Magnesium and Aging

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Abstract: Over the past decades, the clinical relevance and biological significance of magnesium (Mg) have been documented. Deficiency in Mg, aside from having a negative impact on the energy production pathway required by mitochondria to generate ATP, also reduces the threshold antioxidant capacity of the aging organism and its resistance to free-radical damage. Mg also acts as an antioxidant against free radical damage of the mitochondria. Chronic inflammation and oxidative stress have both been identified as pathogenic factors in aging and in several age-related diseases. Chronic Mg deficiency results in excessive production of oxygen-derived free radicals and low grade inflammation. Aging is very often associated with Mg inadequacy and with increased incidence of many chronic diseases, muscle loss and sarcopenia, altered immune responses, and vascular and metabolic conditions, such as atherosclerosis, diabetes and the cardiometabolic syndrome.

The most common cause of Mg deficit in the elderly population is dietary Mg deficiency, although secondary Mg deficit in aging may also results from many different mechanisms.

The aim of the present manuscript is to discuss the mechanisms and consequences of the modifications of Mg metabolism with age, the difficulties in the measurement of Mg status, and to review the current evidences suggesting that age-related chronic Mg deficits may be proposed as one of the physiopathological links that may help to explain the interactions between inflammation, and oxidative stress with the aging process and many age-related diseases.

Keywords: Magnesium, aging, Mg deficiency, anti-aging, oxidative stress, chronic inflammation, diabetes, hypertension.

INTRODUCTION

Mg ion plays essential roles in the structure and function of the human body, being the most abundant intracellular cation after potassium and a cofactor for many biological processes, such as protein synthesis, nucleic acid synthesis and stability, and neuromuscular excitability [1]. Through its role in other ions transport systems, Mg affects the conduction of neural impulses, muscle contraction, and normal heart rhythm. Mg is necessary for adenosine triphosphate (ATP) synthesis in mitochondria and exist primarily as a complex with Mg (MgATP). Cell signaling requires MgATP for the phosphorylation of proteins and the synthesis and activation of cell-signaling molecule cyclic adenosine monophosphate (cAMP) involved in many biochemical processes [2,3].

The intracellular abundance of Mg is consistent with its crucial role in regulating a wide variety of fundamental cellular activities and metabolic pathways. Mg is implicated in this pleiomorphic activity because of its role as part of the activated MgATP complex and as necessary cofactor in over 300 enzymatic reactions. Mg is required for the activity of all rate-limiting glycolytic enzymes, protein kinases, and more generally, in all phosphorylation process and in all reactions that involve ATP utilization and transfer. Mg may also bind the enzymes directly (i.e. RNA and DNA polymerases) and alter their structure [1-3]. In particular Mg role ranges from the regulation of enzyme functions (glycolitic enzymes, kinases, ATP'ases etc), all the energy-requiring metabolic processes, being a co-factor for ATP'ases (esp. Na-K ATP'ase; Ca ATP'ase), membrane and channel functions (ion channel translocation and transmembrane ion fluxes, i.e regulation of intracellular concentrations of K and Ca, Ca-channels gating, hormone-receptor binding and signal transduction, stimulus-contraction coupling), calcium antagonist action (muscle-contraction- and relaxation, neurotransmitter release), and structural functions (multienzyme complexes, i.e., G-proteins, N-methyl-D-aspartic acid [NMDA] receptors, mitochondria, polyribosomes, proteins and nucleic acids synthesis, etc.).

For the above mentioned reasons, availability of adequate quantity of Mg is critical for normal cellular and body homeostasis. The role of Mg in the regulation of cellular glucose metabolism, insulin action and sensitivity, as well as in the modulation of vascular smooth muscle tone, and blood pressure homeostasis is well established.

Mg Metabolism

The adult human body contains approximately 24 g (1 mol) of Mg of which about 65% resides in the mineral phase of bone, 34% in the intracellular space. Extracellular Mg accounts for only ~1% 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 it is tightly controlled and maintained within this range [4,5]. In the serum Mg exists in 3 forms: a protein-bound fraction (25% bound to albumin and 8% bound to globulins), a chelated fraction (12%), and the metabolically active ionized fraction (Mg-ion: 55%) [3]. Mg is the fourth most abundant cation in the body (after Na^+, K^+ and Ca^{++}), and the second most abundant cation in the intracellular compartment (after K^+). Mg status in the body is mainly determined by the Mg intake, by its absorption through the gastrointestinal tract, by the renal excretion, and by the requirement of different tissues (i.e. skeletal and cardiac muscle uptake and usage). 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. Although bone is the main storage location of Mg, it cannot quickly exchange with Mg in extracellular fluids, and more prompt requirement of Mg are satisfied from the Mg stored in the intracellular compartment. Renal Mg handling is tightly dependent on Mg body status, since Mg deficiency increases renal Mg reabsorption across all nephron segments [6]. Diuretics, frequently used in the older populations, may also modify renal Mg handling, reducing Mg reabsorption [7,8]. Although no known hormonal factor is specifically involved in the regulation of Mg metabolism, many hormones are recognized to have an effect on Mg balance and

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transport. Among them, parathyroid hormone (PTH), calcitonin, catecholamines and insulin have a major role [1].

Cellular Mg Transport System

The past few years have seen significant progress in the molecular and functional characterization of a family of genes encoding the "Melastatin-related Transient Receptor Potential" (TRPM) cation channels. The TRP superfamily is a newly discovered family of protein that contains both a cation-permeable ion channel and a kinase domain [9-13]. The protein is ubiquitously expressed and represents the only ion channel known that is essential for cellular viability. TRPM7 is a divalent cation-selective ion channel that is permeable to Ca^{2+} and Mg^{2+}. The channel is constitutively open but strongly downregulated by intracellular levels of Mg^{2+} and MgATP and other Mg-nucleotides.

This subgroup of the TRP superfamily consists of eight mammalian members, but isoforms are found in the genomes of practically all eukaryotic organisms. Recently a novel ion channel of this family, TRPM7 was found to conduct significant amounts of trace metals and Mg into cells. TRPM7 is a ubiquitously expressed protein combining a channel and a kinase domain (channel kinase). The function of the kinase domain is not completely understood, but may involve autophosphorylation of TRPM7 as well as phosphorylation of other target proteins such as annexin and myosin IIA heavy chain. The channel plays a key role in Mg homeostasis due to its unprecedented permeation preference for divalent ions. TRPM7 is highly conserved across species, emphasizing its critical role in cellular trace metal and Mg physiology [11,13]. TRPM7 is currently believed to represent a ubiquitous homeostatic mechanism that regulates Ca^{2+} and Mg^{2+} fluxes based on the metabolic state of the cell. Physiologically, the channel may serve as a regulated transport mechanism for these ions that could affect cell adhesion, cell growth and proliferation, and even cell death under pathological stress such as anoxia. Reducing the cellular levels of these regulators leads to activation of TRPM7-mediated currents that exhibit a characteristic nonlinear current-voltage relationship with pronounced outward rectification due to divalent influx at physiologically negative voltages and monovalent outward fluxes at positive voltages [13].

Magnesium has the largest hydrated radius among all cations, whereas its ionic radius is the smallest. It remains obscure how Mg transporters selectively recognize and dehydrate the large, fully hydrated Mg cation for transport [11].

Mg Measurements Methods

One of the main reasons why Mg metabolism has not become more the focus of routine attention in the clinical practice has been the difficulties in obtaining an easily available, accurate, and reproducible measurement of Mg status. The levels of Mg in the plasma of healthy people are extremely constant, with a reference interval for total serum levels of 0.75-0.96 mmol/L, and a mean of 0.85 mmol/L. Total serum Mg concentrations (MgT) not always reflect accurately the body Mg status Fig. (**1**); MgT has proved useful and it has been extensively utilized in epidemiological studies, but it may not be helpful for the detection of subclinical Mg deficit in an individual basis.

More precise and expensive techniques, such as ^{31}P-NMR spectroscopy, remain mainly a research tool. The development of Mg-specific ion-selective electrodes, measuring the metabolically active ionized fraction of Mg, has been particularly useful, allowing measuring extracellular free levels of Mg (Mg-i), with a higher sensitivity than MgT in detecting subclinical Mg deficits in several medical conditions [1,14].

Mg and Inflammation

Hypomagnesemia has been associated with inflammation and increased production of free oxygen radicals. Poor magnesium status may trigger the development of a proinflammatory state both by causing excessive production and release of interleukin (IL)-1β and tumor necrosis factor (TNF)-α, and by elevating circulating concentrations of proinflammatory neuropeptides that trigger activation of low-grade chronic inflammation [15,16]. *In vitro*, low levels of Mg increase platelet aggregability and adhesiveness [17]. Mg deficiency inhibits endothelial growth and migration and stimulates the synthesis of nitric oxide and some inflammatory markers, thus directly modulating microvascular functions [18,19]. 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 [20].

In animals, several studies have shown that Mg deprivation causes marked elevation of proinflammatory molecules TNF-α, IL-

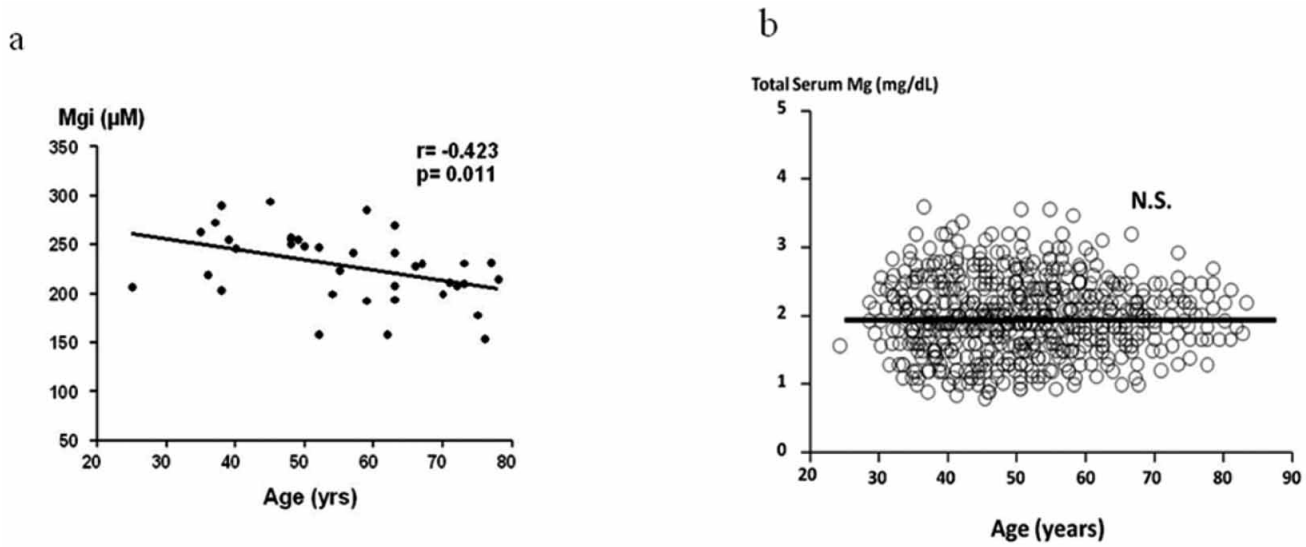

Fig. (1). Relationship of intracellular free Mg (Mgi) (panel a, from Ref. 21, with permission) and total serum Mg (panel b) with aging.

1β, IL-6, vascular cell adhesion molecule (VCAM)-1, and plasminogen activator inhibitor (PAI) 1 [16,18,21-23], increased circulating inflammatory cells [23], and increased hepatic production and release of acute phase proteins (i.e. complement, α2-macroblobulin, fibrinogen) [24]. A direct mechanistic link has been made available for the association of low Mg and increased production and secretion of TNF-α and IL-1β in cultured alveolar macrophages [25]. In humans, clinical data have shown that low serum Mg levels as well as inadequate dietary Mg are strongly related to low-grade systemic inflammation [26,27,28]. Data from the Women's Health Study, have shown that Mg intake is inversely related to systemic inflammation, measured by serum C-reactive protein (CRP) concentrations, and with the prevalence of the metabolic syndrome in adult women [28]. Using the 1999–2002 NHANES database, King *et al.* found that dietary magnesium intake was inversely related to CRP levels. Among the 70% of the population not taking supplements, magnesium intake below the RDA was significantly associated with a higher risk of having elevated CRP [26]. In diabetic men, higher Mg intake was associated with higher adiponectin levels [29]. Several other studies have confirmed an inverse relationship among Mg intake, serum Mg and TNF-α, IL-6, and CRP levels in children and adults [30-32]. In a cross-sectional study, a higher TNF-α concentration was inversely correlated with serum Mg and in a multi-variate analysis, those with the lowest serum Mg were 80% more likely to have higher circulating levels of TNF-α [32].

Mg and Oxidative Stress

In both, experimental animal models and in humans, Mg deficiency has been associated with increased oxidative stress and decreased antioxidant defense due, at least in part, to increased inflammation parameters [22,33,34]. Previous studies have shown convincingly that Mg deficiency results in increased production of oxygen-derived free radicals in various tissues, increased freeradical-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 [20,35-37]. There is also data suggesting that Mg, when present in sufficient amounts, prevents oxygen radical formation by scavenging free radicals and by inhibiting xanthine oxidase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [38]. Furthermore, it has been shown that Mg deficiency in rats causes decreased hepatic glutathione, superoxide dismutase (SOD), and vitamin E along with increased lipid peroxidation and malondialdehyde (MDA) levels secondary to upregulated NADPH oxidase acitivity [39]. Several intervention studies in animal models of Mg deficiency have provided convincing evidence of the link between Mg, inflammation, and oxidative stress. In stroke-prone spontaneously hypertensive rats, Mg deficiency results in marked increases in systolic blood pressure, blunted endothelial function, superoxide accumulation, and mitogen-activated protein kinase (MAPK) activation, all of which were attenuated with a SOD mimetic [40]. In experimental diabetes, a decreased intracellular Mg level and increased Mg urinary excretion were associated with an increased plasma MDA, a decreased expression of hepatic SOD and of glutathione S-transferase, with all these effects being corrected by Mg supplementation [36]. In a small case-control study, hypomagnesemia was positively associated with increased serum MDA levels and with CRP [31]. Interventional studies have shown that treatment with antioxidant therapies (vitamin C, E, and glutathione) may improve insulin sensitivity in diabetic subjects [41-43]. Some of these studies imply that improvement in endogenous antioxidant capacity (GSH:GSSG ratio) and blunting of oxidative stress (decreased GSH:GSSG, increased lipohydroperoxides, increased TBARS, and decreased total antioxidant capacity), are associated with improved whole body glucose disposal, which involves cellular Mg homeostasis [41-43]. Altogether, data are consistent with a role of Mg deficiency in reducing antioxidant capacity and in promoting oxidative stress, inflammation, and lipid oxidation, hence, promoting insulin resistance, pancreatic β-cell dysfunction, vascular remodeling, atherosclerosis, diabetes and cardio-metabolic syndrome [1,44].

Mg and Immune Responses

There is evidence that magnesium may plays a role in the immune response as a co-factor for immunoglobulin (Ig) synthesis, C'3 convertase, 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 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 an 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, splenomegalia and leukocytosis have been reported as well in rats given an Mg-deficient diet. A reduced proportion of CD8-T cells has been shown under these conditions, which has been related to a decreased interferon (IFN)-γ concentration in spleen homogenates [49]. Several changes in gene expression, including up-regulation of TNF receptor 1 and IL-1 receptor type I, have also been demonstrated in rat thymocytes in early Mg deficiency [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 is 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].

MG AND AGE RELATED PROBLEMS

Mechanisms of Mg Deficiency with Aging

Aging represents a major risk factor for Mg deficit. Conflicting data exist regarding levels of Mg in the blood and Mg status in the elderly [35,53-61]. Total plasma magnesium concentrations do not differ with age [55]. Differences may depend mainly on the heterogeneity of the mechanisms inducing magnesium deficits and on the age-related diseases and alterations in renal function. Studies using 24-hour Mg retention have revealed an increased Mg retention in the elderly, suggesting a significant subclinical Mg deficit, not detected by total serum Mg [59]. In healthy subjects both lymphocyte and intracellular free Mg have been found to decrease with age [60,61]. We have specifically studied the behavior of intracellular Mg content with age, using the gold standard method (^{31}P-NMR spectroscopy) in peripheral red blood cells in healthy young and elderly subjects and have shown a continuous age-dependent fall of intracellular Mg levels in healthy elderly subjects [61], while total serum Mg is not significantly altered with age Fig. (**1**).

Recent studies have suggested a primary role for a decreased intake of Mg in the age-related Mg deficit. Epidemiological data have shown that inadequate Mg intake is common in older persons [62-67]. The typical Western diet, high in processed foods and very low in whole grains and green vegetables, is often severely Mg deficient. Although it has been shown that Mg requirement do not change with age [67], dietary Mg deficiency in the elderly is more prevalent than generally suspected. Data from the National Health and Nutrition Examination Survey (NHANES) III found that Mg

daily intake decreases with age, independently of sex and race [62] and that older adults, affected by chronic conditions and on chronic drug treatment, are less likely than younger adults to consume enough Mg to meet their needs. Analyses from the same NHANES III survey have shown Mg intake in the older US population is well below the recommended minimal quantity (average of 225 and 166 mg/day vs. recommended 420 and 320 mg/day for men and women, respectively) [62]. Among US adults, 68% consume less than the recommended daily allowance (RDA) of Mg, 45% consume less than 75% of the RDA, and 19% consume less than 50% of the RDA [26]. In Europe the "Suppléments en Vitamines et Minéraux AntioXydants" (SU.VI.MAX) study showed that 77% of women and 72% of men have dietary Mg intakes lower than RDA; 23% of women and 18% of men consumed less than 2/3 of these RDA [63].

In addition to inadequate nutrient intakes, Mg deficit in the elderly may be related to a decreased Mg absorption and/or increased urinary Mg loss, or multiple drug use. The efficiency of Mg absorption declines with age. Mg absorption appears to be greatest within the duodenum and ileum and occurs by both passive and active processes. A reduction of the absorption of Mg from the intestines in the elderly may be influenced by the alterations of vitamin D metabolism with age. Renal active reabsorption of Mg takes place in the loop of Henle, in the proximal convoluted tubule, and is influenced by both the urinary concentration of sodium, and urinary pH. An increased Mg loss linked to a reduced tubular reabsorption is a likely condition in the elderly with a latent primary renal disorder. Drug use or pathological conditions associated to aging may as well contribute to Mg deficit. Secondary Mg deficiency are associated with a variety of pathologies (i.e. type 2 diabetes mellitus, hyperadrenoglucocorticism, insulin resistance, alcoholism, HIV/AIDS, acute myocardial infarction, stroke, etc.) and therapies (i.e. long-term treatment with loop diuretics, digitalis, cardiopulmonary bypass) [35,53-55].

Mg and Age-Related Sarcopenia

Older age is frequently characterized by sarcopenia, loss of skeletal muscle mass and function [68], a strong independent risk factor for disability and mortality [69,70]. Mg depletion may cause muscle cells structural damage through increased oxidative stress and impaired intracellular calcium homeostasis [71]. Previous studies conducted in young volunteers found that Mg status strongly affects muscle performance, probably due to Mg's key role in energetic metabolism, transmembrane transport and muscle contraction and relaxation [1]. Mg supplementation (up to 8 mg/kg daily) enhanced muscle strength in young untrained individuals [72]. Similarly, physically active young subjects experienced improved endurance performance and decreased oxygen use during sub-maximal exercise after Mg supplementation [73]. 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, which was consistent across several muscle parameters for both men and women [74], this data being consistent: a) with the relation of Mg status to muscle ATP and the role of Mg in energetic metabolism; b) the increased reactive oxygen species (ROS) production in Mg deficiency; and, c) the proinflammatory effect of Mg depletion.

Mg and Vascular and Metabolic Age-Related Diseases

Although it is not known to what extent Mg depletion and/or suboptimal intakes may affect the aging process, increased inflammation and oxygen free radical production associated with Mg depletion may contribute to the pathophysiology of aging and of several human diseases [1,35].

Chronic Mg deficits have been linked to an increased risk of numerous preclinical and clinical outcomes, mostly observed in the elderly population, including hypertension, stroke, atherosclerosis, ischemic heart disease, cardiac arrhythmias, glucose intolerance, insulin resistance, type 2 diabetes mellitus, endothelial dysfunction, vascular remodeling, alterations in lipid metabolism, platelet aggregation/thrombosis, inflammation, oxidative stress, cardiovascular mortality, asthma, chronic fatigue, as well as depression and others neuropsychiatric disorders [75-82].

Old age is frequently associated with insulin resistance, glucose intolerance and type 2 diabetes mellitus [1,60]. Hypomagnesaemia has been associated with an increased risk to develop glucose intolerance and diabetes [83]. It has been suggested that intracellular Mg depletion may contribute to insulin resistance in the peripheral tissues and may lead to the glucose intolerance in otherwise healthy aged persons [84,85]. The hypothesis that alterations of Mg metabolism would induce and/or exacerbate insulin resistance is confirmed by data, in both humans and experimental animals, showing that dietary-induced Mg deficiency is correlated with insulin resistance [82,86-89].

Inflammation and oxidative stress have been proposed to be the link between Mg deficit and insulin resistance/metabolic syndrome [30-32]. More generally, chronic hypomagnesaemia and conditions commonly associated with Mg deficiency, such as type 2 diabetes mellitus and aging, are all associated with an increase in free radical formation with subsequent damage to cellular processes [1,35,85]. Furthermore, Mg may itself possess antioxidant properties, scavenging oxygen radicals, possibly by affecting the rate of spontaneous dismutation of the superoxide ion [90]. Increased substance P and TNF-α in bone from Mg-deficient rats provide a possible explanation for the increased osteoclastic bone resorption accompanying Mg depletion, supporting the hypothesis that dietary Mg deprivation is a risk factor for osteoporosis [91].

Mg and the Aging Process

The consequences of Mg imbalance in elderly people related to defective membrane function, inflammation, increased oxidative stress and immune dysfunction may include not only an increased vulnerability to age-related diseases and particularly to cardiovascular diseases and diabetes, but may also contribute to the aging process itself. In cellular systems, Mg, at physiologically relevant concentrations, is highly required to maintain genomic stability. Mg has stabilizing effect on DNA and chromatin structure, and is an essential cofactor in almost all enzymatic systems involved in DNA processing [92]. Magnesium is an essential cofactor in cell proliferation and differentiation and in all steps of nucleotide excision repair and is involved in base excision repair and mismatch repair [92-95]. DNA is continuously damaged by environmental mutagens and by endogenous processes. Mg is required for the removal of DNA damage generated by environmental mutagens, endogenous processes, and DNA replication [51,92-94].

Levels of free intracellular Mg increase in cells undergoing apoptosis. This increase is an early event in apoptosis, preceding DNA fragmentation and externalization of phosphatidylserine, and is likely due to a mobilization of Mg from mitochondria. A raise in intracellular free Mg appears to serve as a "second messenger" for downstream events in apoptosis [51].

There is increasing evidence from animal experiments and epidemiological studies, that Mg deficiency may decrease membrane integrity and membrane function, increasing the susceptibility to oxidative stress, cardiovascular heart diseases, as well as accelerated aging.

Several studies have reported alterations in cell physiology with senescence features during Mg deficiency in different cell types. Mg related alterations may include reduced oxidative stress defense, cell cycle progression, culture growth, and cellular viability [18,37,95-97] and activation of the expression of proto-oncogene (*e.g., c*-fos, *c*-jun) and of transcription factors (*e.g.,* NF-κB) [98]. Recent data have shown that Mg deficiency may accele-

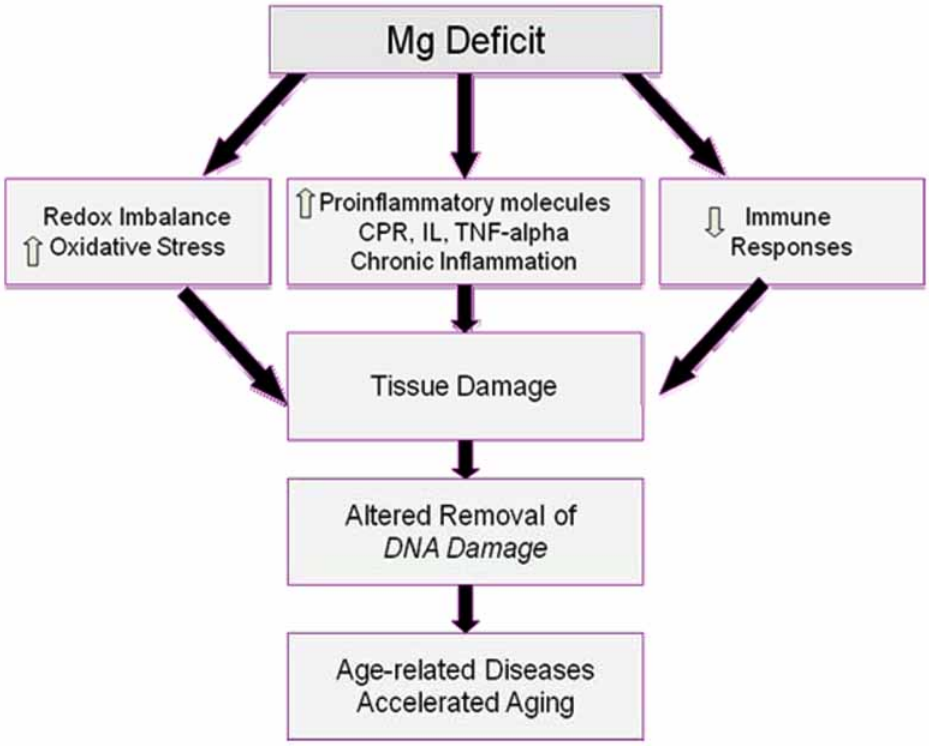

Fig. (2). Overall hypothesis in which chronic Mg deficits has been proposed as one of the physiopathological links that may help to explain the interactions among inflammation, oxidative stress, altered immune responses with the aging process and age-related diseases.

rate cellular senescence in cultured human fibroblasts [99]. Continuous culture of primary fibroblasts in magnesium-deficient media resulted in a 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 also accelerated in cell populations from Mg-deficient cultures, suggesting that the long-term consequence of inadequate Mg availability in human fibroblast cultures was accelerated cellular senescence [99].

CONCLUSIONS

Aging is very often associated with Mg inadequacy and with increased incidence of many chronic diseases. Chronic Mg deficiency may result in excessive production of oxygen-derived free radicals and inflammation and has been associated to an increased incidence of diverse chronic diseases associated to aging, such as atherosclerosis, vascular diseases, type 2 diabetes and cardiometabolic syndrome. A chronic, low-grade inflammation and oxidative stress have been proposed as an underlying condition present in many age-related diseases, and to be involved in the aging process itself. Previously reported findings showing a relationship between Mg and inflammation may suggest a role of Mg in the aging process. Hence, chronic Mg deficits has been proposed as one of the physiopathological links that may help to explain the interactions between inflammation, oxidative stress with the aging process and many age-related diseases Fig. (**2**).

A working hypothesis is that maintaining an optimal Mg balance throughout life might help in preventing or significantly retarding the manifestations of some aging-related diseases. This need to be proven by prospective studies. Much remains to be done on this field to further clarify these aspects. In particular, 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. Prospective studies are needed to assess the true place of Mg deficit in the pathophysiology of aging and to examine whether Mg supplementation can reduce inflammation and the risk of chronic disease related to aging.

ABBREVIATIONS

ATP	=	Adenosine Triphosphate
Ca	=	Calcium
cAMP	=	cyclic Adenosine Monophosphate
CRP	=	c-Reactive Protein
GSH	=	Reduced Glutathione
GSSG	=	Oxidized Glutathione
Ig	=	Immunoglobulin
IFN	=	Interferon
IL	=	Interleukin
InCHIANTI	=	“Invecchiare in Chianti” (Aging in Chianti)
K	=	Potassium
MAPK	=	Mitogen-Activated Protein Kinase
MDA	=	Malondialdehyde
Mg	=	Magnesium
Mg-i	=	extracellular free levels of Magnesium
MgT	=	Total serum Magnesium concentrations
Na	=	Sodium
NADPH	=	Nicotinamide Adenine Dinucleotide Phosphate

NHANES	=	National Health and Nutrition Examination Survey
NMDA	=	N-methyl-D-aspartic acid
NMR	=	Nuclear Magnetic Resonance
P	=	Phosphate
PAI	=	Plasminogen Activator Inhibitor
PMN	=	Polymorphonuclear
RDA	=	Recommended Daily allowance
ROS	=	Reactive Oxygen Species
SOD	=	Superoxide Dismutase
SUVIMAX	=	Suppléments en Vitamines et Minéraux AntioXydants
TBARS	=	Thiobarbituric Acid Reactive Substances
TNF	=	Tumor Necrosis Factor
TRPM	=	Melastatin-related Transient Receptor Potential
VCAM	=	Vascular Cell Adhesion Molecule

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