Hypomagnesemia and its relation with chronic low-grade inflammation in obesity

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SUMMARY

Introduction: The accumulation of visceral fat in obesity is associated with excessive production of proinflammatory adipokines, which contributes to low-grade chronic inflammation state. Moreover, the literature has shown that mineral deficiency, in particular of magnesium, has important role in the pathogenesis of this metabolic disorder with relevant clinical repercussions.

Objective: To bring updated information about the participation of hypomagnesemia in the manifestation of low-grade chronic inflammation in obese individuals.

Method: Articles published in PubMed, SciELO, LILACS and ScienceDirect, using the following keywords: “obesity,” “magnesium” and “low grade inflammation.”

Results: Scientific evidence suggests that magnesium deficiency favors the manifestation of low-grade chronic inflammation in obese subjects.

Conclusion: From literature data, it is evident the participation of magnesium through biochemical and metabolic reactions in protecting against this metabolic disorder present in obesity.

Keywords: obesity, magnesium, low-grade inflammation.

INTRODUCTION

White adipose tissue is the main energy source in the body, mobilizing fatty acids according to metabolic need.¹ In excessive amounts, this tissue produces proinflammatory adipokines, a process influenced by the anatomical location of fat deposits. Visceral fat, being metabolically more active, favors an increase in the production of these substances, contributing to chronic low-grade inflammation in obesity.²,³

Low-grade chronic inflammation differs from other types of inflammation as it leads to latent tissue damage for extended periods of time, lasting for decades, silently.¹,² Studies have shown that in obese individuals the inflammatory state favors an increase in the formation of reactive oxygen species that can lead to an overload of the antioxidant defense system, contributing to the manifestation of oxidative stress and, consequently, cell damage and death.⁴,⁵

Biochemical and nutritional disorders present in obese individuals are being extensively investigated in order to elucidate the mechanisms involved in the pathogenesis of obesity. In this sense, minerals have been the subject of extensive research in order to identify their relation with metabolic disorders.

Magnesium in particular has attracted great interest from researchers as it plays a role in glucose metabolism, insulin homeostasis, synthesis of adenosine triphosphate, proteins and nucleic acids, as well as in membrane stability and regulation of hormonal and immunological function.⁶,⁷

Magnesium deficiency is characterized as a nutritional problem that leads to changes in the cellular function and biological activity of the molecules, and may contribute to the onset of metabolic disorders related to the inflammatory process, especially in obese individuals, who present low serum and dietary concentrations of this mineral.⁸-¹⁰

In view of the biochemical and metabolic aspects of magnesium, as well as the importance of the functions of this mineral, particularly in mechanisms involved in
the pathogenesis of chronic diseases such as obesity, the objective of this review was to bring updated information on the participation of hypomagnesemia in the manifestation of low-grade chronic inflammation in obese individuals.

**Method**

The literature search was carried out in PubMed, SciELO, LILACS and ScienceDirect databases with no restrictions as to year of publication, considering the following inclusion criterion: studies on the metabolic and physiological aspects of magnesium, which presented relevant aspects on the role of this mineral in the manifestation of chronic low-grade inflammation in obese individuals. The articles were selected based on originality and relevance, taking into account the accuracy and adequacy of the experimental design and the sample number. Established and recent works were preferably used.

The search for bibliographic references was performed using the following keywords: “obesity,” “magnesium” and “low grade inflammation.” The literature search included the following types of studies: randomized or quasi-randomized controlled clinical trials, case-control study, and review articles.

**Metabolic and physiological aspects of magnesium**

Magnesium is the second most abundant intracellular cation and is involved in about 300 biochemical reactions related to anabolic and catabolic actions in the body, such as glycolysis and protein and lipid metabolism. This mineral contributes to increase the production of intracellular adenosine triphosphate and the use of glucose, acting as a cofactor in all reactions that involve energy transfer.

On average, the body of an adult contains 1 mole of magnesium. About half of the mineral content is present in the bone and the other half in soft tissues. More precisely, 0.3% of the total is found in serum, 0.5% in erythrocytes, 19.3% in soft tissues, 27% in muscles, and 52.9% in bones. In serum about one-third of the magnesium is bound to proteins. Of this total, 25% is bound to albumin and 8% to globulins. Of the remaining magnesium, about 80% is in the form of free ion (55% of total magnesium) and about 20% is combined with phosphate, citrate and other compounds.

Magnesium homeostasis in the body is dependent on the amount ingested, intestinal absorption, renal excretion and need presented by various tissues. About 25 to 60% of ingested magnesium is absorbed into the gastrointestinal tract by passive or active transport. The transport of this nutrient through the paracellular pathway is responsible for 80 to 90% of its absorption, which occurs predominantly between microvilli of the small intestine through simple diffusion, and this process is stimulated when intraluminal concentrations of this mineral are high. This absorption pathway occurs mainly in the ileum and distal parts of the jejunum, where the permeability to this ion is greater. This is because in these sites there is a low expression of claudin proteins 1, 3, 4, 5 and 8, which participate in the formation of paracellular barriers and pores, regulating the passage of substances through the epithelium.

However, in the case of low intraluminal concentrations, the magnesium is absorbed through the action of specific transporters belonging to the family called transient receptor potential channel of melastatin type (TRPM6 and 7), and this process occurs by the active absorption of sodium ions, followed by water. This transport requires strict regulation since magnesium ions cross two cell membranes. The active absorption of the mineral occurs mainly in the colon and, to a lesser extent, in the jejunum and ileum.

It is important to emphasize that excessive calorie intake promotes an increase in the intestinal absorption of magnesium, since the mechanism involved in this process is energy dependent. However, the absorption of this mineral can be impaired in the presence of lipids, phosphorus, phytates and oxalate. Diets low in protein (< 30 g/day) also slow the absorption of magnesium.

The kidneys are the main excreting organs involved in magnesium homeostasis, and 70% of the entire content of filtered mineral is reabsorbed in the thick ascending branch of the loop of Henle via the paracellular route. The driving force for magnesium reabsorption is positive transluminal epithelial tension generated by the recycling of potassium through the apical membrane, which is linked with sodium, water and calcium. In the distal convoluted tubule, magnesium transport mainly occurs by active process mediated by TRPM6, and is characterized by negative and highly resistant luminal tension, a specific process that does not depend on calcium absorption.

In a situation of reduced oral intake of magnesium, the kidneys are able to reduce their excretion. The other routes of magnesium excretion are feces and sweat, with the fecal concentration of the mineral being about 150 to 200 mg/day, while sweating contributes about 15 mg daily loss. The balance of magnesium in the body is maintained by the regulation of urinary excretion, which can be exacerbated by the action of thyroid hormones, acidosis, aldosterone, and depletion of phosphate and potassium. On the other hand, calcitonin, glucagon and parathyroid hormone increase reabsorption of glomerular filtrate.
The evaluation of nutritional status relative to magnesium can be obtained by assessing its contents in plasma, erythrocyte, urine and diet. Plasma magnesium has been widely used. However, this marker does not reflect its total content since, even after reduction in mineral intake, plasma concentrations remain constant for a long period of time.\textsuperscript{6,11} The reference values for normal plasma magnesium concentrations are between 0.75 and 1.05 mmol/L.\textsuperscript{18,19}

Erythrocyte magnesium concentration is approximately 2.5 mmol/L and since it has a half-life of 120 days, medium and long-term evaluations of the mineral’s stock in the body can be performed.\textsuperscript{24,25} As for urinary magnesium, approximately 3 to 4 mmol of the nutrient is lost daily through this excretion route. Urine is considered a good indicator for recent changes in nutritional status regarding magnesium, because in cases of stock depletion, excretion is reduced by renal reabsorption mechanisms to maintain its homeostasis in the body.\textsuperscript{24}

The main food sources of magnesium are whole grains, dark green vegetables, legumes, walnuts, seeds, chestnuts and almonds.\textsuperscript{26} The dietary recommendation of this mineral is 400 to 420 and 310 to 320 mg daily for adult men and women, respectively.\textsuperscript{17}

**Hypomagnesemia and low-grade chronic inflammation**

The literature has shown that the diet of obese individuals has reduced magnesium content, which is a nutritional problem of great relevance.\textsuperscript{28,29} Huang et al.\textsuperscript{30} and Song et al.\textsuperscript{31} found that dietary intake of magnesium is inversely proportional to body mass index, waist circumference, and body fat percentage.

The reduced intake of magnesium by obese individuals can be explained mainly by the high consumption of processed foods containing low magnesium and by the reduced intake of food sources of magnesium, which seems to contribute to the reduction of its concentrations in the blood compartments.\textsuperscript{15}

Studies have found reduced plasma concentrations of magnesium in obese individuals.\textsuperscript{32,33} Guerrero-Romero and Rodríguez-Morán\textsuperscript{34} have shown that individuals with normal body weight but metabolically obese exhibit reduced serum magnesium concentrations compared to the obese who are metabolically healthy. Table 1 shows data on the status of magnesium in obese individuals, as well as its participation in chronic low-grade inflammation.

Magnesium deficiency seems to affect the activation of proinflammatory pathways in obese individuals.\textsuperscript{40} In this regard, several researchers have observed that the reduced intake of this mineral and its low serum concentration are strongly related to the increase in the plasma concentration of inflammatory biomarkers, such as C-reactive protein, tumor necrosis factor alpha (TNF-\(\alpha\)) and interleukin 6 (IL-6).\textsuperscript{26,33,41}

Nielsen et al.\textsuperscript{42} found that magnesium intake in amounts below estimated average requirement (EAR) shows a positive correlation with plasma C-reactive protein and body mass index in adults. Guerrero-Romero et al.\textsuperscript{43} found severe hypomagnesemia in individuals with metabolic syndrome, being this parameter strongly related to serum concentrations of C-reactive protein and TNF-\(\alpha\).

A study conducted by Oliveira et al.\textsuperscript{35} revealed reduced dietary magnesium content and urinary excretion in obese women. In addition, a positive correlation was observed between urinary magnesium and serum concentrations of C-reactive protein in these patients, suggesting the influence of hypomagnesuria on this inflammatory marker.

Reduced concentrations of magnesium in plasma compromise its intracellular homeostasis and contribute to the development of a proinflammatory state through overproduction and release of cytokines such as interleukin 1\(\beta\) (IL-1\(\beta\)) and TNF-\(\alpha\), and increased serum concentrations of neuropeptides.\textsuperscript{11,44,45}

It is important to mention that the mechanisms involved in the inflammatory response present in magnesium deficient obese individuals are not yet clearly elucidated. However, according to the literature, the opening of calcium channels and the activation of N-methyl-D-aspartate (NMDA) receptors, as well as the priming of phagocytic cells, induce the entry of calcium into the cell, release of neurotransmitters, such as substance P, membrane oxidation and activation of nuclear transcription factor kappa B (NF-kB), which favors the inflammatory process.\textsuperscript{22,45,46}

The inflammatory response is mainly related to the change in the extracellular concentration of magnesium, since the deficiency of this mineral reduces its plasma concentrations but does not alter its intracellular concentration. Thus, it is important to emphasize the action of magnesium as a natural calcium antagonist and that the reduction of magnesium in the extracellular compartment induces an increase in the concentration of intracellular calcium, favoring the activation of phagocytic cells and the production of cytokines.\textsuperscript{35,46}

One of the mechanisms that seem to justify the increase of intracellular calcium is that of NMDA receptor activation. The decline in extracellular magnesium decreases the concentrations of amino acids such as glutamate needed to activate this receptor. Activation of NMDA, in turn, allows the influx of calcium into the neural cells. In the presence of obesity, this effect can be accentuated.
### TABLE 1. Studies evaluating the status of magnesium in obese individuals or their relationship to chronic low-grade inflammation.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study design</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Oliveira et al.</td>
<td>65 obese and 66 non-obese women</td>
<td>Obese women had plasma and erythrocyte magnesium concentrations similar to the control group. Obese women had lower than normal values of magnesium in the urine. Correlation between urinary concentrations of magnesium and C-reactive protein.</td>
</tr>
<tr>
<td>Farhangi et al.</td>
<td>40 obese and 42 non-obese women</td>
<td>Obese women had lower serum magnesium concentrations than the control group.</td>
</tr>
<tr>
<td>Cruz et al.</td>
<td>55 obese and 59 non-obese women</td>
<td>Obese women had plasma and erythrocyte magnesium concentrations similar to the control group. Obese women presented values of urinary magnesium lower than normal.</td>
</tr>
<tr>
<td>Zemva e Zemva</td>
<td>32 obese and 32 non-obese individuals</td>
<td>Obese individuals had lower plasma and erythrocyte magnesium values compared to the control group.</td>
</tr>
<tr>
<td>Corica et al.</td>
<td>19 obese normotensive, 19 obese hypertensive, and 15 non-obese individuals</td>
<td>Lower plasma, erythrocyte and platelet magnesium levels in the normotensive and hypertensive obese group compared to the control group.</td>
</tr>
<tr>
<td>Bertinato et al.</td>
<td>276 southern Asian and 315 Caucasian individuals.</td>
<td>Obese women had lower serum magnesium values than normal and overweight women.</td>
</tr>
<tr>
<td>Suliburska et al.</td>
<td>78 obese and 20 non-obese adolescents</td>
<td>Obese adolescents presented lower serum magnesium compared to the control group.</td>
</tr>
<tr>
<td>Song et al.</td>
<td>11,686 women aged ≥ 45 years</td>
<td>Inverse association between plasma C-reactive protein concentrations and dietary magnesium content after adjustment for age and body mass index.</td>
</tr>
<tr>
<td>Guerrero-Romero et al.</td>
<td>51 women and 47 men</td>
<td>Severe hypomagnesemia in individuals with metabolic syndrome, a parameter strongly related to the serum concentrations of C-reactive protein and TNF-α.</td>
</tr>
<tr>
<td>Mosleh et al.</td>
<td>69 overweight women</td>
<td>Magnesium serum concentrations were inversely correlated with C-reactive protein before supplementation. However, supplementation with magnesium did not alter the serum concentrations of this mineral, and did not reduce the levels of C-reactive protein and IL-6.</td>
</tr>
<tr>
<td>Rodriguez-Hernandez et al.</td>
<td>38 obese women</td>
<td>No reduction in C-reactive protein concentrations was observed in obese women treated with supplements.</td>
</tr>
<tr>
<td>Simental-Mendia et al.</td>
<td>62 men and women diagnosed as pre-diabetic</td>
<td>Oral magnesium supplementation reduced levels of C-reactive protein in subjects with pre-diabetes and hypomagnesemia.</td>
</tr>
<tr>
<td>Niranjan et al.</td>
<td>62 obese children and 60 controls</td>
<td>Reduced serum magnesium concentrations were seen in the case group compared to the control, as well as of C-reactive protein.</td>
</tr>
</tbody>
</table>
by leptin, a hormone that also favors the receptor’s activation. Thus, excessive calcium influx into the neuronal tissue promotes the release of neurotransmitters, such as substance P, which triggers an inflammatory response through the release of cytokines, histamine and free radicals (Figure 1).

In adipose tissue, the increase of the intracellular calcium content derives from the opening of the L-type calcium channels, which is regulated by magnesium binding sites. In the presence of deficiency of this nutrient, the blockage of these channels is compromised, increasing the influx of calcium to the adipose cells. Excess intracellular calcium, in turn, results in the activation of calcium-dependent processes, such as the release of proinflammatory cytokines. Note that one of the major events in the calcium-mediated inflammatory process is the activation of NF-kB.46,48,49

NF-kB is a potent proinflammatory gene transcription factor. When activated, it binds to specific genes, stimulating the production and release of the proinflammatory cytokines, namely TNF-α and IL-6, and adhesion molecules. These cytokines, when released in excess, favor the secretion of C-reactive protein by the liver.35

It is important to say that TRPM7 channels appear to regulate magnesium concentrations in tissues, and are therefore important in the homeostasis of this mineral.50 Note, however, that TRPM7 is not selective for magnesium, and its expression may also mediate calcium influx and consequently inflammation, which depends on the serum concentrations of both minerals. That is, in situations of magnesium deficiency, calcium competes with magnesium and enters the cells.51,52

Magnesium deficiency appears to increase the production of free radicals and the sensitivity of cells to the attack of reactive oxygen species.53,54 Hypomagnesemia favors the infiltration of neutrophils and macrophages in the affected cells, which potentiates the activity of the enzyme nicotinamide adenine dinucleotide phosphate oxidase

![FIGURE 1](image-url)  
**FIGURE 1** Action of magnesium as an anti-inflammatory nutrient in the brain. The increase of calcium in the intracellular medium promotes the transcription of inflammatory mediators through the release of substance P. Magnesium can inhibit this inflammatory pathway by its action as a natural calcium antagonist, blocking the increase of intracellular concentrations of this mineral. 

Ca<sup>2+</sup>: calcium; Mg<sup>2+</sup>: magnesium; NMDAR: N-methyl-D-aspartate receptor; GLU: glutamate.
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FIGURE 2

Action of magnesium as an anti-inflammatory nutrient in adipose tissue. The increase of calcium in the intracellular medium promotes the oxidation of cell membranes and the transcription of inflammatory mediators through the activation of NF-κB and its translocation into the nucleus, and increases the oxidative stress through the activation of the NO synthase and NADPH oxidase. Magnesium can inhibit this inflammatory pathway by its action as a natural calcium antagonist, blocking the increase of intracellular concentrations of this mineral.

Ca²⁺: calcium; Mg²⁺: magnesium; NF-κB: nuclear factor kappa B; NO synthase: nitric oxide synthase.

Combined with this, in the presence of hypomagnesemia, intracellular ionic calcium contributes to the excessive production of uric acid and hydroxyl radical, which reacts with nitric oxide, which is also high in hypomagnesemia, forming peroxynitrite. Thus, excessive production of reactive species in magnesium-deficient individuals also contributes to the inflammatory state present in obese individuals (Figure 2).

Some studies have been conducted to evaluate the effect of magnesium supplementation in obese or overweight individuals. However, no reduction in the concentration of inflammatory biomarkers was observed. Moslehi et al. found that supplementation with 250 mg/day of magnesium oxide for 8 weeks was not able to reduce levels of C-reactive protein in overweight women. Rodriguez-Hernandez et al. did not observe reduced concentrations of this inflammatory protein in obese women supplemented with 450 mg of magnesium chloride for 4 weeks, either.

**Final considerations**

Scientific evidence as presented in this review suggests that magnesium deficiency favors the manifestation of chronic low-grade inflammation in obese individuals. Nevertheless, mineral supplementation does not seem to influence the reduction of inflammatory biomarkers. Although some explanations have been proposed with a view to clarifying the role of the mineral in this disorder, the mechanisms are not yet fully identified. Therefore, new studies on the subject may provide biochemical
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The authors declare no conflict of interest.

Hipomagnesemia e sua relação com a inflamação crônica de baixo grau

Palavras-chave: magnésio, níveis séricos, inflamação crônica de baixo grau.

Resumo

Hipomagnesemia e sua relação com a inflamação crônica de baixo grau na obesidade

Introdução: O acúmulo de gordura visceral na obesidade está associado à produção excessiva de adipocinas pró-inflamatórias, o que contribui para o estado de inflamação crônica de baixo grau. A literatura também tem mostrado que a deficiência de minerais, em particular do magnésio, possui papel importante na patogênese desse distúrbio metabólico com repercussões clínicas relevantes.

Objetivo: Trazer informações atualizadas sobre a participação da hipomagnesemia na inflamação crônica de baixo grau em indivíduos obesos.

Método: Bases de dados Pubmed, SciELO, Lilacs e ScienceDirect, utilizando as palavras-chave: “obesity”, “magnesium” e “low grade inflammation”.

Resultados: As evidências científicas sugerem que a deficiência de magnésio favorece a manifestação da inflamação crônica de baixo grau em indivíduos obesos.

Conclusão: É evidente a participação do magnésio, por meio de reações bioquímicas e metabólicas, na proteção contra esse distúrbio metabólico presente na obesidade.

Referências

Hypomagnesemia and its relation with chronic low-grade inflammation in obesity


