



# The Impact of Trace Elements on Osteoarthritis

Guoyong Li<sup>1</sup>, Tao Cheng<sup>2\*</sup> and Xuefeng Yu<sup>1\*</sup>

<sup>1</sup> Department of Orthopaedics, The Fourth Affiliated Hospital of Nanchang University, Nanchang, China, <sup>2</sup> Department of Orthopaedics, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

Osteoarthritis (OA) is a progressive degenerative disease characterized by cartilage degradation, synovial inflammation, subchondral sclerosis and osteophyte formation. It has a multifactorial etiology with potential contributions from heredity, endocrine function, abnormal mechanical load and nutrition. Of particular considerations are trace element status. Several trace elements, such as boron and magnesium are essential for normal development of the bone and joint in human. While cadmium correlates with the severity of OA. The present review focuses on the roles of trace elements (boron, cadmium, copper, iron, magnesium, manganese, selenium, zinc) in OA and explores the mechanisms by which they act.

**Keywords:** trace elements, excess, deficiency, role, osteoarthritis

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### \*Correspondence:

Tao Cheng  
dr\_tao.cheng@hotmail.com  
Xuefeng Yu  
yxf\_1958@sina.com

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## INTRODUCTION

Osteoarthritis (OA) is a prevalent age-related degenerative disease, which is characterized by degeneration of articular cartilage and damage to the other joint tissues (1). The process of OA may begin with some specific parts of joint but ultimately manifests as the whole joint tissue (2). According to the Global Burden of Disease Study 2017, the prevalence of OA is more than three hundred million with the incidence nearly to fifteen million (3). The incidence of OA may continue to accelerate owing to the prevalence of obesity and the increase of life expectancy worldwide (4). Progressive pain and stiffness of the joints, induced by OA, result in poor quality of life (5) and shorten life expectancy of the elderly worldwide (6). It is therefore of global importance to treat this debilitating disease. However, to date, no known ideal method for the treatment of OA is available (7). Consequently, OA has become one of the major health problems for the global aging of the population (8).

OA involves oxidative stress, articular cartilage degradation, synovitis and their interplay (9). During the progression of OA, there are more protein catabolism than anabolism, which causes irreversible changes in the articular cartilage structure. As a result, proteoglycans and collagen fibers were degraded (10). The complex pathogenesis of OA includes the interaction of many factors ranging from genetic predisposition to gene expression changes through mechanical load alteration experienced by articular cartilage (11). Disorders in the molecular repertoires can induce the degradation of articular cartilage and trigger the onset of OA (12).

OA is viewed as a multifactorial disorder with predisposition factors such as heredity, endocrine disorder, age, gender, joint biomechanics, abnormal mechanical load, weight gain, history of joint surgery and nutrition (13–19). During the long-term remodeling, the joint adapts to specific contents of trace elements. Any changes in the trace element level exhibiting in the excess or deficiency in the joint may impair the function of the joint system and predispose the joint to OA (20). The effects of trace elements mainly depend on their type and content. Some trace elements such as boron and magnesium can prevent and treat OA (21, 22). However, exposure to toxic elements like cadmium may result in the onset and

progression of OA (23). The positive or negative effects of trace elements are decided by very narrow concentration range. Trace elements such as copper are beneficial to bones and joints at appropriate concentrations (24). But too low or too high concentrations may trigger OA (25, 26) (Figure 1). This paper reviews the contemporary knowledge of the effects of eight trace elements on OA, and explores their mechanisms in OA (Table 1).

## IMPACT OF EIGHT TRACE ELEMENTS ON OA

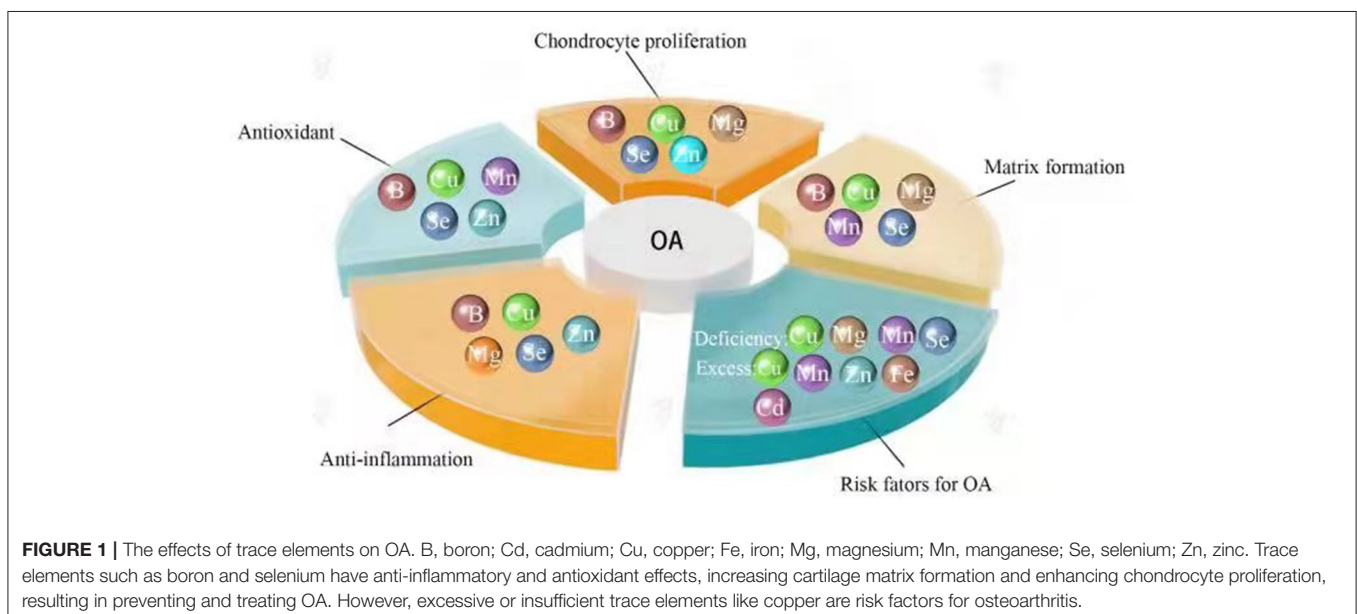
### Boron

Dietary boron supplementation may affect the metabolism of substances such as calcium, magnesium, reactive oxygen species and reactive nitrogen (27, 28). Boron-deficient diets have been linked to OA. Korkmaz et al. (29) have indicated that in areas where boron intakes usually are 1.0 mg or less/day, incidence of OA ranges from 20 to 70%, while the incidence of OA is between 0% and 10% in areas where boron intake is usually between 3 and 10 mg. Serum boron concentration was significantly lower in patients with OA, and negatively correlated with the duration and severity of the disorder (29). Newnham et al. (30) found lower boron contents in the femur heads and synovial fluid from patients with OA as compared to those without this disease.

Oral or intraperitoneal injection of boron is beneficial to rats with induced OA (30). Compared with the placebo group, the boron supplementation trial group obtained significant favorable effects to 6 mg boron/day supplement (30). Pietrzowski et al. (31) have demonstrated that both twice-daily 108 mg dose of calcium fructoborate group and the 216 mg calcium fructoborate in a single dose group exhibited significant improvement in the symptoms of knee OA, while no significant change was found in the placebo group. The intraarticular injection of boron significantly improved the function of patients suffering from

OA (21). Boron can effectively treat OA by relieving pain and discomfort and reducing inflammation (32).

Boron can adjust inflammatory reactions in OA states by downregulating some enzyme activities at the inflammatory sites, inhibiting the inflammatory response, and influencing the production of inflammatory cytokines resulting from cartilage cells and cells involved in the inflammatory reaction (33, 34). C-reactive protein levels are related to OA progression (35). Boron, in combination with plant-derived calcium, such as calcium fructoborate, has been indicated to significantly reduce blood level of C-reactive protein in patients suffering from OA (103). Moreover, boron can inhibit simultaneously both prostaglandins and leukotrienes that are mediators in inflammatory state (104). On the other hand, some boron-compounds, such as calcium fructoborate, boric acid or borax, show promising antioxidant properties. Supplementation of boric acid or borate can improve antioxidant defense mechanism, stimulating activities of superoxide dismutase, glucose-6-phosphate dehydrogenase, catalase, glutathione peroxidase and glutathione-S-transferase enzymes, detoxifying reactive oxygen species and reactive nitrogen, reducing oxidative stress, and lowering DNA damage and lipid peroxidation (36). Furthermore, it has been found that the addition of calcium fructoborate to human diets has beneficial effects on various anti-inflammatory processes. calcium fructoborate regulates macrophage to produce inflammatory mediators, inhibits the development of endotoxin related diseases and suppresses cytokine formation. The anti-inflammatory activity of calcium fructoborate might be owing to the regulation of serine proteases released by inflammation-activated leukocytes: reducing leukotriene synthesis, lowering reactive oxygen species concentration and inhibiting the biosynthesis of arachidonic acid derived pro-inflammatory prostaglandins. Moreover, calcium fructoborate is an effective superoxide ion scavenger with anti-inflammatory activity (33, 37).



**TABLE 1** | Summary table of the effects of boron, cadmium, copper, iron, magnesium, manganese, selenium, and zinc on osteoarthritis.

Element	Function	Mechanism	References
Boron	Supplementation: Preventing OA; Alleviating pain and discomfort; Reducing inflammation; Improve joint function; Repairing osteochondral defects; Deprivation: Decreasing chondrocyte density	Downregulating some enzyme activities; Inhibiting inflammatory response, reducing inflammatory cytokines; Enhancing antioxidant defense; Improving absorption of calcium, phosphorus and magnesium, and retention of calcium and magnesium	(21, 22, 26–35)
Cadmium	Increase risk of OA; Inducing cartilage degradation, resulting in osteophyte formation, subchondral sclerosis, synovitis	Reducing proteoglycan and glycosaminoglycan, inhibiting aggrecan and COL II; Producing IL-1β and IL-6, activating MMPs, destroying ECM; Aggravating homeostasis imbalance; Promoting production of ROS; Displacing essential elements, such as zinc, iron, copper, manganese, nickel, chromium	(36–43)
Copper	Relieving OA symptom; Promoting cartilage injury healing; Enhancing cartilage formation; Promoting articular cartilage and subchondral bone regeneration;  Deficiency: Destroying cartilage integrity; Increasing incidence of OA; Excess: Developing early-onset OA	Activating cartilage immune response; Enhancing anti-inflammatory cytokine secretion, inhibiting inflammatory response, reducing cartilage tissue lesion; Restraining NO release, enhancing anti-catabolism; Improving collagen cross-linking, enhancing COL II synthesis; Increasing chondrocyte viability; Promoting chondrocyte proliferation and maturation; Raising chondrogenic gene expression, enhancing chondrogenesis differentiation of MSCs Impairing cross-linking between collagen and elastin, weakening cartilage	(44–51)  (44, 52–54)
Iron	Excess: Impairing cartilage; Exacerbating pathogenesis and progression of OA	Raising oxidation capacity, damaging joint Releasing pro-inflammatory cytokines, triggering chondrocyte catabolism; Inducing hydroxyl radical driven chondrocyte apoptosis and matrix decomposition; Producing ROS, causing oxidative stress, activating MMPs, degrading ECM, reducing cartilage resistance; Reducing expression of transcripts for COL II and aggrecan, increasing transcriptional counts of pro-inflammatory cytokines, establishing OA-related phenotype	(55, 56) (57–70)
Magnesium	Relieving mechanical allodynia and thermal hyperalgesia; Alleviating pain; Reducing cartilage degeneration and articular cartilage lesion; Retarding OA progression;  Deficiency: Exacerbating progression of OA; Delaying cartilage and bone differentiation; Causing lack of orderly arrangement of chondrocyte columns, reducing bone formation	Inhibiting inflammatory cytokines and neurotransmitters; Reducing chondrocyte apoptosis; Increasing synthesis of cartilage matrix, alleviating degeneration of cartilage matrix, inducing assembly of cartilage matrix, inhibiting expression of inflammatory cytokines and proteases, promoting adhesion of synovial MSCs and collagen, raising adhesion of human synovial MSCs to osteochondral defects; Enhancing formation of chondrocytes from synovial MSCs, promoting chondrocyte proliferation and improving effect of growth factor;  Elevating CRP; Increasing proinflammatory cytokines; Activating of immune response cells; Inducing fibroblasts senescence	(71–80)  (81–85)
Manganese	Relieving OA symptoms, improving imaging indicators; Retarding articular cartilage degeneration, Repairing cartilage; Alleviating OA severity  Deficiency: Causing cartilage dysplasia	Enhancing synthesis of glycosaminoglycan, proteoglycan, and COL II; Regulating metabolism of cartilage matrix; Scavenging oxygen free radical and antioxidant, reducing oxidative stress; Enhancing chondrocyte viability, protecting ECM  Impairing glycosaminoglycan biosynthesis	(86–89)  (90)
Selenium	Enhancing cartilage regeneration, improving repair of metaphyseal injury	Scavenging ROS, improving immune system function, enhancing antioxidant defense, maintaining cartilage homeostasis and redox balance; Blocking expression of pro-inflammatory gene, reducing inflammatory response; Enhancing proliferation and differentiation of chondrogenic progenitor cells; Promoting proliferation of ATDC5 chondrogenic cells	(71–78, 83–85, 91, 92)

*(Continued)*

TABLE 1 | Continued

Element	Function	Mechanism	References
	Deficiency: Causing joint abnormality; Increasing risk for OA	Compromising cartilage metabolism; Inducing articular fibrocartilage formation, causing cartilage degradation; Inhibiting expression of chondrogenic genes SOX9, aggrecan, and COL II, reducing the alkaline phosphatase activity, disturbing chondrogenic differentiation of ATDC5 cells; Influencing chondrogenic differentiation of MSCs, affecting endochondral ossification; Impairing homeostasis of cartilage matrix	(78–80, 93, 94)
Zinc	Alleviating OA symptom; Preventing OA progression	Reducing expression of proinflammatory cytokines, possessing anti-inflammatory activity; Scavenging ROS, exerting antioxidant effect, alleviating oxidative injury; Activating Phosphoinositide 3-kinase (PI3K)-Akt signaling pathway, increasing matrix synthesis, raising chondrocyte survival; Promoting expression of IL-10 mRNA, blocking expression of IL-1 $\beta$ mRNA and MMPs-13 protein, raising IL-10 levels, reducing MMPs-13 and IL-1 $\beta$ ; Increasing chondrocyte proliferation, promoting differentiation of MSCs into chondrocytes, enhancing growth and maturation of cartilage;	(87–90, 95–97)
	Deficiency: Impairing cartilage maturation Excess: Damaging articular cartilage	Inhibiting multiplication of chondrocytes, resulting in chondrocytes disorganization;	(95)
		Up-regulating transcription of IL-6 and IL-11, inducing expression of MMPs, releasing cytokines and MMPs, causing articular cartilage injury and synovium; Activating ZIP8-Zn-MTF1 axis, increasing MMPs-13 synthesis, aggravating cartilage damage	(98–102)

OA, osteoarthritis; COL II, type II collagen; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-6, interleukin-6; IL-11, interleukin-11; ECM, extracellular matrix; MMPs, matrix metalloproteinases; ROS, reactive oxygen species; NO, nitric oxide; MSCs, mesenchymal stem cells; MTF1, metal regulatory transcription factor-1.

In addition, boron is helpful to prevent OA, possibly by enhancing absorption of calcium, phosphorus, and magnesium, and retention of magnesium and calcium (38). Boron can effectively repair osteochondral defects, which may make boron a promising method for the treatment of cartilage injury in OA (21).

## Cadmium

Bone is the main target organ of cadmium accumulation owing to chronic exposure (39). Krachler et al. (40) have indicated that cadmium concentration in serum of patients with OA is 0.114 mg/kg, which exceeds the maximum reference limit without occupational exposure. Cadmium can reduce the content of proteoglycan and glycosaminoglycan and inhibit the expression of type II collagen and aggrecan in the extracellular matrix of articular cartilage (41).

Bodo et al. (42) have observed that the gene expression of matrix metalloproteinase-13, which destroys extracellular matrix, increases after being exposed to a CdCl<sub>2</sub> concentration of 1  $\mu$ M for 3 days. Cadmium can aggravate the homeostasis imbalance in the joint tissue, inducing the cartilage degradation, resulting in osteophyte formation, subchondral sclerosis, chondrocyte apoptosis and synovitis (43).

Martínez-Nava et al. (23) have noted that cadmium exposure may influence negatively the level of essential elements, such as zinc, iron, manganese, nickel, chromium at the cartilage, possibly exacerbating cartilage degeneration due to the reduction of proteoglycan and glycosaminoglycan, which are key components in the extracellular matrix of articular cartilage. Epidemiological studies have showed that exposure to cadmium, may stimulate OA progression due to its ability to

trigger oxidative stress (44, 105). This is because cadmium easily displaces elements such as Fe<sup>2+</sup> and Cu<sup>2+</sup> in the membrane and cytosolic proteins and interacts with the sulfhydryl groups in the mitochondrial membrane proteins and antioxidants, such as catalase, glutathione and superoxide dismutase, thereby promoting the production of reactive oxygen species such as hydrogen peroxide and hydroxyl radicals (41, 45). This results in production of interleukin-1 $\beta$  and interleukin-6, which activate matrix metalloproteinases (MMP-1, MMP-3, MMP-9, MMP-13) that destroy the extracellular matrix and affect the expression of aggrecan and type II collagen (46).

Understanding the mechanisms of cadmium on OA are of great significance for taking prevention measurements when dealing with this metal, preventing consumption of contaminated food and supporting consumption of food rich in antioxidants or essential elements, such as zinc, selenium, iron, which can counteract the harmful effects of cadmium. At present, it is only known that the level of blood cadmium is related to the duration and severity of OA, and the relationship between cadmium and OA has not been widely studied. Hence, the role of cadmium in OA should be further revealed, thereby making a direct impact conducive to preventing and avoiding the pathogenesis and progression of OA.

## Copper

Copper is essential for the normal growth, development and bone health and affects the homeostasis of cellular and humoral immunity. It is an intermediate part of the function of many immune cells and maintains the stability of the body's defense system (47). Copper can promote the regeneration of both articular cartilage and subchondral bone by activating the



immune response of cartilage, which is conducive to the reconstruction of osteochondral interface and the recovery of cartilage lesion (24). The underlying mechanism may be associated with the activation of hypoxia inducible factor (HIF) mediated by copper, then further increasing the transformation of macrophages into macrophage 2 phenotype which enhances the secretion of anti-inflammatory cytokines. Consequently, copper can inhibit the inflammatory response, reduce the damage of cartilage tissue and promote the proliferation and maturation of chondrocytes (48–50). Yassin et al. (51) have demonstrated that the remission degree of OA symptoms in the copper combined with indomethacin group was better than that in the indomethacin group alone, in terms of safety and efficacy parameters, the lowest dose of copper combined with indomethacin synthetic agent is better. The experimental results verify the effective anti-inflammatory role of copper in OA.

Copper functions as a cofactor of some enzymes in cartilage, such as superoxide dismutase, cytochrome C, ascorbate oxidase, and lysyl oxidase. Particularly, lysyl oxidase, a copper-dependent amine oxidase, is a key enzyme for collagen and elastin cross-linking, which further enhances the cartilage formation (24, 106). Furthermore, Amarilio et al. (48) have noted that copper may regulate cartilage homeostasis by modulating activity of hypoxia inducible transcription factor and chondrogenic associated proteins, which is vital for chondrocyte survival. At the same time, copper reduces bone turnover by inhibiting the function of osteoblasts and osteoclasts, which is essential for the maturation of collagen tissue and is conducive to the balance and stability of joint tissue (52). In addition, copper can significantly enhance chondrogenesis differentiation of mesenchymal stem cells. Specifically, copper could promote the cytoskeleton change of mesenchymal stem cells, enhance glycosaminoglycan deposition, and significantly raise the chondrogenic gene expression including Sox9, aggrecan and collagen, resulting in considerable benefits for the application and development of cartilage repair (53).

It should be noted that copper is vital to maintain the integrity and homeostasis of cartilage tissue. The disorder of copper metabolism is closely related to the pathogenesis of OA (54). Copper deficiency results in the disorder of lysine oxidase, which impairs the cross-linking between collagen and elastin, reduces the strength of bone matrix, weakens cartilage, brings about cartilage susceptible to undergo subsequent fragmentation and damages the integrity of cartilage (25, 107, 108). Consequently, copper deficiency could reduce bone strength, impair cartilage integrity and increase the incidence of OA (24). Dietary copper supplementation has been reported to reduce the severity of osteochondrosis and other developmental cartilage lesion, possibly due to improved collagen cross-linking and enhanced synthesis of type II collagen (55). The protective effect of copper on cartilage may be attributable to the anti-catabolism of  $\text{Cu}^{2+}$  that eliminates the decomposition of cartilage matrix proteoglycan by restraining the release of nitric oxide (56). However, it has been found that patients with Wilson's disease, a hereditary disorder of copper metabolism, develop early-onset OA. This early-onset OA correlates closely with the excessive accumulation of copper in Wilson's disease (26). With the

increase of free copper ion content, the oxidation capacity of copper exceeds its own antioxidant capacity, thereby damaging joints (109).

Therefore, the acquired diseases, deficiency or excess of copper in diet result in the change of copper level in human body beyond their own compensation ability, which can also cause certain damage to the joint. Consequently, the effect of copper on OA may be bidirectional. Balanced copper intake undoubtedly exerts a positive effect on OA.

## Iron

Iron is a ubiquitous element that participates in many physiological processes. It can promote collagen synthesis and the conversion of 25 hydroxyvitamin D to its active form (110, 111). Meanwhile, it stimulates the synthesis of bone matrix by activating lysyl hydroxylase, activates 25 hydroxycholecalciferol hydroxylase and supports the mineralization of bone matrix through vitamin D. Díaz-Castro et al. (57) have found that severe iron deficiency results in poor bone mineralization, alters bone microstructure, reduces bone strength, and decreases biochemical markers of bone formation, such as N-terminal peptide of type I procollagen.

However, the beneficial iron concentration window is narrow. Nugzar et al. (58) have noticed that elevated serum ferritin correlates with more severe knee cartilage injury in patients with primary OA. Higher ferritin is associated with narrower joint space (59). Yazar et al. (54) have observed that the iron concentration in synovial fluid of patients with OA is significantly higher than that of patients with rheumatoid arthritis and age-matched healthy subjects. Hereditary hemochromatosis is an iron overload disease in the body. OA is one of the most common complications in patients with hereditary hemochromatosis. Iron overload exacerbates the pathogenesis and progression of OA (60, 61). It is worth noting that osteophytes usually occur in patients with systemic iron overload caused by hemochromatosis (62). The link between osteophyte formation and iron overload may be located in the BMP/SMAD signal pathways shared by transforming growth factor 1 (TGF-1) and iron regulator hepcidin (63). Burton et al. (64) have indicated that systemic iron overload lead to iron accumulation in chondrocytes. Excessive iron is related to the early onset and progression of OA in 12-week-old Strain 13 guinea pigs. These evidences suggest that iron may play a role in the pathogenesis of OA and have a potential mechanical connection between these coinciding conditions.

The role of iron in the pathogenesis of OA has been explored in some studies. Nieuwenhuizen et al. (65) have shown that iron overload synovial cells release pro-inflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor- $\alpha$ , which trigger the catabolism of chondrocytes. In addition, high level of iron has been found in the infrapatellar fat pads of iron overload animals, which is owing to the accumulation in macrophages (111). The infrapatellar fat pad plays an important role in the homeostasis of knee joint (66). It is composed of adipocytes, fibroblasts and leukocytes, which is prone to become a source of inflammatory mediators that may lead to OA (67). Moreover, iron directly affects cartilage by inducing hydroxyl radical driven chondrocyte apoptosis and matrix decomposition

(65, 68). Excessive iron also can produce reactive oxygen species through Fenton or Haber Weiss reaction, resulting in oxidative stress (69). This will over activate matrix metalloproteinases that degrade extracellular matrix, thereby reducing the resistance of cartilage to mechanical stress and exacerbating OA (70).

Chondrocyte exposure to iron raised the expression of matrix degrading enzymes, resulting in decreased synthesis of extracellular matrix. Cartilage degeneration brought with reduced expression of transcripts for aggrecan and type II collagen in iron overload animals (112). The cartilage injury caused by systemic iron overload is also related to the increased transcriptional counts of pro-inflammatory cytokines such as interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  in the cartilage and infrapatellar fat pad (70). Iron overload can destroy the metabolism of chondrocytes and promote the establishment of an OA-related phenotype (112). These changes of gene expression support the increase of OA related lesions in iron overload animals.

However, with the increase of age, due to the lack of the main mechanism of iron excretion in human body and the lack of effective blood circulation in articular cartilage, iron continues to accumulate in cartilage. We can speculate that the degenerative cartilage changes in middle-aged and elderly OA patients may be related to the cartilage damage caused by iron overload in the joint. Because of the complexity of the molecular mechanism of iron metabolism, there is still a relative lack of research on the relevant mechanism and signal molecules of bone and cartilage injury caused by iron overload. Further research is needed to clarify the exact mechanism of joint injury and provide new ideas for developing new strategies to prevent or reverse iron overload related cartilage damage.

## Magnesium

Magnesium is a key cofactor in any reaction driven by adenosine triphosphate (ATP) and acts as a calcium channel antagonist (113). Moreover, magnesium may be a pain mediator by altering the levels of inflammatory cytokines and neurotransmitters in the organism (81). Low-grade systemic inflammation is closely associated with the pathogenesis of OA. Konstari et al. (82) have indicated that low dietary magnesium intake is related to elevated serum C-reactive protein, which is the most sensitive biomarker of inflammation. Some proinflammatory cytokines, such as interleukin-6, tumor necrosis factor- $\alpha$ , increase under the condition of magnesium deficiency. The activation of immune response cells (macrophages, neutrophils, endothelial cells) is also related to magnesium deficiency. Low magnesium may be a contributing factor leading to the progression of OA via inflammatory and immune mechanisms (83, 84). Additionally, Zeng et al. (84) have demonstrated that low magnesium diet intake is related to OA. Magnesium deficiency can lead to delayed cartilage and bone differentiation (85). Hypomagnesemia has been proved to result in the lack of orderly arrangement of chondrocyte columns and reduce bone formation (91).

Ryu et al. (92) have shown that interleukin-6 is an important cytokine in the pathogenesis of OA. Latourte et al. (71) found that the blockade of interleukin-6 signaling pathway could

alleviate OA in mice. Magnesium can significantly inhibit the expression of interleukin-6 in both the cartilage and synovium (72). The serum magnesium level in patients with severe OA was significantly lower than patients with mild OA (73). Serum magnesium concentration may be negatively correlated with knee radiographic OA (74).

A study on juvenile Wistar rats has indicated that magnesium supplementation can reduce articular cartilage lesions. The combination of vitamin E and magnesium has a better protective effect on articular cartilage (75). The degree of cartilage degeneration was significantly lower in OA rats injected with magnesium sulfate than that in OA rats treated with intramuscular normal saline. In OA rats treated with magnesium sulfate, thermal hyperalgesia and mechanical allodynia were relieved, and the chondrocyte apoptosis in OA rats was reduced (22). Shmagel et al. (113) have noticed that magnesium nutritional supplementation could slow down the progression of OA and relieve the pain of affected joints. Intra articular injection of magnesium can alleviate pain and reduce cartilage damage in patients with OA (76).

Magnesium can enhance the formation of chondrocytes from synovial mesenchymal stem cells, promote chondrocyte proliferation and improve the effect of growth factor through continuous effects in the process of cartilage formation (77). Baker et al. (78) have shown that the chondrocytes treated with magnesium sulfate combined with local anesthetic were more viable than those treated with local anesthetic alone. The proliferation and redifferentiation of chondrocytes increased in a dose-dependent manner after the addition of magnesium sulfate. However, with increasing extracellular magnesium concentration, cartilage formation was inhibited (77). Magnesium promoted the adhesion of synovial mesenchymal stem cells and collagen on the first day after administration, and induced the assembly of cartilage matrix 2 weeks after treatment. Moreover, magnesium increased the cartilage matrix synthesis through integrin 1 during the chondrogenesis of synovial mesenchymal stem cells *in vitro* (79). Yao et al. (72) have noted that magnesium can significantly alleviate the degeneration of cartilage matrix *in vivo* and inhibit the expression of inflammatory cytokines and proteases in articular cartilage, which may contribute to the reduction of cartilage degeneration in OA. Additionally, magnesium raises the adhesion of human synovial mesenchymal stem cells to osteochondral defects (79). Magnesium can also influence fibroblasts, more specifically, magnesium deficiency can induce cellular senescence of human fibroblasts (80).

High concentration of extracellular magnesium may suppress the mineralization of mesenchymal stem cells during osteogenic differentiation by magnesium transporter SLC41A1 (93). Magnesium can also promote the proliferation of mesenchymal stem cells and induce osteogenic differentiation by activating Notch1 signal (94). After incubation with high concentration of magnesium, the adhesion of the mesenchymal stem cells to the substrate was enhanced by phosphorylated focal adhesion kinase within the first 24 h. Then, within the next 1–2 weeks, mesenchymal stem cells were programmed to differentiate into cartilage and osteogenesis (77).

The increasing studies have demonstrated that magnesium is a promising treatment for OA. Intra articular injection of magnesium sulfate is an effective method for the treatment of OA (22, 114). However, there are not enough clinical trials to determine the potential therapeutic mechanism responsible. It is necessary to prove the clear mechanism of magnesium in OA and verify the specific method of administration *in vivo*. An in-depth understanding of the mechanism of magnesium in the treatment of OA will provide new discoveries for the self-healing process of cartilage, and design a feasible method to cure early OA.

## Manganese

Manganese is a cofactor for numerous enzymes, including mitochondrial superoxide dismutase, phosphoglucomutase and glycosyltransferase. Glycosyltransferase is involved in the synthesis of glycosaminoglycan, proteoglycan and type II collagen in cartilage extracellular matrix (86). There are high manganese concentrations that range from 1.37  $\mu\text{g/g}$  to 2.21  $\mu\text{g/g}$  in articular cartilage, which is necessary for the normal metabolism of articular cartilage (87).

Manganese can slow down the degeneration of articular cartilage and is beneficial to the repair of articular cartilage. Das et al. (88) have reported that the combined use of manganese, glucosamine and chondroitin can regulate the metabolism of articular cartilage matrix, relieve the symptoms of OA and improve imaging indicators. Manganese deficiency impairs glycosaminoglycan biosynthesis, resulting in cartilage dysplasia characterized by OA and deformity (90).

Oxidative stress has been implicated in the onset and progression of OA. Manganese dioxide has strong antioxidant capacity by scavenging oxygen free radical, which can reduce the oxidative stress of articular cartilage caused by inflammation and alleviate OA severity without the adverse effects of chronic use of pain medication. Moreover, Manganese dioxide can enhance chondrocyte viability and protect extracellular matrix (89). Thus, manganese dioxide can serve as a promising approach for cartilage protection in OA.

## Selenium

Selenium supplement has become an indispensable part in the process of health care for many people (95). Significant health benefits have been attributed to selenium which exerts important role in the thyroid hormone metabolism, male reproduction, immune function, anti-inflammation and free radical detoxification (96–100). However, selenium deficiency is related to impaired immune system and increased susceptibility to various diseases such as OA (101, 102, 115). Some studies have indicated detrimental effects of selenium deficiency, such as growth retardation, compromised bone and cartilage metabolism, joint abnormalities (116, 117). Mice fed a selenium deficient diet induced articular fibrocartilage formation, eventually resulting in articular cartilage degradation (118). Selenium level in the serum of patients with OA is significantly lower than that of normal controls (119). Likewise, Jordan et al. (120) have showed the link between low selenium contents in toenails and OA related pain and disease severity. It is apparent that selenium deficiency may be a potential risk factor for OA.

Several studies have shown that oxidative load accumulates in chondrocytes undergoing changes in OA (120, 121). The harmful effects of reactive oxygen species on cartilage homeostasis can be effectively relieved by enhancing cellular antioxidant activity, and OA can be treated through targeting the regulatory factors involved in cartilage oxidative stress (122, 123). The abnormal production of reactive oxygen species and the impairment of cellular antioxidant capacity result in oxidative stress. Selenium is incorporated into selenoprotein for forming the active site of selenoenzymes. One of selenoenzymes is glutathione peroxidase, which is involved in scavenging reactive oxygen species (124). Meanwhile, selenium can protect chondrocytes from oxidative injury. The protective effect of selenium on cartilage is mainly attributed to antioxidant defense function (125). Additionally, selenium appears in the form of selenomethionine, which can block the expression of pro-inflammatory gene induced by interleukin-1 $\beta$ , thereby reducing the inflammatory response (126).

Selenium plays beneficial roles on enhancing proliferation and differentiation of chondrogenic progenitor cells (127). The ATDC5 cell line is originated from mouse teratoma cells and characterized by a chondrogenic cell line, which experiences a sequential process similar to chondrocyte differentiation. ATDC5 chondrocytes are differentiated from ATDC5 cell line (128). Selenium supplementation promoted the proliferation of ATDC5 chondrogenic cells by inducing the expression of cyclin D1, even under serum deprivation (129). Selenium deficiency disturbed the chondrogenic differentiation of ATDC5 cells by inhibiting the expression of chondrogenic genes SOX9, aggrecan, and type II collagen and reducing the alkaline phosphatase activity (130). Consistent with the impacts of selenium and selenoprotein on chondrogenic progenitor cells observed *in vitro*, deficient intake of selenium seriously influenced chondrogenic differentiation of mesenchymal stem cells, thereby affecting the endochondral ossification of mice (116). Sun et al. (131) have shown that selenium deficiency impairs the homeostasis of cartilage matrix. Low selenium decreased the expression level of type II collagen regulated by SOX9, which is known as the main regulator required for keeping cartilage matrix homeostasis. Selenium deficiency stimulated the expression of the chondrocyte hypertrophy marker gene type X collagen in the articular cartilage (116). The expression of parathyroid hormone related protein (PTHrP), which inhibits chondrocyte maturation in the period of endochondral ossification, increased in the hypertrophic growth plate and articular cartilage following selenium deficiency (132).

Selenium can improve the antioxidant activity of chondrocytes under oxidative stress, scavenging reactive oxygen species, reducing the adverse effect of reactive oxygen species on cartilage homeostasis, relieving the cartilage damage induced by oxidative stress, thereby protecting cartilage. Moreover, selenium can enhance cartilage regeneration, improve the repair of metaphyseal injury, and increase the proliferation and differentiation of cartilage progenitor cells. In addition, selenium can improve immune system function, enhance antioxidant defense, and maintain cartilage homeostasis and redox balance. Therefore, strategies aimed at optimizing the role of selenium should be considered in the prevention and treatment of OA, and

selenium supplementation plans should be carefully formulated to enhance the benefit of selenium in OA.

## Zinc

Zinc is a component of more than 300 enzymes and participates in synthesis of protein, DNA and RNA by zinc finger proteins (133, 134). Zinc is also involved in oxidative stress, homeostasis, immune responses, aging and apoptosis (135, 136). Moreover, zinc is a co-factor of superoxide dismutase (SOD), an inducer of metallothionein, and an inhibitor of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. It is essential for antioxidant defense and suppressing prostaglandin synthesis (137, 138). Moreover, zinc, which is known as zinc signal, is regarded as a regulator in immunity and redox metabolic signaling pathways (139). Zinc enhances the growth and maturation of cartilage, improving the activity of vitamin D and stimulating synthesis of metallothionein (85). Zinc has additional benefits in promoting the differentiation of mesenchymal stem cells into chondrocytes in osteochondral defects (140). Rodríguez and Rosselot (141) have demonstrated that low dose of zinc ( $<0.5\mu\text{M}$ ) can increase the cultured chondrocyte proliferation by 40–50%. While dietary zinc deficiency inhibits the multiplication of chondrocytes and leads to chondrocyte disorganization, which may be associated with matrix metalloproteinase disorder (142).

Glutathione is the first line of defense against oxidative injury and can scavenge reactive oxygen species. The reactive oxygen species catalyze the production of hydrogen peroxide from oxygen anions, which is subsequently decomposed into water by glutathione peroxidase or catalase. All of these are called the intracellular antioxidant defense systems (143). Kloubert et al. (144) have noticed that zinc is necessary for the activation of these defense enzymes. Zinc exerts anti-inflammatory effect through reducing the expression of proinflammatory cytokines, which can alleviate OA (145). Moreover, zinc supplementation significantly promotes the expression of interleukin-10 mRNA and blocks the expression of interleukin-1 $\beta$  mRNA and matrix metalloproteinases-13 protein, thereby massively raising serum interleukin-10 levels and reducing matrix metalloproteinases-13 and interleukin-1 $\beta$  levels (146). Interleukin-10 disturbs the secretion of proinflammatory cytokines and decreases the production of matrix metalloproteinases in chondrocytes (147). Additionally, nuclear factor erythroid 2-related factor (Nrf2) is a main regulator of antioxidant defense genes that can adjust the redox disorder by the upregulation of responsive antioxidant enzymes (148). The activation of the Phosphoinositide 3-kinase(PI3K)-Akt signaling pathway can increase matrix synthesis and raise chondrocyte survival (149). Zinc may enhance nuclear factor erythroid 2-related factor(Nrf2) expression and promote the upstream active regulator, Phosphorylated-Akt (p-Akt) expression, showing that the Phosphoinositide 3-kinase(PI3K)-Akt/nuclear factor erythroid 2-related factor(Nrf2) pathway is associated with the zinc actions (150). Huang et al. (133) revealed that zinc supplementation

of 1.6 mg/kg/day was sufficient to prevent the progression of OA, while zinc supplementation of 8.0 mg/kg/day had no better effect.

However, zinc overload damages articular cartilage, for example, increased levels of zinc ion, ZIP8 protein and its related mRNA are common in OA articular cartilage. zinc participates in zinc finger protein Zc1 up-regulating the transcription of interleukin-1 $\beta$  through interleukin-1 family proteins, which directly induces the expression of matrix metalloproteinase. The release of cytokines and matrix metalloproteinases causes the injury of articular cartilage and synovium (151, 152). Moreover, when the ZIP8-Zn-MTF1 (metal regulatory transcription factor-1) axis is activated, the increased synthesis of matrix metalloproteinase-13 will aggravate the cartilage damage of OA (151, 153). In addition, the overexpression of ZIP8 results in the increase of zinc influx in chondrocytes, which enhances the activity of zinc dependent matrix metalloproteinases, inducing cartilage rupture. The cartilage fragments resulting from these enzymes are subsequently recognized as danger signals by immune cells, which triggers intimal inflammation, known as synovitis, which feedbacks to further exacerbate the response (154).

## CONCLUSIONS

Osteoarthritis (OA) is a degenerative joint disease, with an age-associated increase in both incidence and prevalence. The hallmark of OA is pathological changes of the joint structure, such as cartilage erosion and synovial inflammation. So far, no efficient treatment can alter the pathological progression of OA. The current therapy roughly include pharmaceutical and non-pharmaceutical approaches prior to surgical intervention. However, its morbidity cannot be reduced using these measures, suggesting non-pharmaceutical prevention may be achieved by lifestyle and nutrition. As described in this article, OA is associated with trace elements in the environment, which can be essential, deleterious, or both, depending on the type and level of trace elements (Table 1). Undoubtedly, many trace elements affect the onset and progression of OA. Some trace elements such as boron and magnesium are conducive to the prevention and treatment of OA. By contrast, other trace elements like cadmium are toxic even at low concentrations and can induce OA. Furthermore, it is worth noting that some trace elements are dose-dependent, and the safe concentration range of these trace elements is narrow. Deficiency or excess of trace elements such as copper may bring about OA (Figure 1). To a certain extent, the status of trace elements depends on the external environment (nutrition) and internal factors (individual absorption and metabolism of trace elements, genetic tendency, age and gender). The roles of trace elements depend not only on their content, but also on the interaction among them. Though recent advances in knowledge in this area, much remains to be discovered to fully elucidate the effects of trace elements on OA. The protective effects of selected trace elements on OA have been found. However, theoretical and practical issues



of supplementation in the prevention and treatment of OA are still unknown. Data concerning the impact of individual trace element is limited, partly due to the obtainment of these elements in combination. Additionally, the homeostasis of trace elements in organisms depends on various factors such as diet, age and gender. Further studies are required for confirming the effects of different doses, concentrations and interactions of individual trace element on OA, thereby, preventing and treating OA.

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## AUTHOR CONTRIBUTIONS

All authors have contributed to the design, interpretation of data, writing, and supervision of the final version of this manuscript.

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