signaling molecule cyclic adenosine monophosphate (cAMP), involved in multiple biochemical processes. Magnesium is a necessary cofactor in over 300 enzymatic reactions; it is required for the activity of

Aging
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TABLE 16.1 Physiological Role of Magnesium in the Body

ENZYME FUNCTION	
Enzyme Substrate	*Direct Enzyme Activation*
• Kinases	• Phosphofructokinase
• ATPases/GTPases	• Creatine kinase
• Cyclases	• 5-Phosphoribosyl-pyrophosphate synthetase
	• Adenylate cyclase
	• Na-K-ATPase
STRUCTURAL FUNCTION	
• Proteins	
• Polyribosomes	• Multiple enzyme complexes
• Nucleic acids	• Mitochondria
CALCIUM ANTAGONIST	
• Muscle contraction/relaxation	
• Neurotransmitter release	
• Action potential conduction in nodal tissue	
MEMBRANE FUNCTION	
• Cell adhesion	
• Transmembrane electrolyte flux	

TABLE 16.2 Characteristics of Ionic Magnesium

Element category	Alkaline earth metal
Atomic number	12
Atomic weight	24.305 g/mol
Valence	2
Normal serum	0.75-0.95 mmol/L 1.7-2.5 mg/dL
Total body content	24 g
Distribution in serum	– free ionized 70-80% – protein-bound 20-30% – complexed 1%

TABLE 16.3 Magnesium Equilibrium

- Main determinants are gastrointestinal absorption and renal excretion
- Healthy individuals need to ingest 0.2-0.4 mmol/kg of body weight/day to stay in balance
- Extracellular Mg is in equilibrium with that in the bone, kidneys, intestine, and other soft tissues
- Bone is the main reservoir of Mg
- Primary renal disorders cause hypomagnesemia by decreased tubular reabsorption of Mg
- Osmotic diuresis results in magnesium loss
- Drugs may cause magnesium wasting

all rate-limiting glycolytic enzymes, protein kinases, and, more generally, all ATP and phosphate transfer-associated enzymes. Magnesium may also bind the enzymes directly (i.e. RNA and DNA polymerases) and alter their structure.[2,3] Therefore, the availability of an adequate quantity of Mg may be considered a critical factor for normal cellular and body homeostasis and function (Table 16.1).

MAGNESIUM METABOLISM IN OLDER ADULTS

The adult human body contains approximately 24 g (1 mol) of Mg, of which about 65% resides in the mineral phase of bone, about 27% is found in muscle, and 6–7% is found in other cells. Extracellular Mg accounts for only 1% or so of total body Mg. The normal serum Mg concentration ranges from 0.75 to 0.95 mmol/L (1.7–2.5 mg/dL or 1.5–1.9 meq/L) and is tightly controlled and maintained in this range. In the serum, about 70–80% of Mg exists in the biologically active ionized (free) form, while the remainder is bound to circulating proteins (e.g. albumin) (20–30%) or complexed to anions (e.g. bicarbonate, phosphate) (1%). The cytosolic Mg concentration ranges between 0.5 and 1.0 mmol/L in various types of cell[2,6] (Tables 16.2 and 16.3). The magnesium status in the body is determined mainly by absorption through the gastrointestinal tract, the requirement of different tissues (i.e. skeletal and cardiac muscle uptake and usage), and renal excretion. The small intestine is the main site for Mg absorption. Healthy individuals need to ingest 0.15–0.2 mmol/kg/day to stay in balance. The kidney exerts the most predominant impact in controlling body Mg status. Diuretics, frequently used in older populations, may also modify renal Mg handling, reducing Mg reabsorption.[2,6]

Bone is the main storage location of Mg, which cannot be quickly exchanged with the Mg in extracellular fluids; more prompt requirements for Mg are satisfied from the Mg stored in the intracellular compartment. There is wide-ranging variability in Mg intake, absorption, conservation, and excretion. Alterations in Mg metabolism that have been associated with aging include a reduction in Mg intake and intestinal absorption, and an increase in Mg urinary and fecal excretion (Figure 16.1). Although no known hormonal factor is specifically involved in the regulation of Mg metabolism, several hormones are recognized to have an effect on Mg balance and transport. Among them, parathyroid hormone (PTH), calcitonin, catecholamines, and insulin have a major role.[2,6]

One of the main reasons why Mg metabolism has not become a greater focus of routine attention in clinical practice has been the difficulties in obtaining an easily available, accurate, and reproducible measurement of Mg status in the body. Total serum Mg concentrations (MgT) do not always reflect accurately the body Mg homeostasis; MgT has proved useful and it has been extensively utilized in epidemiologic studies, but it may not be helpful for the detection of a subclinical Mg deficit on an individual basis. MgT does not change with age, while intracellular free Mg tends to decrease with age.[6]

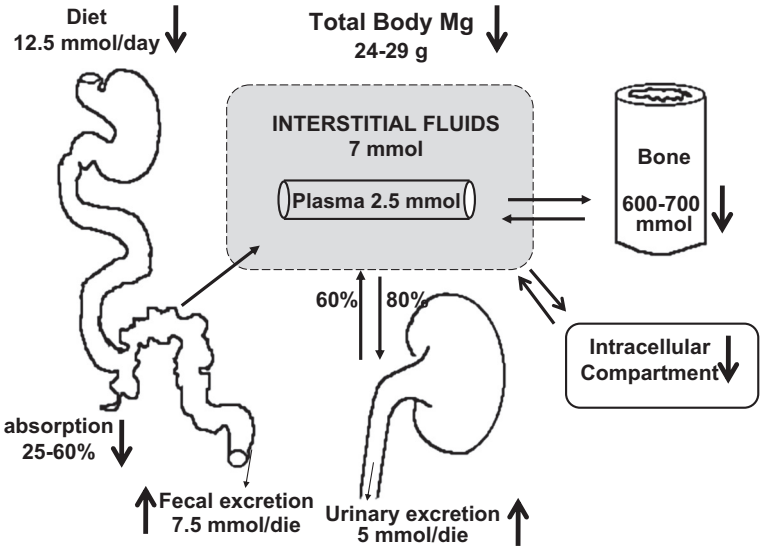

FIGURE 16.1 Magnesium homeostasis with age (arrows indicate possible sites of alteration with aging).

TABLE 16.4 Main Mechanisms of Magnesium Deficit with Aging

PRIMARY MAGNESIUM DEFICIT
• Inadequate Mg dietary intake • Reduced efficiency of Mg absorption (associated with reduced vitamin D levels) • Increased urinary excretion of Mg (associated with age-dependent reduction of kidney function and of Mg tubular reabsorption)
SECONDARY MAGNESIUM DEFICIENCY
• Associated with age-related diseases and comorbidities • Increased urinary Mg loss secondary to drugs (i.e. diuretics) frequently used in older persons

TABLE 16.5 Mechanisms by Which Low Magnesium Status May Affect Muscle, Increasing Oxidative Stress

• Energetic metabolism (oxygen uptake and energy production) • Transmembrane transport • Muscle contraction and relaxation (by means of MgATP and the release of calcium)

However, more precise and expensive techniques for measuring intracellular free Mg concentrations remain mainly at the research level, while available measurements of serum ionized free Mg, the active part of serum Mg, may still have some technical flaws.[2,6]

Aging represents a major risk factor for Mg deficit. The total body Mg content and intracellular Mg tend to decrease with age.[2] The most common mechanisms which may cause Mg deficits with aging are summarized in Table 16.4;[6] they include primary Mg deficit (inadequate Mg nutrient intake, reduced efficiency of Mg absorption, and increased urinary excretion of Mg), and secondary Mg deficiency (associated with drug use or pathologic conditions associated with aging).

MAGNESIUM, MUSCULAR PERFORMANCE, AND AGING MUSCLE

An adequate cellular Mg concentration seems necessary for maintaining optimal muscle performance and exercise tolerance. Magnesium status strongly affects muscle performance, probably due to the key role of magnesium in energetic metabolism, transmembrane transport, and muscle contraction and relaxation.[7] Magnesium is involved in numerous processes that affect muscle function, including oxygen uptake and energy production. Myofibrillar contraction and relaxation is strictly connected to Mg and MgATP, as is the uptake and release of Ca from the sarcotubules. Thus, intracellular concentrations of Mg, even within narrow limits, can profoundly affect the contractile performance of the muscle cell (Table 16.5).

Magnesium supplementation (up to 8 mg/kg daily) was shown to enhance muscle strength (20% increase of peak knee-extension torque) in young individuals,[8] improve endurance exercise performance, and decrease oxygen use during submaximal exercise.[9] Exercise induces a redistribution of Mg in the body to accommodate metabolic needs, accounting for changes in Mg concentration in extracellular fluids, blood cellular components, myocytes, and adipocytes. It has been suggested that Mg deficiency may impair exercise performance and increase the oxidative stress linked to strenuous exercise.[10] Conversely, exercise increases urinary and sweat losses of magnesium, and thus the Mg requirement is increased in an individual performing exercise. A low Mg intake in athletes may result in a Mg-deficient status, and may thus reduce their performance. Magnesium supplementation, or increased dietary intake, is beneficial to physically active persons with a low or deficient Mg status to enhance strength

and to improve exercise performance.[8,9] There is less evidence for Mg supplementation in physically active persons with an adequate Mg status for enhancing physical performance.[10]

A large portion of the energy used for physiologic functions in humans is produced by mitochondria through the movement of electrons in the respiratory chain. Magnesium in the mitochondria accounts for one third of total cellular Mg; it is present as a complex with ATP and as a component of membranes and nucleic acids. Magnesium is critical for basic mitochondrial functions, including ATP synthesis, electron transport chain complex subunits, and oxygen detoxification.[2,6] As discussed below, Mg seems fundamental for controlling oxidative stress and for the preservation of normally functioning muscle mitochondria. An inadequate availability of Mg may lead to reduced mitochondrial efficiency and increased production of reactive oxygen species (ROS), and subsequent structural and functional impairment of proteins that may lead to the decline in skeletal muscle mitochondrial function associated with aging in humans.[11]

In rats, Mg depletion is associated with structural damage to muscle cells, mitochondrial swelling and an altered ultrastructure that was shown to be associated with an increased production of ROS, lipid and protein damage, and impaired intracellular calcium homeostasis. Both Mg deficit and exercise contribute to the occurrence of oxidative stress.[12] Although the importance of Mg as a determinant of muscle performance in young athletes is well established, its role in maintaining muscle integrity and function in older adults is largely unknown.

Lukaski and Nielsen[7] examined the effects of different levels of dietary Mg on biochemical measures and physiologic responses in postmenopausal women (45 to 71 years old) during submaximal exercise, in relation to changes in erythrocyte and skeletal muscle Mg concentrations. The women consumed diets containing conventional foods with varying Mg content, totaling 112 mg/8.4 MJ (2000 kcal) supplemented with 200 mg of Mg daily for 35 days (control), then 112 mg/8.4 MJ for 93 days (depletion) followed by 112 mg/8.4 MJ supplemented with 200 mg of Mg daily for 49 days (repletion), in a depletion–repletion experiment. The concentration of Mg in erythrocytes, Mg retention, and skeletal muscle Mg content decreased when dietary Mg was restricted. Peak oxygen uptake, total and cumulative net oxygen uptake – determined by using indirect calorimetry – and peak heart rate increased during standardized submaximal work with restricted compared with adequate dietary Mg.[7] These findings indicate that dietary Mg depletion, in otherwise healthy women, results in a significant increase in energy needs and adversely affects cardiovascular function during sub-maximal work. These data, showing a decreased work economy and functional impairment in older women on restricted dietary Mg, extend the knowledge of magnesium status in young athletes to older women not participating in intense physical activity.

Older age is frequently characterized by sarcopenia, defined as a loss of skeletal muscle mass, quality, and function.[13] Sarcopenia of aging is almost a universal phenomenon, occurring in a wide range of species, from nematodes to flies, rodents, non-human primates, and humans. Muscle changes in humans start in the fourth decade of life. Sarcopenia in the aging population is a strong independent risk factor for disability and mortality. What gererally occurs with aging is a decrease in the rate of synthesis of several muscle proteins, specifically myosin heavy chain and mitochondrial proteins. The underlying causes of the reduction in mitochondrial activity and ATP production seem to be related to a decrease in mitochondrial DNA and in messenger RNA. Reduced ATP production has been suggested to be the basis of reduced muscle protein turnover, which requires energy[13] (Table 16.6). Magnesium depletion, because of the fundamental role of Mg in the MgATP complex, may play a role in this phenomenon, causing structural damage in muscle cells through increased oxidative stress (see below) and impaired intracellular calcium homeostasis. Both aerobic exercise and resistance exercise enhance muscle protein synthesis and mitochondrial activity. We do not know the role of Mg in aging-related muscle mitochondrial dysfunction, or the role of reduced physical activity. Because Mg status is strictly related to muscle ATP, and both Mg deficiency and sarcopenia tend to be more prevalent at older ages, we hypothesized that poor Mg status contributes to late life sarcopenia. Using data from the InCHIANTI study, a well-characterized representative sample of older men and women, we found a significant, independent, and strong relationship between circulating Mg and muscle performance; this was consistent across several muscle performance parameters for both men and women,[14] suggesting a role for Mg status in helping to maintain muscle function with age. As discussed below, in addition to the role of Mg in energetic metabolism, at least two other mechanisms may help to explain these findings: (i) increased oxidative stress in the presence of Mg deficiency, and (ii) the proinflammatory effect of Mg depletion.

TABLE 16.6 Effects of Aging on the Mitochondria by Which Oxidative Stress May Be Increased

- Decreased number
- Morphology modifications
- Increased DNA mutations
- Decreased biogenesis
- Decreased autophagy
- Increased apoptosis

MAGNESIUM, EXERCISE, AND OXIDATIVE STRESS

Studies on cultured cells, in experimental animal models, and in humans, have consistently shown that Mg deficiency is associated with increased oxidative stress and decreased antioxidant defense. Several studies have shown convincingly that Mg deficiency results in increased production of oxygen-derived free radicals in various tissues, increased free-radical-elicited oxidative tissue damage, increased production of superoxide anion by inflammatory cells, decreased antioxidant enzyme expression and activity, decreased cellular and tissue antioxidant levels, and increased oxygen peroxide production.[6,15-23] Magnesium deficiency in rats causes decreased hepatic glutathione, superoxide dismutase, and vitamin E, together with increased lipid peroxidation and malondialdehyde (MDA) levels secondary to upregulated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity.[24]

In stroke-prone spontaneously hypertensive rats, Mg deficiency results in marked increases in oxidative stress, superoxide accumulation, mitogen-activated protein kinase (MAPK) activation, and the development of hypertension.[25] Magnesium has antioxidant capacities and may prevent oxygen radical formation by scavenging free radicals and by inhibiting xanthine oxidase and NADPH oxidase.[26] Magnesium supplementation may reduce oxidative stress. In experimental diabetes, a decreased intracellular Mg level and increased Mg urinary excretion were associated with increased plasma MDA and decreased expression of hepatic superoxide dismutase and glutathione S-transferase; all of these effects were corrected by Mg supplementation.[27]

We have shown that antioxidant capacity and the action to reduce oxidative stress of glutathione and vitamin E (measured as decreased reduced/oxidized glutathione ratio, increased lipohydroperoxides, and increased thiobarbituric acid-reactive substances) are associated with an increase in the intracellular concentration of Mg.[28,29]

MAGNESIUM, OXIDATIVE STRESS, AND THE AGING MUSCLE: THE ROLE OF INFLAMMATION

A state of chronic inflammation has been proposed as one of the main causes of frailty in older persons.[30] Poor Mg status may trigger the development of a pro-inflammatory state both by causing excessive production and release of IL-1β and TNF-α,[31] and by elevating circulating concentrations of pro-inflammatory neuropeptides that trigger activation of low-grade chronic inflammation.[32]

Several interventional studies in animal models of Mg deficiency have provided convincing evidence of the link between Mg, inflammation, and oxidative stress. Oxidative mitochondrial decay linked to aging may itself favor hypomagnesemia. Magnesium deficiency inhibits endothelial growth and migration, and it stimulates the synthesis of nitric oxide and some inflammatory markers, thus directly modulating microvascular functions.[33,34] Experimental studies in rats have shown that Mg deficiency induces a chronic impairment of redox status associated with inflammation, which could contribute to increased oxidized lipids, and may promote hypertension and vascular disorders,[35] confirming the link between oxidative stress and inflammation.

Several other experimental studies have demonstrated that Mg deprivation determines a pro-inflammatory state, confirmed by the elevated circulating plasma level of several markers of inflammation, including interleukin-6 (IL-6), IL-1β, tumor necrosis factor (TNF)-α, vascular cell adhesion molecule (VCAM), and plasminogen activator inhibitor (PAI)-1; other markers of inflammation, such as increased circulating inflammatory cells and increased hepatic production and release of acute phase proteins (i.e. complement, alpha2-macroglobulin, alpha1-acid glycoprotein, fibrinogen), have been reported as well.[33-39] A direct mechanistic link has been reported for the association of low Mg and increased production and secretion of TNF-α and IL-1β in cultured alveolar macrophages.[40]

Because Mg acts as a natural calcium antagonist, the molecular basis for the inflammatory response may also be the result of a modulation of the intracellular calcium concentration. Potential mechanisms include the priming of phagocytic cells, the opening of calcium channels, activation of *N*-methyl-D-aspartate (NMDA) receptors, and/or the activation of nuclear factor-kappaB (NFκB).[2,6]

Studies in humans have confirmed the clinical relevance of the link between low serum Mg levels, as well as inadequate dietary Mg, and low-grade systemic inflammation.[41-44] Data from the Women's Health Study have shown that Mg intake is inversely related to systemic inflammation, measured by serum C-reactive protein concentrations, and to the prevalence of the metabolic syndrome in adult women.[41] Likewise, using the 1999–2002 NHANES databases, King et al found that dietary Mg intake was inversely related to C-reactive protein levels. Among the 70% of the population not taking supplements, Mg intake below the RDA was significantly associated with a higher risk of having elevated C-reactive protein.[42] Other clinical studies have suggested that serum Mg levels are also inversely related to oxidative stress and inflammation markers, including C-reactive protein and TNF-α concentrations.[43,44]

MAGNESIUM, IMMUNE RESPONSES, AND OXIDATIVE STRESS

There is evidence that Mg plays a role in the immune response. Magnesium has a strong relationship with the immune system, in both non-specific and specific immune responses, while magnesium deficit has been shown to be related to impaired cellular and humoral immune function. Magnesium deficiency leads to immunopathologic changes that are related to the initiation of a sequential inflammatory response. Magnesium is a cofactor for immunoglobulin (Ig) synthesis, immune cell adherence, antibody-dependent cytolysis, IgM lymphocyte binding, macrophage response to lymphokines, and T helper-β cell adherence.[45,46] In addition, Mg deficiency seems to accelerate thymus involution. One of the most remarkable results regarding the effects of Mg deficiency on the organism is the higher level of apoptosis shown in thymuses from Mg-deficient rats as compared with controls.[47] Altered polymorphonuclear (PMN) cell number and function have been shown in rats fed a Mg-deficient diet for 8 days, together with the characteristic inflammatory response. In fact, an increased number of neutrophils, related to an increased activity of phagocytosis, has been found in Mg-deficient rats compared with control rats.[48] Clinical signs of inflammation, splenomegaly, and leukocytosis, have been reported as well in rats given a Mg-deficient diet. A reduced proportion of CD8-T cells has been shown under these conditions, which has been related to a decreased concentration of interferon (IFN)-γ in spleen homogenates.[49] Several changes in gene expression, including upregulation of TNF receptor 1 and IL-1 receptor type I, have also been demonstrated in rat thymocytes in early Mg deficiency.[21] A recent study discovered a key role for Mg in the T cell antigen receptor signaling pathway from the study of a novel primary immunodeficiency.[50] There are studies confirming the involvement of Mg in human cell apoptosis. Fas-induced β-cell apoptosis is Mg-dependent. Increased cytosolic free Mg levels are required for Fas molecule binding expression on the β-cell surface to initiate multiple signaling pathways that result in apoptotic cell death.[51] *In vitro* incubation of granulocytes in media with different Mg composition resulted in significant changes in chemotactic peptide-induced calcium transients.[52]

Because physical exercise may deplete Mg, many aspects of immune function can be depressed temporarily by either severe exercise or a longer period of excessive training.[53] Although the disturbance is usually quite transient, it has been suggested that it may be sufficient to allow clinical episodes of infection, particularly upper respiratory tract infections.[53] The risk may be higher in older persons who already have a reduced immune capacity and a consequent propensity to infections. However, regular and moderate exercise has been reported to improve the ability of the immune system to protect the host from infection.[53] Strenous exercise has been associated with an acute increase in oxidative stress free radical (ROS) production.[13] ROS may contribute to the development of muscle fatigue *in situ*, but there is still a lack of convincing direct evidence that ROS are able to impair exercise performance *in vivo* in humans. It remains unclear whether exercise-induced oxidative stress modifications may have clinical significance. Conversely, the antioxidant actions of Mg[26] may have a role in muscle protection in the aging population. Even though this needs to be proven by specific trials, it is likely that maintaining a good quality Mg homeostasis throughout life, and in particular in older persons, may help to protect from muscle performance decline associated with aging.

CONSEQUENCES OF MAGNESIUM IMBALANCE WITH AGE

The consequences of Mg imbalance in elderly people related to defective membrane function, chronic inflammation, increased oxidative stress, and immune dysfunction may include an increased vulnerability to age-related diseases and particularly to sarcopenia and frailty.

Several studies have reported alterations in cell physiology with senescence features during Mg deficiency in different cell types. Magnesium is an essential cofactor in cell proliferation and differentiation and in all steps of nucleotide excision repair. Magnesium deficiency-related alterations may include reduced oxidative stress defense, cell cycle progression, culture growth, cellular viability,[54-57] activation of proto-oncogenes (i.e. c-fos, c-jun), and expression of transcription factors (e.g. NFκB).[58] Magnesium deficiency may accelerate cellular senescence in cultured human fibroblasts. Continuous culture of primary fibroblasts in Mg-deficient media resulted in the loss of replicative capacity with accelerated expression of senescence-associated biomarkers. A marked decrease in the replicative lifespan was seen compared to fibroblast populations cultured in standard Mg media conditions. Human fibroblast populations cultured in Mg-deficient conditions also showed an increased senescence-associated β-galactosidase activity. Additionally, activation of cellular aging (p53 and pRb) pathways by Mg-deficient conditions also increased the expression of proteins associated with cellular senescence, including p16INK4a and p21WAF1. Telomere attrition was found to be accelerated in cellular populations from Mg-deficient cultures, suggesting that the long-term consequence of inadequate Mg availability in human fibroblast cultures is an accelerated cellular senescence.[59] Features of cellular senescence induced by low magnesium concentrations have also been reported in other cell types, e.g. endothelial cells.[60] Intracellular free Mg is a 'second messenger' for downstream events in apoptosis. There is increasing evidence from animal

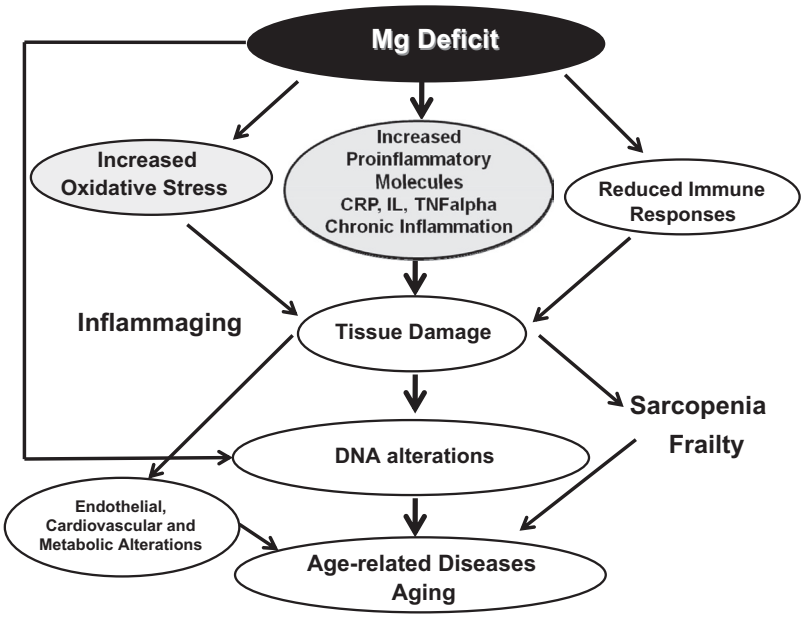

FIGURE 16.2 Overall hypothesis in which a chronic Mg deficit has been proposed as one of the physiopathologic links that may help to explain the interactions among inflammation, oxidative stress, and altered immune responses with sarcopenia of aging and with the aging process.

experiments and epidemiologic studies that Mg deficiency may decrease membrane integrity and membrane function, increasing the susceptibility to oxidative stress, cardiovascular disease, and accelerated aging. It is likely that many of these Mg effects may have relevance also to the aging of muscle and sarcopenia, as well as to many other age-related diseases.

CONCLUSIONS

Aging is very often associated with Mg inadequacy. Chronic Mg deficiency may result in excessive production of oxygen-derived free radicals. Oxidative stress and a chronic, low-grade inflammation have been proposed as an underlying condition linked to aging muscle, sarcopenia, and frailty. A chronic Mg deficit has been proposed as one of the physiopathologic mechanisms that may help to explain the interactions among inflammation and oxidative stress with sarcopenia, frailty, and a number of age-related diseases (Figs 16.2 and 16.3).

Magnesium status is strictly connected to muscle performance in older persons. A possible mechanism of this association is the effect of Mg concentrations on mitochondrial function in muscle, which may be particularly critical in the aging muscle.

Despite the physiologic importance of Mg, the multiple problems associated with its deficiency, and the ease of supplementation, inadequate Mg intake remains highly prevalent in various populations. Because Mg supplementation is inexpensive and in general well tolerated, it should be a key consideration in older subjects at particular risk for Mg deficiency. Although existing data confirm that the availability of an adequate quantity of Mg is a critical factor for normal cellular and body homeostasis, much remains to be done in this field to further clarify the potential role of Mg supplementation.

Even if the role of Mg supplementation as a possible intervention approach for delaying or preventing muscle aging deserves some consideration, a number of questions still need to be answered. What is the role of oxidative stress and inflammatory cytokines in mediating the adverse effect of Mg deficiency on muscle? Is low Mg a component of the frailty syndrome leading to sarcopenia of aging? Can Mg supplementation influence muscle strength/performance and cytokine concentrations in older persons? The possible role of Mg supplementation in aging-associated conditions remains unclear. At present, there are no data to support a potential role of dietary Mg supplementation as a possible health strategy in the aging population. Very few open and double-blind studies on the effects of the treatment of Mg deficiencies in geriatric populations have been done. The possibility that maintaining an optimal Mg balance throughout life might help in preventing or significantly retarding the oxidative stress and inflammation process, and the manifestations of chronic diseases, including sarcopenia and frailty, is a working hypothesis that needs to be tested in future prospective studies.

SUMMARY POINTS

- Mg is a key intracellular cation because it is an essential cofactor in a wide variety of biologic processes, including protein synthesis, nucleic acid synthesis and stability, neuromuscular excitability and conduction of neural impulses, stimulus–contraction coupling, and muscle contraction; it is also an antioxidant.

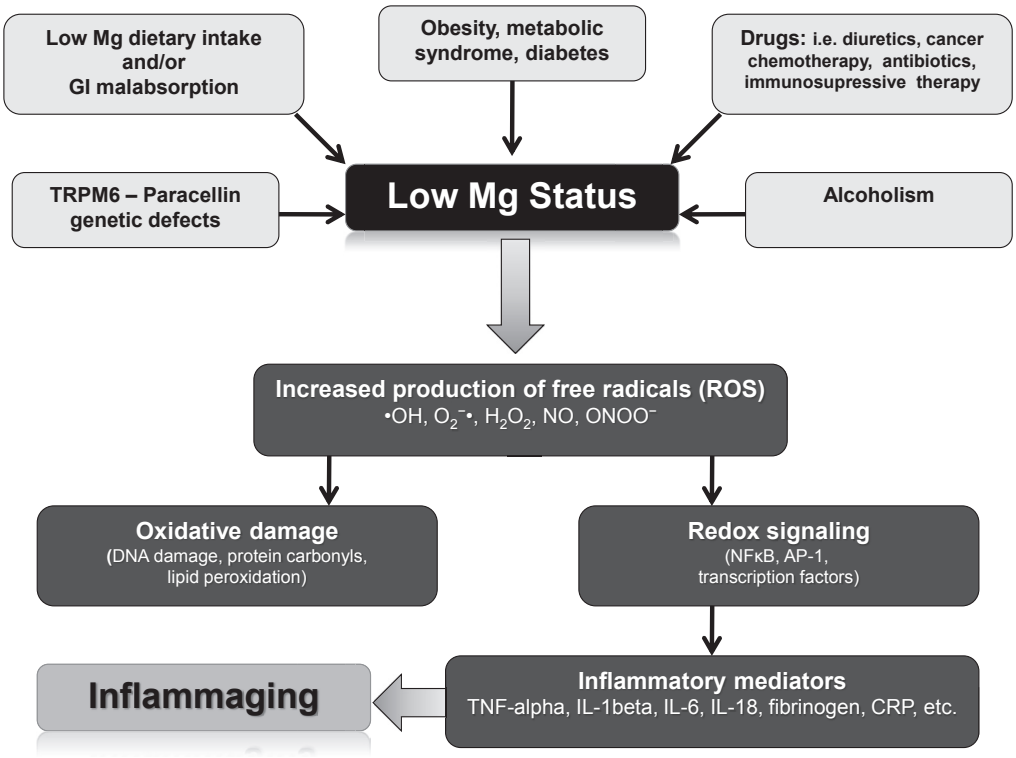

FIGURE 16.3 Low Mg status has different determinants that may converge in old age. Because Mg reduces the production of free radicals by the mitochondria as an antioxidant, its deficit may lead to the accumulation of oxidative damage and the release of inflammatory mediators. These events have been identified as 'inflammaging', that is, the low-grade chronic inflammation frequently seen in old age, which is associated with age-related conditions.

- Aging is frequently associated with a Mg deficit due to dietary reduced intake and/or absorption, increased renal wasting and/or reduced tubular reabsorption, age-related diseases, and/or drugs, leading to increased oxidative stress and chronic inflammation.
- Magnesium status affects muscle performance, probably due to the key role of magnesium in energetic metabolism, transmembrane transport, and muscle contraction and relaxation. Magnesium is integral to the function of ATP.
- Aging is associated with sarcopenia, defined as the loss of skeletal muscle mass, quality, and function. Sarcopenia of aging is a strong independent risk factor for disability and mortality.
- Oxidative stress and chronic, low-grade inflammation have been proposed as an underlying condition linked to aging muscle, sarcopeni, and frailty.
- Magnesium acts as an antioxidant against free radical damage of the mitochondria. Chronic Mg deficiency results in excessive production of oxygen-derived free radicals and low-grade inflammation.

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