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REVIEW

Breaking down the barrier: understanding how magnesium deficiency contributes to periodontitis

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A common disturbing dental malaise which ultimately results in low quality of life is periodontitis, a chronic bacterial infections disease that is caused by the dental plaque biofilm. Both tissues and blood need enough magnesium, this is a natural and one of essential minerals that is highly abundant in the human body. Different diseases due to a magnesium deficiency can be formed. Results from clinical and nutritional data supported this hypothesis. However, The relationship between magnesium deficiency and periodontitis requires further research. This paper examines some possible ways in which these two are connected. This article focuses on presenting a valuable and resourceful material for those who are eager to acknowledge the role that magnesium level plays in periodontal disease as well as providing potential means to the creation of advanced and effective periodontitis prevention and treatment approaches.

Keywords: magnesium, periodontitis, immune reaction, nutrition, microelement

Introduction

Magnesium acts as an important catalyst as the fourth most active element in a human body and the second most in cells (1).It is specifically present in bones and soft tissue among others. It not only plays a key role in energy metabolism, nucleic acid, and protein synthesis, which ensure the survival of all tissues and cells in the human body, but it is also an indispensable nutrient necessary for maintaining human life. Despite the fact that the biomarker of magnesium concentration in serum does not reflect the magnesium levels existing inside the cell, there is ample evidence associating the content of this metal with the various pathological conditions including cardiovascular diseases, diabetes, hypertension, and osteoporosis, which are systemic conditions as a result of the periodontal disease (2, 3). Chronic inflammation of the periodontal supporting tissues is known as periodontitis (4). Prostaglandin E2 (PGE2), tumor necrosis factor-α (TNF-α), and other pathogenic factors can be secreted by periodontal bacteria and metabolites, which can activate immune cells and cause persistent inflammation that damages periodontal tissue and absorbs bone from the alveolar bone (5). Furthermore, injury to periodontal tissue might be caused by the endotoxin of several gram-negative bacteria found in periodontal microorganisms (6). The hard and soft tissues that surround teeth are affected by the frequent oral illness known as periodontitis. Gum

edema, the development of periodontal pockets (7), the absorption of alveolar bone that follows, and ultimately the loosening and shedding of teeth are the key symptoms of the early stages of periodontal disease, which have a major negative impact on people's lives and health. The adult tooth loss rate can range from 10 to 15%, whereas the incidence rate can reach up to 90% (8). Thus, the current focus of research in mouth-related domains is on regeneration of periodontal tissue. Controlling inflammation, halting the spread of the disease, and restoring the architectural structure and functionality of healthy periodontal tissue are the goals of periodontal therapy (9). Currently, basic treatment, surgical treatment, and adjuvant medication treatment are the typical ways to treat periodontitis (10). However, these treatments have their own advantages and disadvantages. Basic treatment and drug treatment can alleviate inflammation and temporarily stop the development of lesions, but bone regeneration cannot be achieved yet. Since the 1980s, researchers have gradually explored the cellular and molecular mechanisms related to magnesium and inflammation through *in vivo* and *in vitro* experiments. However, there is limited literature summarizing the correlation between magnesium and periodontitis, despite the fact that periodontitis is also associated with magnesium (11). Therefore, this review aims to provide a preliminary summary of the relationship between magnesium and periodontitis as well as to infer the pathogenic mechanism of magnesium on periodontitis based on current research.

The role of magnesium in periodontitis

Clinical research by Meisel revealed a strong correlation between serum magnesium ion concentration and periodontal probing depth, which prevents attachment loss and tooth loss (12). Furthermore, magnesium shortage and the induction of pro-inflammatory cytokines may be the reason for the low periodontal bone mass in patients with periodontitis. Through a cross-sectional study, they looked further into the relationship between blood magnesium concentration and periodontal health in 4290 people and discovered that 35% of patients with periodontitis had hypomagnesemia. After that, they compared the periodontal-related parameters between the patients who took and did not take magnesium supplements. They discovered that patients who took drugs containing magnesium had a significant correlation between their serum magnesium levels and periodontal health, indicating that taking magnesium supplements could both prevent tooth loss and improve periodontal health (13). Furthermore, researchers have examined the serum magnesium levels of individuals with chronic periodontitis both before and after scaling and root planning, and they have discovered that the elevation of serum magnesium levels occurs following the resolution of inflammation during scaling (14). However, from a nutritional perspective, it has been discovered that trace minerals can influence the course of periodontitis, and a chronic deficiency in magnesium will result in weakening of the alveolar bone, swelling of the gingiva, loosening of the teeth, and early loss (15). However, the height of alveolar ridge and tooth loss caused by magnesium deficiency may reduce bone loss if magnesium supplements are taken orally in time (16). In rodents, pro-inflammatory cytokines, associated proteins, and gingival congestion will all rise in response to a drop in serum magnesium ion concentration (17). Nevertheless, other research likewise revealed no distinction in serum magnesium concentrations between individuals consuming magnesium supplements and those who did not (16). Because people with hypomagnesemia can only benefit from substantial doses of magnesium to raise their serum magnesium content (18). From a biological perspective, magnesium modulates immune cells to influence the onset and progression of periodontitis. A lack of magnesium will impair adaptive immune cells' ability to respond, trigger the innate immune system, and so increase inflammation (3). Isolated from animals lacking in magnesium, macrophages and neutrophils exhibit hyperreactivity to a range of stimuli, maybe linked to the reduction in magnesium concentration in inflammatory responses (19). Neutrophils contribute to tissue degradation and preserve inflammation (20). Hypomagnesemia can be caused by activated neutrophils (21). Additionally, magnesium controls the immune system's reaction (22). As a result, reduced magnesium concentration can intensify the bacterially-induced inflammatory response (23). Nevertheless, some research has shown that a drop in serum magnesium levels does not always translate into a drop in salivary magnesium concentrations. In fact, some investigations have shown that an increase in the magnesium content of calcified tissues can cause salivary magnesium concentrations to rise. Patients with gingivitis and periodontitis had, on average, higher concentrations of magnesium in their saliva, according to research by Shetty et al. (24). According to some researches, the variation in the amount of magnesium in saliva could be useful in assessing the severity of periodontal disease (25). Manea and Nechifor (26) did note, however, that periodontitis patients' saliva did not exhibit a statistically significant rise in magnesium concentration (26). Based on similar studies, saliva contains more magnesium than 8 parts per milligram (ppm). This could be a sign of periodontal disease or a sign that therapy is working.

Possible mechanisms of magnesium deficiency leading to periodontitis

Magnesium regulates periodontitis by regulating other trace elements

Diseases can arise from an imbalance in the intricate and comprehensive ecosystem prevailing in the oral cavity. Abnormalities in trace elements might result from an imbalance in magnesium. Periodontitis and the ratio of calcium to magnesium, as well as the difference in serum calcium levels between smokers and non-smokers, were assessed in a long-term study conducted in Japan among the senior population. In the examination of disease progression, the researchers even concluded that the ratio of calcium to magnesium was more significant than the individual measurement of calcium concentration. They discovered that smokers had lower serum calcium levels than non-smokers (27). The ratio of calcium to magnesium in the human diet should ideally be maintained at 2.0 (28). However, there aren't enough pertinent scientific studies to back up this conclusion. Magnesium can influence oxidative stress and inflammation because it is a physiological calcium channel inhibitor. For instance, a deficiency in magnesium causes an increase in the entry of calcium ions into the cell via calcium channels from the outside (25). Elevated calcium levels can trigger integrin activation, hence facilitating the specific adhesion between leukocytes and endothelial cells (29). The first sign of hypomagnesemia is neutrophil activation. Lowering the magnesium content will exacerbate the inflammatory response since a high concentration of magnesium will prevent the creation of free radicals. Nonetheless, it has been discovered that low calcium concentrations will lessen the incidence and progression of inflammation (30). It has also been discovered that through magnesium ion-sensitive potassium channels, a magnesium deficit can enhance the outflow of potassium ions from cells from the inside out. As a result, the concentration of potassium will be impacted by changes in magnesium in periodontal disease patients' saliva or gingival crevicular fluid, and potassium will also react to these changes in magnesium (31). According to Yost et al. (32), an increase in potassium in gingival crevicular fluid was accompanied by a decrease in the expression of human β-defensin 3 (HBD-3), which has antibacterial and immunomodulatory properties, an increase in the expression of the cytokines TNF-α and IL-6, and an activation of RANKL. As a result, it is reasonable to assume that the combined concentration of magnesium and potassium in saliva will reflect clinical conditions and be useful in the diagnosis of disorders affecting the periodontal tissue.

Magnesium regulates periodontitis by regulating vitamins

Magnesium functions as an auxiliary in enzymatic reactions and is a crucial auxiliary component for activating a variety of transporters and enzymes (33). A shortage in magnesium will result in decreased levels of vitamin D receptors in cells as well as reduced parathyroid hormone output and response. It can only be fixed by adjusting to magnesium supplementation (34). Furthermore, the only way to strengthen rickets' resistance to vitamin D is with appropriate magnesium intake (35). In addition, vitamin D, a crucial component of the kidney, bone, parathyroid gland, and small intestine, controls the levels of calcium and phosphorus in order to preserve the normal function of bones. As an illustration, VDR binds and activates vitamin D, which has the ability to upregulate calcium channels and enhance calcium and phosphate absorption. In addition, a lack of vitamin D will raise the release of parathyroid hormone, decrease the absorption of calcium, increase the activity of osteoclasts, and encourage bone deterioration. Consequently, magnesium is required for the metabolism and synthesis of vitamin D. Supplementing animals with vitamin D can improve their absorption of calcium and magnesium (36). Moreover, vitamin D influences the development of periodontal disorders as well as their health through immunomodulation and anti-inflammatory properties, such as boosting bone density, lowering bone resorption, and squelching periodontal inflammation (37). Vitamin D is an important hormone that regulates calcium and phosphorus metabolism in the body. It is mainly synthesized by the skin under sunlight, and a small amount can be obtained through diet. The active form of vitamin D is mainly 1,25-dihydroxyvitamin D. Research has demonstrated that 1,25-dihydroxy vitamin D3 helps to enhance the immune defense and barrier function of oral epithelial cells. By triggering the production of human antimicrobial peptide LL-37, which possesses antibacterial and endotoxin-resistant properties, it can also influence the immunological response (38).

As an antioxidant and reducing agent, vitamin C can scavenge free radicals. It is an essential nutrient. Without enough vitamin C, oxidative stress levels will rise and pro-inflammatory cytokines will be released, hastening the inflammatory process and encouraging tissue damage. GSH, a chain-breaking antioxidant that may control a cell' s redox state, can convert vitamin C, also known as ascorbic acid, from an oxidized state to dehydroascorbic acid, which can then be converted into a non-free radical state. Supplementing with vitamin C has also been demonstrated in studies to sustain GSH (39). Alveolar bone is impacted by osteogenesis, which is another gene that vitamin C can encourage bone cells to create. Progression of periodontitis can be exacerbated

by an inflammatory response brought on by a shortage of magnesium and an oxidative stress brought on by a deficiency of vitamin C (40). Thus, in order to suppress the development of osteoclasts and encourage the production of new bones, supplements containing magnesium should also be used in addition to vitamin C while treating periodontitis. Conversely, the anti-inflammatory properties of magnesium and the anti-oxidative properties of vitamin C work together.

Magnesium regulates periodontitis by regulating immune response

A diet low in magnesium has the potential to heighten the body' s vulnerability to lipopolysaccharide and augment the reactions of macrophages and neutrophils (41). In comparison to physiological settings, more free radicals are created in this situation (19). As the first line of defense against bacteria in periodontal tissues, macrophages have the ability to interact with microorganisms that cause periodontal plaque, secrete a multitude of proinflammatory cytokines and chemokines, and take part in the phagocytosis and inflammation of pathogenic microorganisms that cause periodontal inflammation. Furthermore, the polarization imbalance between M1 and M2 is linked to alveolar bone resorption in periodontitis, indicating that M1-type macrophages play a significant role in alveolar bone resorption. It has been discovered that magnesium stimulates the M2 type differentiation of mononuclear macrophages, which in turn secrete cytokines that promote bone formation and reduce inflammation. Furthermore, magnesium has the ability to lower macrophage production of the pro-inflammatory factors TNF-α, IL-6, and IL-1β (17). Increasing the concentration of magnesium might also decrease immune cells' production of nitric oxide and reactive oxygen species, which means that biomaterials containing magnesium may have anti-inflammatory characteristics (42). A lack of magnesium increases the expression of cell surface adhesion molecules, leukocyte adhesion, IL-8, MCP1, and other molecules (43). In the early stages of inflammation, IL-8 absorbs neutrophils and triggers their release of several components, which leads to tissue damage. Because low magnesium concentrations activate NF-κB, they can also cause inflammation by inducing a significant number of inflammatory mediators. Additionally, it has the ability to release chemokines and cytokines, upregulate adhesion molecules, and increase the adherence of leukocytes and endothelial cells. TNF-α and IL-1 are two of them that can promote osteoclast production, which in turn can lead to bone loss (44). IL-1 increases the production of macrophage colony factor (M-CSF) to stimulate osteoclast activity (45).

Magnesium regulates periodontitis by regulating oxidative stress

Apart from the previously mentioned plausible pathways, it has been discovered that a magnesium deficit can cause oxidative stress, which is linked to inflammation. Overproduction of oxidation products and an imbalance between oxidation and antioxidation are the results of oxidative stress and reactive oxygen species (ROS). Unbalanced reactive oxygen species, both free radical and non-free radical, can cause oxidative stress by damaging cells and activating particular signaling pathways that lead to tissue damage brought on by cytokines (46, 47). Overabundance of ROS will facilitate the signal molecules that trigger cells to generate osteoclasts and result in the absorption of bone in the alveolar space. Low magnesium levels have been reported to cause the release of pro-inflammatory cytokines including IL-6, TNF-α, and PGE2, as well as to upregulate stress proteins and activate the NF-κB pathway. Thus, a lot of reactive oxygen species are produced (48). It is related to periodontitis that these cytokines produce. Additionally, high ROS influences the bone resorption caused by periodontitis by interfering with MAPK, Nrf2, and other signal pathways. Consequently, the rate at which periodontal disease progresses and its severity may be influenced by the increased oxidation brought on by a magnesium deficit.

Discussion

A great deal of research has already shown that there is a connection between inflammation and low magnesium levels. Other studies have even looked at the possible pathways that could connect low magnesium to periodontitis. Research has shown that the start of periodontitis and other trace elements like potassium, calcium, and phosphorus, which can cause inflammation, are somewhat related to magnesium insufficiency brought on by vitamin imbalances. In a cross-sectional epidemiological study where periodontal health was identified and associated with serum magnesium and calcium concentrations, magnesium intake was inversely associated with the prevalence of periodontitis (49). Magnesium, of its unique ability to reduce inflammation caused by bacterial toxins, may play an important role in preventing periodontal disease (50). A toothpaste containing magnesium salt can reduce the incidence of periodontitis (51). Mg was also found to have local analgesic and anti-inflammatory effects in previous studies, especially in the presence of alkaline pH (52). Periodontitis may develop as a result of immunological responses impacted by a magnesium imbalance, which could cause immune cells to release cytokines. A shortage in magnesium can also cause oxidative stress, and the reactive oxygen species (ROS) that come from this can

take part in a number of inflammatory and periodontal bone resorption processes. The development and course of periodontitis are clearly influenced by magnesium deficiency in an indirect manner.

The exact cause of magnesium deficiency-induced periodontitis, the effects of magnesium on local periodontal microorganisms and their functions, the difference between the effects of magnesium on extracellular and intracellular periodontal tissue, the temporal and spatial influence of magnesium deficiency on other trace elements in the context of periodontitis, and the best ways to supplement with magnesium to treat periodontitis caused by magnesium deficiency are all subjects of further in-depth mechanistic studies that are necessary to clarify the matter. This covers issues like which form and use of magnesium supplements is best, as well as whether systemic or local supplementation is preferable. Biodegradable magnesium biomaterials have emerged as a possible treatment option for various human ailments, as biomaterials research continues to advance. Investigations into the possible application of biomaterials containing magnesium to improve and treat periodontitis have resulted from this. These results may provide more effective methods of treating and preventing periodontitis.

Author contributions

MW: Conceptualization. YC: Preparation and revision of the manuscript. YC and MY: Data curation. All authors participated in the manuscript's revision process and gave their approval before it was submitted to this publication.

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Conflict of interest

The research was carried out without any financial or commercial ties that might be seen as having a conflict of interest.

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