The central role of magnesium in skeletal muscle: from myogenesis to performance

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Abstract. A physiological concentration of magnesium (Mg) is essential for optimal skeletal muscle function. Indeed, Mg plays a crucial role during the differentiation process (myogenesis), in muscle fiber composition, muscle contraction and performance. This narrative review describes in detail the relevance of Mg in skeletal muscle, highlighting the importance of adequate Mg intake to ensure optimal skeletal muscle cell function and performance in individuals of all ages.

Key words: magnesium, skeletal muscle, myogenesis, muscle fibers, muscle contraction, muscle performance.

Skeletal muscle, comprising approximately 45-50% of body mass, constitutes a complex and heterogeneous organ with central roles in providing support and generating locomotion through the coordinated movement of the skeleton [1, 2]. The structure of the skeletal muscle is organized through three layers of connective tissue: the epimysium is the outer layer that covers the entire muscle; the middle layer is the perimysium which wraps the fascicles; the endomysium wraps the muscle fibers inside the fascicles. The presence of blood vessels in skeletal muscle ensures nutrients and oxygen supply and waste removal. The motoneuron that innervates the muscle transmits the nervous stimulus, initiating muscle contraction.

In the last years, many evidences demonstrated the critical role of magnesium (Mg) in skeletal muscle. Mg is an essential element of life, the fourth most abundant mineral in the body [3]. More than half of the body's Mg is located in bones, while about ¼ is in the skeletal muscles. Mg is essential for all living cells since it is involved in all the cellular processes [3]. It is required for DNA replication, transcription, translation and ribosomal stabilization. Mg is required for the activity of ATP, forming a complex that renders ATP biologically active. Indeed, upon the binding of Mg^{2+} to ATP, ATP adopts a conformation in which the terminal O-P bond is weakened, thereby facilitating phosphate (P) transfer [4]. Thus, Mg plays a key role in all cellular energy mechanisms and is also crucial for the phosphorylation and activation of proteins in various signalling pathways. Most of intracellular Mg is bound to ATP, proteins and negatively charged molecules. As a cofactor in more than 600 enzymatic reactions and an activator of additional 200 enzymes, Mg is involved in all metabolic pathways.

Mg is assumed with the diet and, in particular, is mainly contained in water, dark green leafy

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vegetables, legumes, nuts, seeds, and unrefined grains. The Recommended Dietary Allowance for adults is 400-420 mg daily for men and 310-320 mg for women [5]. The reduction of Mg levels in soils and in processed food often causes a suboptimal Mg intake, increasing the risk of developing a chronic Mg deficiency condition. In addition to a long-term low Mg diet, also malabsorption, alcohol abuse, renal dysfunction, diabetes or the use of some medications (some diuretics, proton pump inhibitors, and antibiotics) can induce a severe Mg depletion. Importantly, since the mineral is mainly stored in bones and muscles, the blood level of Mg may not accurately predict total Mg levels in the body and therefore a condition of Mg deficiency is often undetected.

In this review we discuss the physiological role of Mg in the muscle. We start with the importance of Mg during myogenesis, i.e. the formation of skeletal muscle, to proceed with the role of Mg in muscle fiber composition, and in muscle contraction. We conclude with the importance of Mg on muscle performance (*figure 1*).

Magnesium and myogenesis

The muscle fibers, or myofibers, are multinucleated cells that arise from somites, transient structures derived from the paraxial mesoderm

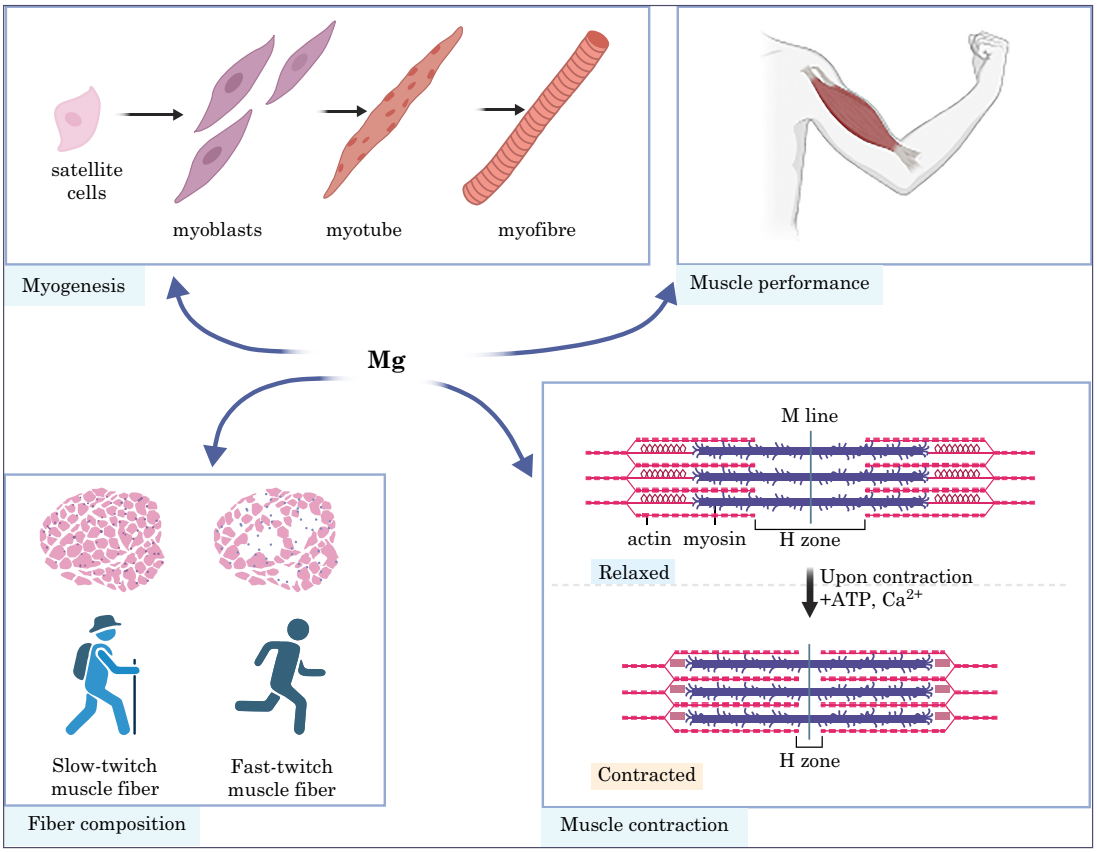

Figure 1. Mg plays a crucial role in myogenesis, muscle fibre composition, muscle contraction and muscle performance. Image created with BioRender.com.

[6]. During the early embryonic phase, primary myofibers are generated from Pax3+ progenitors, providing a scaffold for the secondary fibers. During the late fetal phase, a subset of myogenic progenitors, characterized by the downregulation of Pax3 and expression of Pax7, undergo proliferation, fusion with one another or with primary myofibers, thus generating secondary fibers and contributing to fetal muscle growth.
During this phase, some Pax7+ progenitors give rise to the satellite cell precursors which localize under the basal lamina and become quiescent within 2 month after birth. Satellite cells guarantee tissue renewal and repair of adult muscle. To maintain muscle homeostasis or in response to an injury, satellite cells activate and proliferate becoming myoblasts. During the differentiation process, a sequential and coordinated expression of myogenic regulatory factors (MRFs) occurs. MyoD and Myf5 commit the cells to the myogenic program, while myogenin (Myog) and MRF4 are responsible for the terminal stages of differentiation [7]. Ultimately, differentiated myoblasts fuse with one other to form multinucleated myotubes (*figure 2*).
Mg is involved in myogenesis. In C2C12 murine myoblasts, intracellular Mg concentration fluctuates throughout the differentiation process. Mg decreases in the early phases of myogenesis, then returning to basal levels once the cells are differentiated. These fluctuations in Mg concentrations parallel the modulation of some Mg transporters/channels. The Transient Receptor Potential Cation Channel Subfamily M Member 7 (TRPM7) and the Magnesium Transporter 1 (MagT1) are downregulated during myogenesis. However, while MagT1 expression is restored at the end of the differentiation process, TRPM7 remains down-modulated in myotubes. The expression of Solute Carrier family 41 member A1 (SLC41A1) remains unchanged during differentiation and increases once the cells

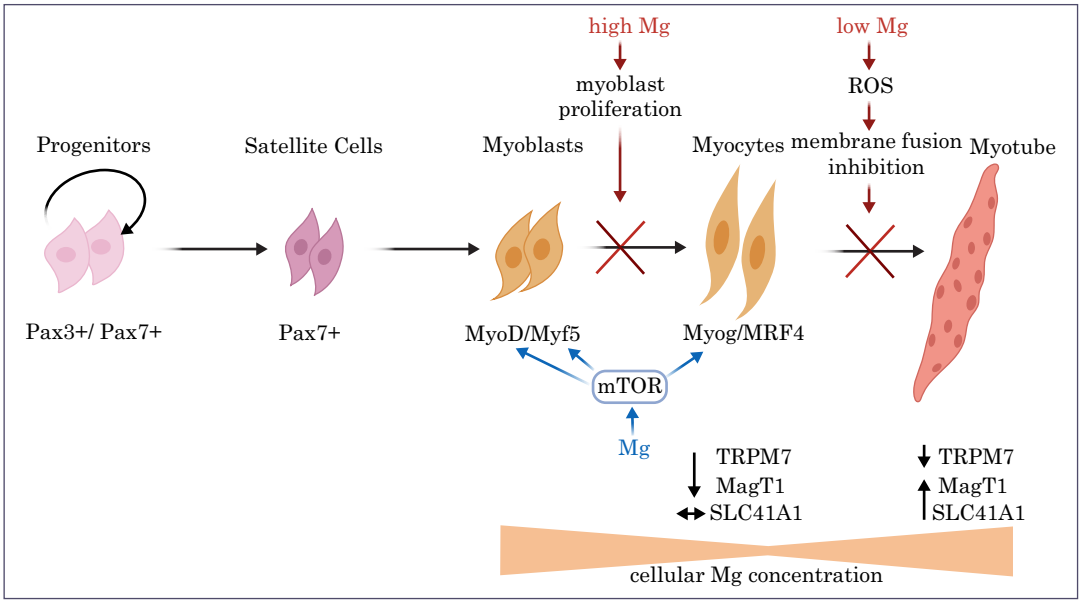

Figure 2. The importance of Mg during myogenesis. An adequate extracellular concentration of Mg is essential to ensure proper differentiation. Mg induces the activation of mTOR, which in turn activates key myogenic genes. During myogenesis the intracellular concentration of Mg fluctuates due to the time-dependent expression of some Mg transporters/channels. Image created with BioRender.com.

have completed differentiation [8] (*figure 2*). Using C2C12 cells as in vitro model, it has been demonstrated that an appropriate extracellular Mg concentration is critical for ensuring proper myogenesis [9, 10], and non-physiological Mg concentrations induce oxidative stress. The increase of reactive oxygen species inhibits the fusion of myoblast membranes, thus impairing myotube formation [9]. Furthermore, high Mg^{2+} concentrations (between 4–10 mM) accelerate cell proliferation, thereby inhibiting differentiation [11] (*figure 2*). Since the availability of Ca^{2+} ions is crucial for myotube formation, maintaining a correct Ca/Mg ratio is fundamental to guarantee a proper muscle regeneration. A high Ca/Mg ratio results in the formation of large myotubes, while a low Ca/Mg ratio results in small myotubes [11].

In experiments on C57BL/6J mice, Mg supplementation promotes muscle regeneration in aged mice through the activation of the AMPK/mTOR signalling pathway [10]. Activation of mTOR has been shown to stimulate the key myogenic genes, such as Myf5, Myod, Myog (*figure 2*). In a senescence-accelerated mouse prone (SAMP) model, where a sarcopenic phenotype emerges around 10 months of age, Cui and co-authors demonstrated that oral Mg supplementation combined with low-magnitude high-frequency vibration (LMHFV) enhanced muscle regeneration and mitigated atrophy through the PI3K/Akt/mTOR pathway [12]. It is known that a reduction of insulin-like growth factor (IGF-1) occurs in the elderly and is responsible for a decrease of Akt phosphorylation. The reduction of Akt phosphorylation triggers the activation of FOXO3, which in turn up-regulates some atrogens such as MAFbx (muscle atrophy F-box) and MuRF1 (muscle ring-finger protein 1) [13]. Mg, by counteracting the decrease of Akt phosphorylation, could play a central role in suppressing atrophy. Two-month old C57BL/6J mice fed a mild Mg-deficient diet showed a significant decline in body weight gain. Although no differences in gastrocnemius muscle weight were detected compared to mice fed a Mg-sufficient diet, the down-regulation of genes involved in muscle regeneration, i.e. Myog, Mef2c (myocyte enhancer factor 2C), Mstn (myostatin), and its receptors (Acvr2a and Acvr2b) was demonstrated [14]. Moreover, a study conducted on two-month-old Sprague-Dawley rats revealed that a Mg-deficient diet (1.5 mg/100 g) induces oxidative stress leading to a weight reduction of the gastrocnemius muscle, although Myod and Myogenin were found upregulated [15].

Magnesium and the fiber composition

Myofibers consist of thousands of myofibrils, long filaments that run parallel to each other and are composed of two types of filaments: thin filaments and thick filaments. The overlapping parallel arrays of thin and thick filaments form the sarcomere, which represents the basic contractile unit and repeats along the myofibers. The length of the thin filaments that do not overlap with the thick filaments constitutes the bright area (I-band) of the sarcomere, while the A-band is the center of the sarcomere and contains both thick and thin filaments.

Thin filaments are composed of two actin chains (F-actin), whose globular monomers (G-actin) contain a myosin binding site. The actin chains are associated with two regulatory proteins, troponin and tropomyosin, which modulate the interaction between actin and myosin. In particular, troponin is a heterotrimeric protein containing three subunits - C, T and I- each with distinct functions [16]. Troponin-C (TnC) binds calcium (Ca^{2+}); troponin-T (TnT) binds tropomyosin and anchors troponin to actin; and troponin-I (TnI) inhibits the adenosine triphosphatase (ATPase) activity of the actomyosin cross-bridge, thereby blocking the myosin-binding site on actin subunits.

The thick filaments are composed of strands of the protein myosin. Myosin is a hexamer constituted by two myosin heavy chains (MHC), two essential light chains, and two regular light chains [17]. The MHC feature a head domain at the N-terminus, which contains the actin and ATP binding sites, and a rod domain that forms a α-helical coiled-coil structure. Three different MHC isoforms can be expressed in skeletal muscles: MHC I, MHC IIa, and MHC IIx. MHC I fibers are slow contracting and contribute to long-term endurance, while MHC IIa and MHC IIx are generally faster and more powerful, respectively, supporting activities requiring rapid force generation [18]. The different muscle fibers exhibit distinct metabolic profiles to meet the energy demand of the tissue. Slow fibers

primarily rely on mitochondrial respiration to produce ATP steadily but continuously, whereas fast fibers predominantly use glycolytic metabolism to rapidly generate ATP, but with limited capacity for rapid ATP replenishment. In particular, MHC IIx fibers use anaerobic metabolism, while MHC IIa fibers are able to generate ATP through both aerobic and anaerobic energy systems.

Mg is necessary to ensure the functionality of the mitochondria. This cation is fundamental for the electron transport chain complex subunits and for ATP synthesis, which, as mentioned above, is active only when associated with Mg [4]. The high levels of Mg contained in mitochondria are important in activating mitochondrial enzymes, such as cytochrome c oxidase, which catalyze the final step of aerobic respiration [19] (*figure 3*). Mitochondrial swelling and altered ultrastructure in muscle were demonstrated in male Wistar rats fed for 12 days a Mg-deficient diet [20]. This underscores the importance of adequate Mg levels for maintaining proper mitochondrial function and overall cellular health.

Mg plays vital roles in various aspects of glucose metabolism and insulin action (*figure 3*). It is required for the activity of key enzymes in glucose metabolism, such as hexokinase, which converts glucose into glucose-6-phosphate [21]. Mg is essential also for the activation of pyruvate

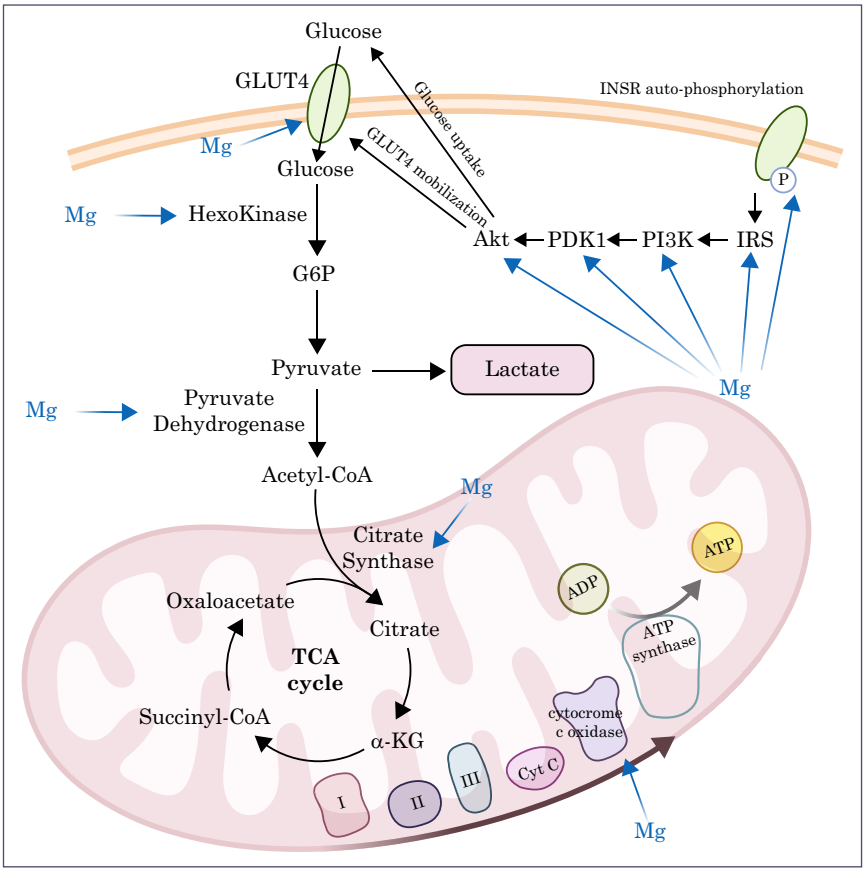

Figure 3. The importance of Mg in muscle cell metabolism. Mg is necessary for the activity of several enzymes involved in metabolic pathways. Refer to the text for details. Image created with BioRender.com.

dehydrogenase [21] a pivotal enzyme in the conversion of pyruvate into acetyl coenzyme A, which is a convergence point between glucose and lipid metabolism. In addition, Mg regulates insulin sensitivity and action, by modulating the PI3K/Akt kinase pathway downstream of the insulin receptor (INSR) [22]. This signalling cascade starts with the auto-phosphorylation of INSR, leading to the activation of insulin receptor substrates (IRS). The subsequent activation of phosphatidylinositol-4,5-bisphosphate-3-kinase (PI3K) activates Akt by 3-phosphoinositide by dependent protein kinase-1 (PDK1). The resulting activation of Akt is involved in the regulation of the metabolic actions of insulin, including glycogen and protein synthesis, lipogenesis and the GLUT4 mobilization to the plasma membrane to enhance glucose uptake. Low-Mg levels impair the tyrosine-kinase activity of the INSR, inhibiting the downstream pathway and decreasing cellular glucose utilization. Accordingly, in two-month old C57BL/6J mice fed a mild Mg-deficient diet the downregulation of the gene encoding the glucose transporter GLUT4, the down-expression of Citrate synthase, which is involved in the first reaction of the Krebs cycle, and alterations in lipid metabolism were demonstrated [14].

Mg also enhances AMP-activated protein kinase (AMPK) activity, which, in turn, has a role in activating the peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α pathway. PGC-1α is a transcriptional coactivator induced by exercise in both mice and human skeletal muscles. Its expression triggers various physiological responses, including mitochondrial biogenesis, shift from fast to slow muscle fiber types, stimulation of fatty acid oxidation, angiogenesis, and resistance to muscle atrophy. Therefore, PGC-1α expression is integral to muscle reprogramming towards muscle endurance [23, 24]. A specific isoform of PGC-1α, known as PGC-1α4, coded by a transcript from the Pgc-1α gene, regulates the IGF1 and myostatin pathways, which are critical regulators of muscle size and strength [24]. A study performed on myotubes obtained from C2C12 murine myoblasts revealed that Mg deficiency induces a phenotypic and metabolic alterations of muscle fibers. Myotubes cultured for 4 days in low Mg conditions exhibited a significant reduction of thickness, increased expression of MHC I vs MHC II, inhibition of glycolysis, and increased beta-oxidation compared to myotubes cultured in physiological Mg [25]. These findings demonstrate that Mg deficiency impacts muscle performance by favouring the slow vs. fast fiber ratio [25]. It is worth to note that a significant atrophy of fast fibers compared to slow fibers is commonly detected in muscles of aged people. Aging is often characterized by Mg deficiency due to either insufficient diet intake or increased urinary Mg excretion caused by reduced kidney function or the use of drugs such as diuretics or proton pump inhibitors. While there is no direct evidence of this correlation, we can speculate that low Mg levels could contribute to accelerate muscle loss.

Magnesium and the contraction mechanism

Skeletal muscle contraction begins with the propagation of an action potential to the neuromuscular junction, which is the synapse between a motoneuron and a muscle fiber. Upon depolarization of the motoneuron membrane, voltage-gated Ca^{2+} channels open, leading to an influx of Ca^{2+}. This influx triggers the release of acetylcholine (ACh) at the neuromuscular junction. ACh then interacts with the nicotinic receptors located on the postsynaptic membrane of the muscle fiber, inducing its depolarization and starting the action potential in the muscle fiber. The action potential propagates along the muscle fiber through the T-tubules, i.e. invaginations of the muscle cell membrane (sarcolemma) within the myofibril. The depolarization of the T-tubules causes a conformational change of their dihydropyridine receptors, leading to the opening of ryanodine receptors (RyRs) on the sarcoplasmic reticulum and the subsequent Ca^{2+} release. The Ca^{2+} released from the sarcoplasmic reticulum binds TnC on the actin filaments, increasing the affinity of TnC for additional Ca^{2+} ions, with each TnC binding up to four Ca^{2+}. Upon Ca^{2+} binding, troponin undergoes a conformational change, displacing tropomyosin from the myosin-binding sites on F-actin and allowing myosin binding to the actin filament [26].

The sliding filament model describes the mechanism by which the thick and thin filaments slide past each other to generate muscle contraction.

Initially, the myosin is bound to ADP and phosphate (P), which are remnants from the previous contraction cycle. When the actin specific site becomes available, myosin head forms cross-bridges with the actin filaments. The subsequent release of ADP and P strengthens the myosin/actin interaction and the myosin head pulls actin toward the M-line located in the center of the sarcomere (the so called power stroke). When ATP binds myosin, myosin head detaches from actin. The intrinsic ATPase activity of myosin hydrolyzes ATP into ADP and P. The energy released during ATP hydrolysis powers myosin to reach the so called cocked position, being ready for the subsequent contraction cycle. Ca^{2+} is then actively transported against a concentration gradient into the sarcoplasmic reticulum through the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) [27].

Mg has a critical role in regulating contraction mechanism. Acting as a Ca^{2+} antagonist, Mg exerts a relaxant effect on skeletal muscle. TnC possess two Ca^{2+}/Mg^{2+} binding sites on the C-terminal domain, which bind Ca^{2+} with high affinity and Mg^{2+} with low affinity. When the muscle is resting, the concentration of Mg^{2+} is about 10,000 times higher that of Ca^{2+}, and Mg^{2+} occupies all the Ca^{2+}/Mg^{2+} binding sites. Upon the arrival of the action potential, Ca^{2+} released from the sarcoplasmic reticulum replaces Mg^{2+} at these binding sites [28]. In conditions of Mg-deficiency, less Ca^{2+} is necessary to displace Mg^{2+} from TnC, causing muscle hypercontractibility, which manifests as cramps and spasms. Several studies investigated the efficacy of Mg supplementation in preventing skeletal muscle cramps, which are often associated with pregnancy and advanced age. Although Mg supplementation does not appear to be effective as cramp prophylaxis in older adults, there are conflicting data regarding its efficacy in preventing pregnancy-associated rest cramps [29]. To our knowledge, no study has examined the efficacy of Mg supplementation in preventing exercise-associated muscle cramps or cramps associated to disease-state-associated muscle (for example amyotrophic lateral sclerosis/motor neuron disease).

Mg is also needed for the activity of creatine phosphokinase (CK), which regenerates ATP through the formation of phosphocreatine. In brief, phosphocreatine, generated by mitochondrial-CK, is shuttled to the cytosol. Here, phosphocreatine and ADP are used to regenerate the ATP necessary for actomyosin ATPase and Ca^{2+}-ATPase, both involved in muscle contraction [30]. If ATP production is impaired, myosin heads may not detach from the actin-binding sites. As a consequence, the cross-bridges between myosin/actin are retained, resulting in muscle rigidity typical of rigor mortis.

Besides being essential for ATP biogenesis, Mg is necessary for ATP hydrolysis [31]. This is relevant for maintaining appropriate intracellular ratios of AMP/ATP and/or ADP/ATP, which are pivotal for activating AMPK and its downstream pathways, as discussed previously. Mg is also involved in the opening of the RyRs that allow Ca^{2+} release from the sarcoplasmic reticulum. Since the opening of RyRs depends on the number of ATP molecules bound to the receptor, variations of the intracellular levels of Mg and Ca^{2+} can influence ATP concentration and, subsequently, the activation of RyRs [32].

Mg is also necessary for the activity of SERCA, which is responsible for pumping Ca^{2+} back into the sarcoplasmic reticulum at the end of the muscle contraction cycle. This process is energy dependent, requiring one molecule of ATP to pump two Ca^{2+} [33]. Sarcoplasmic reticulum membranes isolated from the skeletal muscles of rats fed a Mg-deficient diet exhibit increased activity of ryanodine binding affinity to the Ca^{2+} channel and inhibition of the Ca^{2+}-ATPase pump activity, resulting in Ca^{2+} overload [34]. Interestingly, the sarcoplasmic reticulum membranes showed structural modifications, including low fluidity and high amount of carbonyls, resembling those described in membranes subjected to in vitro peroxidation, supporting the hypothesis that free radical are responsible for skeletal muscle damage associated with low Mg conditions [20].

Studies on magnesium and muscle performance

Due to the key role of Mg in energy metabolism, transmembrane transport, muscle contraction and relaxation, it is not surprising that a correlation exists between Mg status and muscle mass, muscle strength and muscle performance [35] both in young and in old volunteers. A study conducted for 4 weeks on 30 healthy subjects (18-22 years old) supports this correlation. The

participants were divided in 3 groups: (1) a Mg supplementation group (10 mg/kg/day); (2) a Mg supplementation + training group; (3) a training-only group. The results of the study demonstrated that Mg supplementation improved the performance of individuals undergoing training by reducing their lactate levels [36]. Mg-supplementation (8 mg/kg/day) for 7 weeks increases muscle strength in young untrained subjects [37]. The EPIC-Norfolk study demonstrated a strong association between serum Mg concentration and skeletal muscle mass in a UK population of 14,340 middle to older-aged [38]. The cross-sectional association analysis conducted on a large cohort of 156,575 men and women aged 39-72 years unveiled a potential positive correlation between dietary Mg intake and various indicators of musculoskeletal health. Specifically, the study suggested that higher Mg intake may be associated with greater grip strength, skeletal muscle mass, and bone mineral density. Remarkably, this correlation appeared to be more pronounced in men over the age of 60 compared to younger men [39]. The cross-sectional study conducted on 2,570 women aged 18 to 79 years revealed a positive association between higher Mg intake and some indices of skeletal muscle health (fat-free mass as a percentage of body weight, fat-free mass index) and leg explosive power, a measure of the strength and speed of quadriceps muscle contraction. Furthermore, a negative correlation was found between C-reactive protein, a marker of inflammation, and skeletal muscle mass [40].

Mg has a well-known anti-oxidant activity and chronic Mg depletion has been shown to increase ROS production and low-grade inflammation [41]. Oxidative stress and inflammation are known to be pathogenic factors in some age-related disease, and aging often correlates with Mg deficiency, muscle loss and sarcopenia. The evidence from the InCHIANTI study, involving a population of 1,453 older adults, underscores the strong correlation between circulating Mg levels and muscle performance. This finding highlights the significance of optimal Mg intake in maintaining muscle function and overall physical performance in the elderly [42]. A separate study conducted on 139 healthy elderly women (average age of 71) investigated the effects of Mg supplementation during a 12-week exercise program. Participants were either supplemented with 300 mg/day of Mg or received no supplementation. Physical performance was assessed using Short Physical Performance Battery, which consists of three objective physical function tests - 4-meter gait speed, repeated chair stands, and standing balance in increasingly challenging positions - and changes were observed in peak torque isometric and isokinetic strength of the lower limbs and handgrip strength at baseline and after the intervention, demonstrating that Mg supplementation improves physical performance in healthy elderly woman [43].

Mg depletion has also been demonstrated after physical exertions, since long-term exercise increases Mg excretion through sweat and urine. As an example, a significant reduction of serum Mg concentration was showed in swimmers after exercise [44, 45]. Mg excretion associates with high levels of reactive oxygen species (ROS). By acting on myofibrillar proteins to inhibit Ca^{2+} sensitivity, ROS may contribute to the development of muscle fatigue [46]. In addition, Mg deficiency impairs INSR activity inhibiting the downstream pathway and decreasing the cellular uptake of glucose which is necessary to meet the energy requirement during exercise. A study performed on Sprague-Dawley rats treated with $MgSO_4$ (90 mg/Kg) 30 min before treadmill exercise revealed a higher increase of muscle glucose level during exercise compared to untreated rats. This evidence demonstrates that Mg improves muscle performance, increasing glucose availability [47]. Based on these data, studies have been conducted on the effectiveness of Mg supplementation on athletes' muscle performance, providing mixed results. A study on 12 professional basketball players supplemented with 400 mg/day Mg and a non supplemented control group of 12 university students who practiced recreational basketball demonstrates that Mg supplementation contributes to maintain unaltered muscle damage parameters during the season of competition [48]. Another study performed on elite basketball, handball and volleyball players showed an association between Mg intake and muscle strength performance [49]. 16 elite soccer players supplemented or not with 5,500 mg/die Mg creatine chelate for 16 weeks showed the improvement of both speed and power ability [50]. 25 professional male volleyball players reported a significant decrease of lactate production and increase in counter-movement jump and counter-movement jump

with arm swing supplemented with 350 mg/die of Mg compared to the controls. Unexpectedly, plasma Mg concentrations decreases significantly within the supplemented group [51]. A study conducted on elite judo athletes, who are often prone to severe dehydration, demonstrated that significant changes in intracellular water are associated with a significant reduction in strength. Of note, an increase in Mg instead of magnesium levels in red blood cells associates with a mitigation of the loss of strength [52]. Another study was performed on 9 competitive cyclists who rode three simulated 20-km time trials after supplementation with Mg lactate dehydrate and calcium lactate monohydrate or placebo. The study did not show significant differences with respect to time, mean power, or heart rate between supplemented and placebo trials even if a trend toward a faster time in the supplemented trial was underlined [53]. Eighteen male professional cyclists, divided in control group and Mg supplemented group (400 mg/day) were recruited to participate in another research. The study showed that Mg supplementation contributes to maintain physiological Mg levels, assuring muscle recovery after a cycling competition [54].

Conclusions

These data substantiate that an adequate Mg intake is essential to guarantee optimal function and performance of skeletal muscle cells in individuals of all ages. A condition of Mg deficiency is very common in aging populations due to low Mg intake, reduced gastrointestinal absorption, and increased renal excretion. Therefore, maintaining an adequate Mg status is crucial to ensure muscle performance in older individuals [55].

It is also necessary to emphasise that the typical recommended daily intakes of Mg could be insufficient for those expending more energy through training. Mg supplementation may have beneficial effects on active individuals with a deficient Mg status, whereas it could have no effect on individuals with an adequate Mg status [33]. However, further studies are needed to understand whether adequate Mg supplementation can effectively have positive effects on muscle performance in athletes.

Given the importance of Mg, there is an emerging need to monitor body Mg levels, keeping in mind that less than 1% of the body's total Mg is contained in the blood. To overcome the fact that magnesemia might be normal in moderately Mg depleted individuals, it has been suggested to measure intramuscular ionized Mg by phosphorus magnetic resonance spectroscopy (^{31}P-MRS) [56]. This is a better clinical measure of Mg status that could be useful to discover chronic Mg deficiency, to study muscle dysfunction when muscle weakness of unidentified etiology is detected and to plan and monitor dietary or pharmacological interventions, with emphasis on the elderly and immobilized patients.

Disclosure

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