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Review

Unraveling the role of Mg^{++} in osteoarthritis

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ABSTRACT

Mg^{++} is widely involved in human physiological processes that may play key roles in the generation and progression of diseases. Osteoarthritis (OA) is a complex joint disorder characterized by articular cartilage degradation, abnormal mineralization and inflammation. Magnesium deficiency is considered to be a major risk factor for OA development and progression. Magnesium deficiency is active in several pathways that have been implicated in OA, including increased inflammatory mediators, cartilage damage, defective chondrocyte biosynthesis, aberrant calcification and a weakened effect of analgesics. Abundant *in vitro* and *in vivo* evidence in animal models now suggests that the nutritional supplementation or local infiltration of Mg^{++} represent effective therapies for OA. The goal of this review is to summarize the current understanding of the role of Mg^{++} in OA with particular emphasis on the related molecular mechanisms involved in OA progression.

Contents

1. Introduction

Osteoarthritis (OA) is currently one of the most prevalent chronic diseases and is a major source of pain, disability and socioeconomic cost worldwide. Prevalence studies show that OA affects an estimated 10% of men and 18% of women over 60 years of age [1]. Joint replacement is the primary means of treatment for arthritis; however, this procedure has substantial adverse outcomes and a finite prosthesis lifespan. Current goals of OA research include reduction of OA morbidity and new prevention and treatment methods.

The pathogenesis of OA is not fully understood; however, the enhanced production of pro-inflammatory cytokines, predominantly interleukin (IL)-1 and tumor necrosis factor (TNF) α, in addition to extracellular matrix mineralization and cartilage degradation, are important features of OA pathophysiology [2]. Clinically, OA is characterized by joint pain, stiffness and limited mobility [3]. New therapeutic strategies for alleviating pain and mitigating early pathological changes have been proposed for the treatment of early osteoarthritis [4,5].

Mg^{++} is the second most abundant intracellular and fourth most abundant extracellular cation and is a microelement in the human body [6]. The adult human body contains approximately 24 g of

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magnesium—approximately 60%–65% in bones and, teeth and approximately 27% in soft tissues. Magnesium is an essential mineral that is needed for numerous physiological functions. Emerging evidence indicates that magnesium deficiency has a strong relationship with osteoarthritis. The Mg^{++} contents of biological samples (blood, serum, and scalp hair) from rheumatoid arthritis patients are lower than referents in both genders [7]. Numerous studies show that low dietary intake of Mg^{++} is associated with OA [8,9]. Therapeutically, magnesium salicylate, a magnesium salt applied in the treatment of clinical diseases, is effective in treating osteoarthritis [10]. The role of Mg^{++} in OA is currently being studied in detail, and recent investigations have yielded new and exciting knowledge; this review aims to describe this new knowledge.

2. Magnesium and the inflammatory response

Several systematic studies have been conducted in recent years to determine the molecular mechanisms and roles played by Mg^{++} in a state of inflammation. Experimental magnesium deficiency in rats induces a series of inflammatory syndromes characterized by macrophage and leukocyte activation, the release of inflammatory cytokines and acute phase proteins, and the excessive production of free radicals. Elevated levels of pro-inflammatory cytokines (such as interleukin (IL)-6 and TNFα) play pivotal roles in the pathophysiology of OA, as observed in Mg-deficient animals [11,12]. Magnesium deficiency induces an inflammatory response cascade (Fig. 1). Elevated TNFα caused by an Mg^{++}-deficient diet can result in the activation of NF-kB to promote the release of IL-6 and IFN-γ. Mg^{++} deficiency can also induce the synthesis of nitric oxide (NO) and elevated IL-6, substance P (SP) and IL-4 [13–15]. SP can activate immune cells and synovial cells and stimulate the production of prostaglandins and several cytokines, such as IL-1β and IL-6 [16,17]. Mg^{++} can inhibit mitochondrial reactive oxygen species generation [18]. All of these cytokines are intimately involved in inflammation.

2.1. TNFα

A cross-sectional population-based study indicated that elevated TNFα levels are associated with low serum magnesium levels in obese subjects [19]. TNFα receptor in knockout mice can alleviate the adverse effects of magnesium deficiency in bone, suggesting that inflammatory injuries caused by magnesium deficiency primarily occur through TNFα [20].

TNFα, a significant cytokine in inflammation caused by Mg-deficiency, can be increased by an array of stimuli including hypoxia and various cytokines including interleukin 1 (IL-1), interleukin 17 (IL-17) and interferon-γ (IFN-γ). The aforementioned cytokines are increased in culture models of various cells (including human and rats) under hypomagnesemia [11,21]. The combination of TNFα and TNFα receptors can result in outcomes such as apoptosis, transcriptional factor activator protein 1 (AP-1) activation, or nuclear factor-kB (NF-kB) activation and translocation to the nucleus [22]. NF-kB can promote the synthesis of IL-6 and IFN-γ and also can up-regulate the transcription of TNFα, thereby promoting inflammation [23]. Notably, Mg^{++} significantly attenuated the levels of inflammatory mediators and the NF-kB pathway by enhancing phosphoinositide 3-kinase (PI3K)/Akt activity [24,25].

TNFα plays an important role in the inflammatory cytokine cascade that is involved in the pathogenesis of arthritis, and biologic therapies targeting TNFα represent common OA therapies [26]. Anti-TNFα agents are also protective against cerebral infarction, inflammatory bowel diseases and immune-mediated inflammatory diseases (IMIDs) [27–29]. Although TNFα is a key pro-inflammatory cytokine of OA, and anti-TNFα agents represent the most common strategy to treat this disease, one-third of rheumatoid arthritis (RA) patients are unresponsive [29]. The critical role played by Mg^{++} deficiency in a scenario of elevated TNFα levels may represent a new therapeutic pathway.

3. Protective effects of magnesium in cartilage

Extensive studies have revealed that damage to joints induced by a magnesium-deficient diet is identical to that by quinolones [30,31]. A study on juvenile Wistar rats showed that supplementation with Mg^{++} can decrease joint cartilage lesions; a combination of vitamin E and Mg^{++} produced a better protective effect of cartilage [32]. We reasoned that if magnesium protects joint cartilage, Mg^{++} can directly enhance chondrocyte proliferation and increase growth factor effectiveness by consecutive influences during chondrogenesis [33]. Mg^{++} was shown to increase the adhesion of human synovial mesenchymal stem cells (MSCs) to extracellular matrix (ECM) through integrins [34]. Synovium is an important source of MSCs. MSCs have proliferation and superior differentiation potentials and high chondrogenic ability. Integrin, a heterodimer composed of alpha subunit and beta subunit, is a major family of cell surface receptors that mediate adhesive interactions between cells with ECM. The N-terminal of the alpha subunit has a binding domain for bivalent cations and is associated with integrin activity. Integrin containing beta subunit can mediate the adhesion between cells with ECM. Divalent cations, such as Ca^{++}, Mg^{++}, and Mn^{++}, can affect the functioning of integrin, which is involved in MSC differentiation. Mg^{++} (a divalent cation) is used in clinical practice as a therapeutic agent to increase the affinity of integrin to ECM.

Distal femur articular cartilage chondrocyte density and tibial growth plates in rats following a 6-month dietary Mg^{++} restriction were decreased compared with a control group [35]. Furthermore, the transcription factor sex determining region Y-box 9 (Sox9) was decreased in both the articular and growth plate cartilage in a Mg^{++}

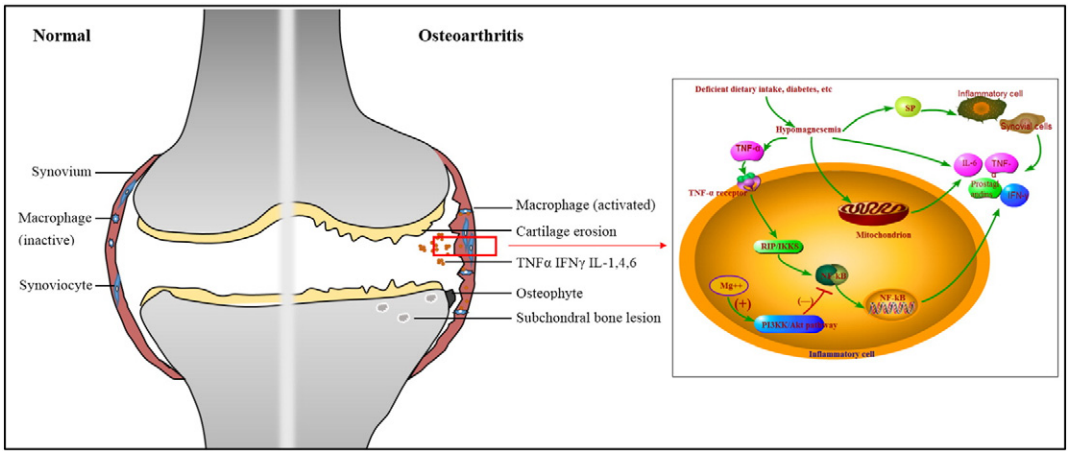

Fig. 1. Schematic representation of the pathological changes of osteoarthritis and the effects of Mg^{++} on inflammatory mediators.