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REVIEW

Meta-analysis of the Relationship Between Zinc and Copper in Patients with Osteoarthritis

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Abstract

This study aims to explore the relationship between osteoarthritis and the trace elements zinc and copper and to provide a theoretical basis for research on the related mechanisms for the prevention, diagnosis, and treatment of osteoarthritis. We searched all the literature indexed in Web Of Science, Embase, and PubMed as of January 10, 2024, summarized the zinc and copper detection indexes in patients with osteoarthritis, obtained clinical data through literature screening, quality assessment, and data extraction, and analyzed the data using Revman 5.4. A total of 13 papers were included in this study, totaling 7983 study subjects. These were divided into osteoarthritis and healthy control groups. The results from the meta-analysis showed that in patients with osteoarthritis, circulating copper levels, but not zinc levels, were significantly higher compared to healthy individuals. The level of copper in the blood of patients with osteoarthritis is significantly higher than that of healthy people.

Keywords Osteoarthritis · Zinc · Copper · Trace element

Introduction

Osteoarthritis (OA) is a common chronic degenerative inflammatory joint disease. Clinical symptoms include joint pain, morning stiffness, and limited joint mobility. In 2021, a study found that more than 22% of adults over the age of 40 were suffering from OA of the knee, and it is estimated that more than half a billion people around the globe are currently affected by OA [1]. Thirty-seven percent of people aged 60 or older who participated in the National Health and Nutrition Examination Survey (based on radiographic examinations) had knee OA [2]. Factors that affect OA include aging, metabolism, infections, genetics, exercise, and other triggers [3]. More women than men are affected by OA, and the prevalence of OA is projected to increase as the population ages, placing a significant economic burden on the health and social care system [4, 5].

Zinc (Zn) and copper (Cu) can influence OA onset and progression since they play an important role in bone and cartilage metabolism, immunity, inflammation, and antioxidant defense. It was confirmed that Zn^{2+} ions could promote the proliferation of bone marrow stromal cells and bone formation in a rat model of bone defect [6]. Huang et al. found that Zn supplementation prevents cartilage degradation and inhibits OA progress both in vitro and in vivo [7]. Endogenous Zn levels impact the quantity and functionality of immune cells, including macrophages, T cells, and B cells [8]. Consequently, the activation of these immune cells can result in the release of pro-inflammatory cytokines, such as interleukin 1, interleukin 6, and tumor necrosis factor, which can lead to joint damage caused by inflammation [9]. Similar to Zn, Cu significantly facilitated the regeneration of cartilage and prevented the development of OA [10]. The underlying mechanism may be associated with Cu reducing the inflammatory response, decreasing the damage of cartilage tissue, and promoting the proliferation and maturation of chondrocytes [11]. In addition, Cu–Zn superoxide dismutase plays a protective role in various types of tissue, protecting them from oxidative damage, which is closely related to inflammatory diseases [12].

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However, high concentrations of Zn and Cu may accelerate the progression of OA [13]. Zhou et al., using the genome-wide analysis, found that genetically high Zn and Cu status were positively associated with OA [14]. Chang et al. found that the expression of five cuproptosis-related genes (FDX1, LIPT1, PDHA1, PDHB, and CDKN2A) was significantly increased in the OA synovium [15]. Ciaffaglione et al. suggest that dysregulation of metal homeostasis is associated with arthritis, and serum levels of Zn and Cu are commonly altered in patients with arthritis [16]. Some clinical trials have demonstrated that patients with OA of the knee also have significantly higher levels of Zn and Cu in their urine than normal subjects, and the determination of urinary levels of trace elements may prove to be informative for the early diagnosis of OA of the knee [17]. Another study reported that among the serum elements, K, Cr, Mn, and Zn showed the strongest negative correlation with joint disease, while Ca, P, Mg, Zn, and Cu showed a positive correlation [18]. However, it has also been proposed that bone metabolism and levels of trace elements such as Zn and Cu change at each stage of degenerative disease [19]. Of course, the concentration of Zn and Cu in the bones of OA depends on many factors, including age, sex, living environment, seafood and fish diet, and physical activity [20]. Although Zn and Cu levels appear to be associated with an increased risk of OA, inconsistencies between the results of previous studies have blurred the current clear recommendations. Meta-analysis is an important tool for revealing trends that may not be apparent. Therefore, we conducted a comprehensive and critical meta-analysis of these studies in order to draw clearer and evidence-based conclusions about the relationship between elemental Zn and Cu levels in OA and OA.

Method

Search Strategy

We searched all written articles indexed in Web Of Science, Embase, and PubMed as of January 10, 2024. The search terms were as follows: (osteoarthritis) and (zinc or copper). The reference list of all eligible studies was screened to identify potentially eligible studies. If necessary, emails were sent to the authors of the identified studies for additional information, and clinical data were obtained through literature screening, quality assessment, and data extraction.

Inclusion Criteria

(1) The study cases were clearly diagnosed as OA patients by doctors' clinical symptoms; (2) the type of study was a case–control study or a cohort study; (3) a study about the relationship between Zn, Cu, and OA; (4) the language was Chinese or English.

Exclusion Criteria

The exclusion criteria are as follows: (1) animal studies, in vitro or laboratory studies; (2) reviews, case reports, conference reports, repetitive literature; (3) those with incomplete or unextractable data for the information; (4) studies that did not provide Zn or Cu levels in patients with OA; (5) subjects with major medical conditions or medication intake that severely interfered with Zn or Cu levels; (6) articles of poor quality (NOS scores < 5).

Search Results

Firstly, the literature was searched according to the keywords, and a total of 1449 pieces of literature were obtained. Preliminary screening of relevant literature was done by reading titles, abstracts, etc., except reviews, animal studies, conference reports, case reports, etc., and then duplicate literature was removed. After that, carefully read the full text through, screen the eligible literature according to the inclusion and exclusion criteria, and check the references, retaining the literature that meets the inclusion conditions of 13 articles as shown in Fig. 1.

Quality Evaluation of Literature

The quality of the included literature was evaluated using the NOS score. The total score of the NOS score was 9 points. If the NOS score was < 5 points, the literature was rejected as being of too low quality. If the NOS score ≥ 5, the literature was considered of good quality and the literature was included in the study (Table 1). The included studies were also assessed using the Cochrane risk of bias tool, which was carried out independently by two researchers (Fig. 2). If there was a high risk in the included literature, it would be excluded.

Data Collation and Analysis

Revman 5.4 software was used to analyze the data statistically. Heterogeneity was analyzed by Cochrane Q test and I2 evaluation: when the results suggested $P > 0.1$ and $I^2 < 50\%$, the fixed effect model (FE) was selected, and when the results suggested $P < 0.1$, $I^2 > 50\%$, the random effect model (RE) was selected, and possible heterogeneity influencing factors were searched for by subgroup analysis. Zn and Cu levels were expressed using mean ± SD, and when the unit of measurement was inconsistent, the combined effect sizes should be described using standardized mean difference (SMD) and 95% confidence interval (95% CI), with $P < 0.05$ indicating that the difference was statistically significant.

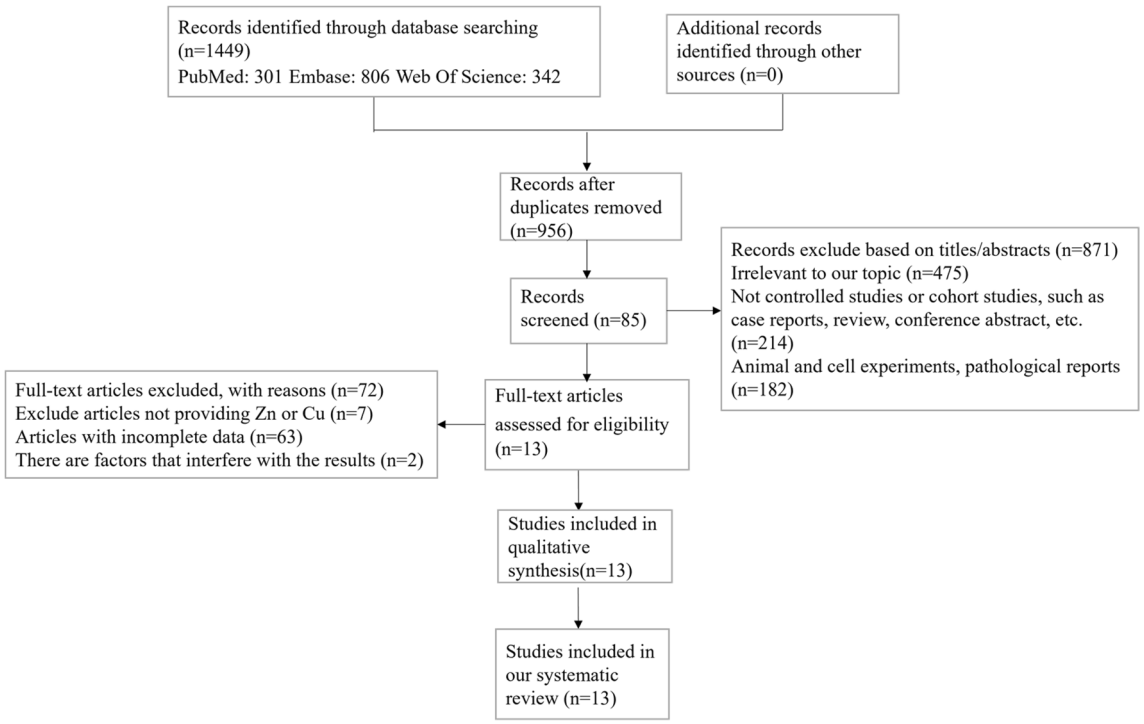

Fig. 1 Document retrieval process

Table 1 NOS quality scores for included studies

Study	Population selectivity	Comparability between groups	Results/exposure factors	NOS
[21] Kennedy, A. C. et al. (1978)	3	1	3	7
[22] Scudder, P. R. et al. (1978)	3	1	1	5
[23] Marrella, M. et al. (1990)	3	2	1	6
[24] Krachler, M. et al. (2000)	3	1	1	5
[25] Yazar, M. et al. (2005)	4	1	1	6
[26] Zioła-Frankowska, A. et al. (2015)	4	2	1	7
[27] Wang, S. et al. (2016)	4	1	1	6
[28] Roczniak, W. et al. (2017)	4	1	1	6
[29] Dabrowski, M. et al. (2021)	4	2	1	7
[30] Amerikanou, C. et al. (2023)	4	1	1	6
[31] Guan, T. et al. (2023)	4	1	2	7
[32] Li, Y. et al. (2023)	4	1	2	7
[33] Yang, WM. et al. (2023)	4	2	2	8

Characteristics of the Study

These 13 studies were conducted in the UK, Italy, Poland, Germany, Denmark, China, and the USA, with a total sample size of 7983. Zn and Cu levels were measured in a variety of ways, including serum, plasma, articular fluids, and bone tissues, as summarized in Table 2 and Fig. 3, and clinical diagnosis was made using the Kellgren and Lawrence classification (K&L) and the American College of Rheumatology (ACR) OA clinical and radiological criteria [34, 35]. Besides OA, 3 studies also include rheumatoid arthritis (RA). Although there are relatively few studies with the same indicators and control groups, each of them has shown that Zn and Cu levels in the body are strongly associated with OA and that the metal elements in different locations vary with increasing degrees of OA.

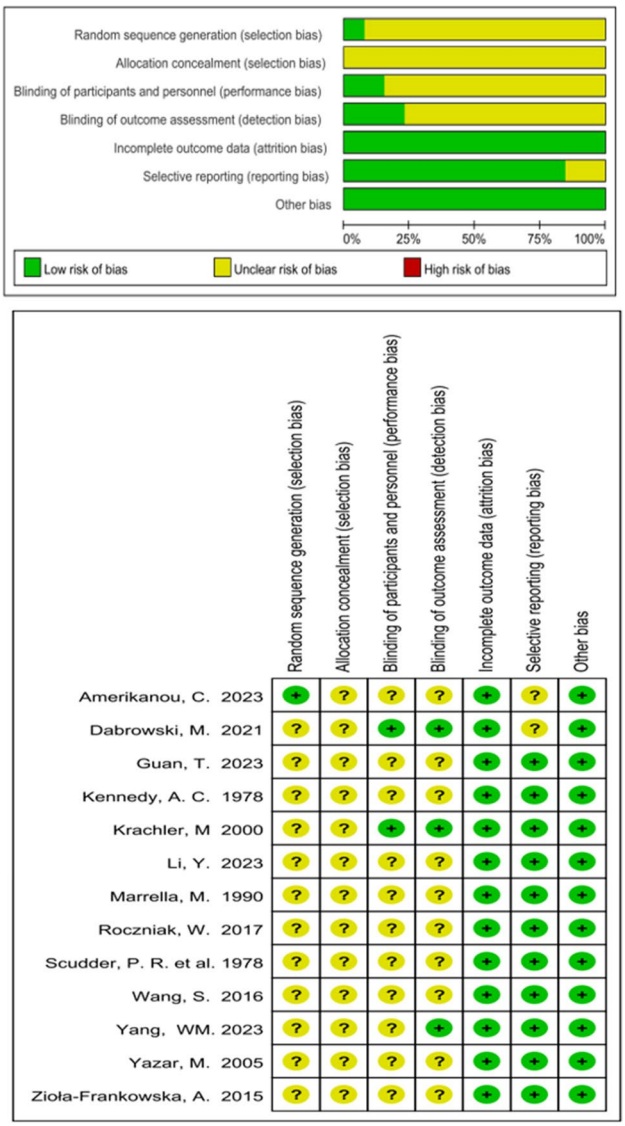

Fig. 2 Risk of bias

Results

Relationship Between Zn/Cu in Serum and OA

Data from 3 included studies were selected to compare serum Zn and Cu levels in OA patients and healthy controls. As shown in Fig. 4A ($P = 0.99 > 0.1$, $I^2 = 0\% < 50\%$), no obvious heterogeneity was found in the included articles, and the FE model was selected. The results showed that there was no significant difference in serum Zn levels in OA patients compared with healthy controls (SMD = −0.23; 95% CI = [−1.28, 0.82]; $P = 0.67$; Fig. 4A). Figure 4B ($P = 0.67 > 0.1$, $I^2 = 0\% < 50\%$) also suggests that there was no heterogeneity between these studies and the FE model was chosen. However, serum elemental Cu levels were significantly higher in OA patients than in the CO group (SMD = 4.17; 95% CI = [2.32, 6.03]; $P < 0.0001$; Fig. 4B).

Relationship Between Zn/Cu in Plasma and OA or RA

Data from 3 included studies were selected to compare plasma Zn and Cu levels in OA patients, RA patients, and healthy controls. As shown in Fig. 5A ($P = 0.89 > 0.1$, $I^2 = 0\% < 50\%$), there was no heterogeneity between these studies, and the FE model was selected. The results showed that there was no significant difference in plasma Zn levels in OA patients compared to RA patients (SMD = 0.63; 95% CI = [−1.72, 2.97]; $P = 0.6$; Fig. 5A). Next, we compared plasma Cu levels between the OA and healthy groups ($P = 0.53 > 0.1$, $I^2 = 0\% < 50\%$; Fig. 5B). There was no heterogeneity between these studies, and the FE model was chosen. However, plasma elemental Cu levels were significantly higher in the OA patients than in the CO group (SMD = 10.05; 95% CI = [0.17, 19.93]; $P = 0.05$; Fig. 5B). Finally, we observed the plasma Cu levels in the OA and RA groups ($P = 0.18 > 0.1$, $I^2 = 45\% < 50\%$; Fig. 5C). There was no heterogeneity among these studies, and the FE model was selected. The results showed (SMD = −23.50; 95% CI = [−32.06, −14.93]; $P < 0.00001$; Fig. 5C) that RA patients had significantly higher plasma Cu concentrations than OA patients. Overall, the plasma Cu concentration shows a trend of RA > OA > CO.

Relationship between Zn/Cu in synovial fluid and OA or RA

The concentration of Zn and Cu in synovial fluid of OA patients, RA patients, and healthy individuals is shown in Table 3. Yazar et al.'s [25] results show that both Zn and Cu levels in synovial fluid significantly increase in OA or RA patients compared to the CO group and exhibit a trend of RA > OA > CO. Similarly, Scudder et al.'s [22] results also show Cu levels in the synovial fluid of RA patients are higher than those of OA patients. In addition, Li et al. [32] found that the Cu level in the synovial fluid of severe OA patients was higher than in mild patients. Taken together, the Cu level in the synovial fluid of OA patients was generally raised, but further observation is still needed.

Relationship Between Zn/Cu in Different Bone Tissues of OA

Data from 2 included studies were selected to compare differences in Zn and Cu levels in the femoral head and neck of patients with OA. It was assessed that there was no heterogeneity between studies ($P = 0.62 > 0.1$, $I^2 = 0\% < 50\%$; Fig. 6A), and the FE model was chosen. The results showed that (SMD = 2.76; 95% CI = [−0.56, 6.08]; $P = 0.1 > 0.05$;

Table 2 General information about the included literature

Study	Country	Type of study	osteoarthritis	Detection index	Subjects
[21] Kennedy, A. C. et al. (1978)	UK	Case–control study	Clinician diagnosis of OA	Plasma Zn	OA ($n=5$) RA ($n=6$)
[22] Scudder, P. R. et al. (1978)	UK	Case–control study	Clinician diagnosis of OA	Synovial fluid Cu	OA ($n=40$) RA ($n=40$)
[23] Marrella, M. et al. (1990)	Italy	Case–control study	Clinician diagnosis of OA	Plasma Cu	OA ($n=26$) RA ($n=77$) CO ($n=25$)
[24] Krachler, M. et al. (2000)	Germany	Case–control study	NA	Synovial fluid/Serum (Zn, Cu)	OA ($n=16$)
[25] Yazar, M. et al. (2005)	Denmark	Case–control study	Clinician diagnosis of OA	Synovial fluid/Serum (Zn, Cu)	OA ($n=25$) RA ($n=25$) CO ($n=25$)
[26] Zioła-Frankowska, A. et al. (2015)	Poland	Cohort study	NA	Femoral head/neck (Zn, Cu)	OA ($n=96$)
[27] Wang, S. et al. (2016)	China	Cohort study	Clinician diagnosis of OA	Serum Zn	OA($n=563$) CO($n=555$)
[28] Roczniak, W. et al. (2017)	Poland	Cohort study	NA	Tibia/Femur/Meniscus (Zn, Cu)	OA ($n=50$)
[29] Dabrowski, M. et al. (2021)	Poland	Cohort study	NA	Femoral head/neck (Zn, Cu)	OA ($n=58$)
[30] Amerikanou, C. et al. (2023)	Greece	Case–control study	Clinician diagnosis of OA	Plasma Cu	OA ($n=34$)
[31] Guan, T. et al. (2023)	USA	Cohort study	medical conditions questionnaire	Serum (Zn, Cu)	OA($n=514$) CO($n=1660$)
[32] Li, Y. et al. (2023)	China	Case–control study	Clinician diagnosis of OA	Synovial fluid (Zn, Cu)	OA ($n=33$)
[33] Yang, WM. et al. (2023)	USA	Cross-sectional study	Medical conditions questionnaire	Serum (Zn, Cu)	OA ($n=525$) RA ($n=123$) CO ($n=3462$)

NA means not acquired, RA means rheumatoid arthritis, CO means control group or healthy person

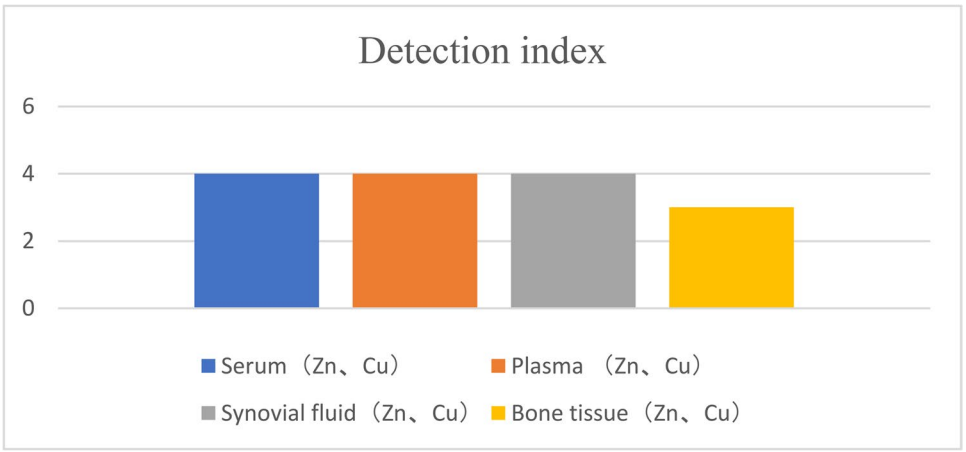

Fig. 3 Detection index of the included studies

Fig. 6F) there was no significant difference in the Zn level in the bone tissues of the femoral head of the patients with OA compared with the femoral neck. The level of Cu in the bone tissues in the femoral head of OA patients and the femoral neck was compared using the FE model ($P=0.20>0.1$, $I^2=39\%<50\%$; Fig. 6B), and there was no significant difference between them (SMD = −0.19; 95% CI = [−0.39, 0.02]; $P=0.07>0.05$ Fig. 6B). Of course, this may be related to the relatively small amount of clinical research literature. From Table 4, we can see that there is more and less Cu content in the femoral head and neck, and there is a conflict between the data of the two literature, which may also be related to the material taken (there will be a difference between the same metal in cortical and cancellous bone) [36, 37].

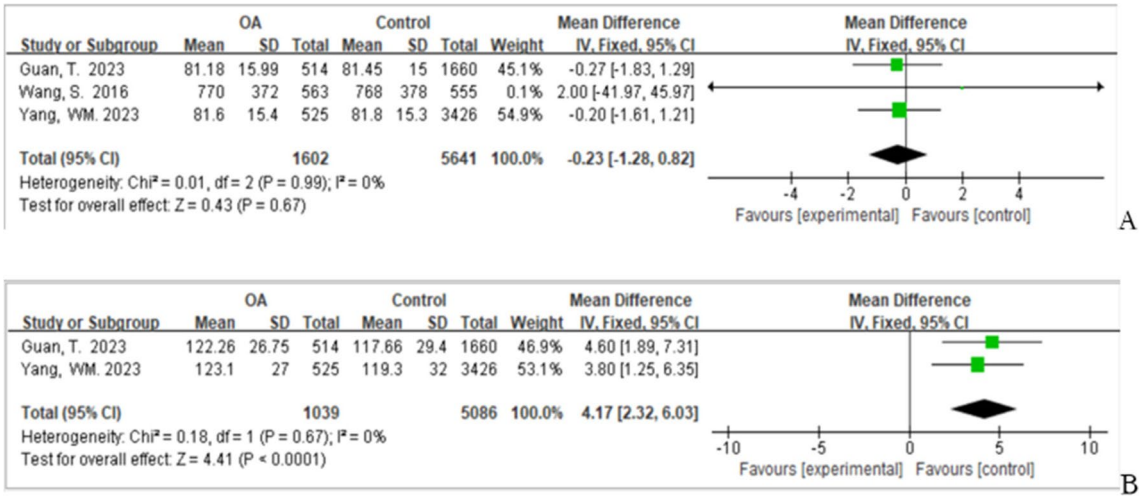

Fig. 4 Forrest plot showing serum (Zn and Cu) levels in OA and healthy control (**A** Serum Zn. **B** Serum Cu)

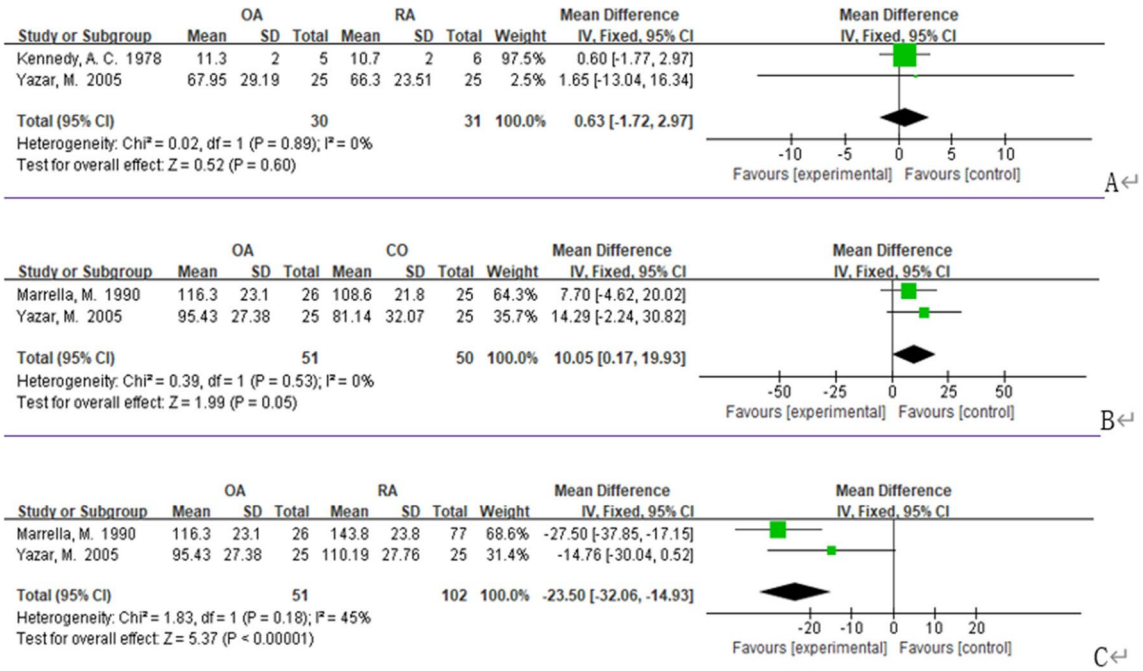

Fig. 5 Forrest plot showing plasma (Zn and Cu) levels in OA, RA, and healthy control (**A** Plasma Zn levels in OA and RA. **B** Plasma Cu levels in OA and healthy control. **C** Plasma Cu levels in OA and RA)

Publication Bias

The publication bias is analyzed by Revman 5.4 software, and the results are shown in Fig. 7. Several clinical studies included were roughly symmetrically distributed, so it can be assumed that the possibility of publication bias in the included literature is unlikely.

Discussion

With the further aging of the population, the number of people suffering from OA is still on the rise and poses a huge economic burden on the community's medical and nursing care [38, 39]. There is a growing body of research on the amount of Zn and Cu in the bone, but there is limited research on OA and the amount of Zn and Cu micronutrients

Table 3 Zn/Cu relationship in OA and RA synovial fluid

Study	Detection index	Control/ Experiment	Results (mean ± SD)	Units
[22]	Synovial fluid Cu	OA/RA	7.7±3.0/13.8±4.8	μmol/L
[24]	Synovial fluid Zn	OA	327±152	μg/kg
	Synovial fluid Cu		441±219	
[25]	Synovial fluid Zn	OA/RA/CO	15.61±13.12/17.00±7.48/ 11.41±5.55	μgr/dL
	Synovial fluid Cu		48.54±28.51/56.6±34.81/ 28.08±7.10	
[32]	Synovial fluid Zn	OA：Mild /Severe group	0.393±0.158/0.396±0.19	mg/L
	Synovial fluid Cu		0.291±0.108/0.366±0.085	

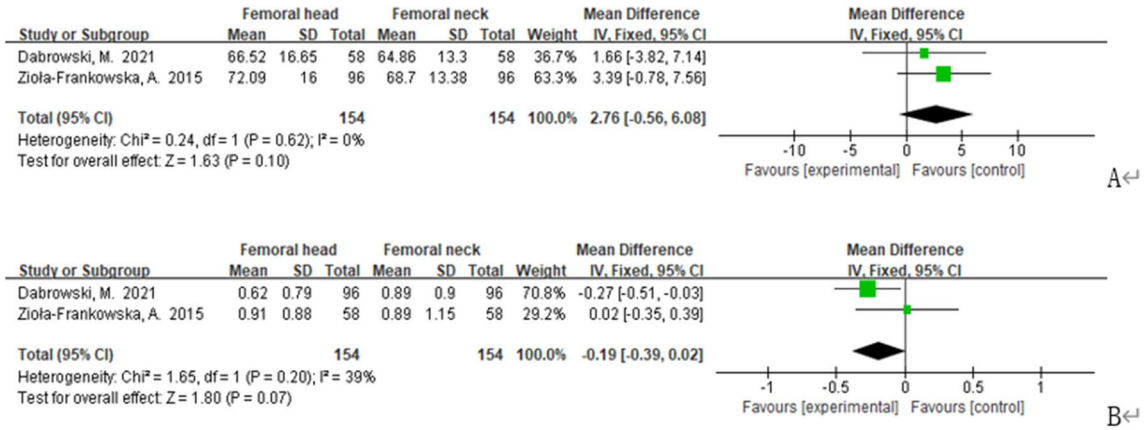

Fig. 6 Forrest plot showing bone tissue (Zn and Cu) levels in OA (**A** Zn, **B** Cu)

in the body. Zn and Cu elements affect joint growth and development. The main finding of this study is that changes in copper elemental levels are closely related to OA. The bone acts as a target organ for trace elements, causing them to bioaccumulate in the bone or become storage sites for trace element homeostasis [40]. Due to slow bone reconstruction, the bone is in a constant state of dynamic equilibrium in terms of composition and structure, and the bone and connective tissue differ in terms of micronutrient content.

It demonstrated that IL-17/TNF-mediated inflammation enhanced the uptake of intracellular Zn by synoviocytes, further increasing inflammation, and these observations suggest a feedback loop between inflammation and Zn uptake [41]. Zn homeostasis affects chondrocyte matrix synthesis and proliferation, and the level of response is related to the source of the chondrocyte (growth plate versus articular cartilage), the stage of development (fetal, neonatal, or adult), and the culture method used. It is now well established that changes in Zn levels are closely related to pathological changes in cartilage [42]. Endochondral ossification is the primary developmental mechanism for bone formation and normal postnatal bone growth. Zn promotes bone regeneration either through endochondral ossification or by directly stimulating bone formation (intramembranous ossification) [43]. Frangos and Maret found that two classes of Zn transporter proteins, the ZIP, and ZnT families, with a total of 24 proteins, regulate cytosolic Zn in humans. ZIP transporter proteins deliver zinc from the extracellular fluid or intracellular vesicles to

Table 4 Bone tissue (Zn, Cu) and OA

Study	Detection index	Control/ experiment	Results (mean ± SD)	Units
[26]	Femoral head/neck Zn ——— Femoral head/neck Cu	OA	72.09±16/68.7±13.38 ——— 0.91±0.88/0.89±1.15	mg/kg
[28]	Tibia/Femur/Meniscus Zn ——— Tibia/Femur/Meniscus Cu	OA	93.53±19.89/77.62±41.74/21.35±25.59 ——— 0.45±0.36/0.93±1.66/0.83±0.29	mg/kg
[29]	Femoral head/neck Zn ——— Femoral head/neck Cu	OA	66.52±16.65/ 64.86±13.3 ——— 0.62±0.79/ 0.89±0.9	mg/kg

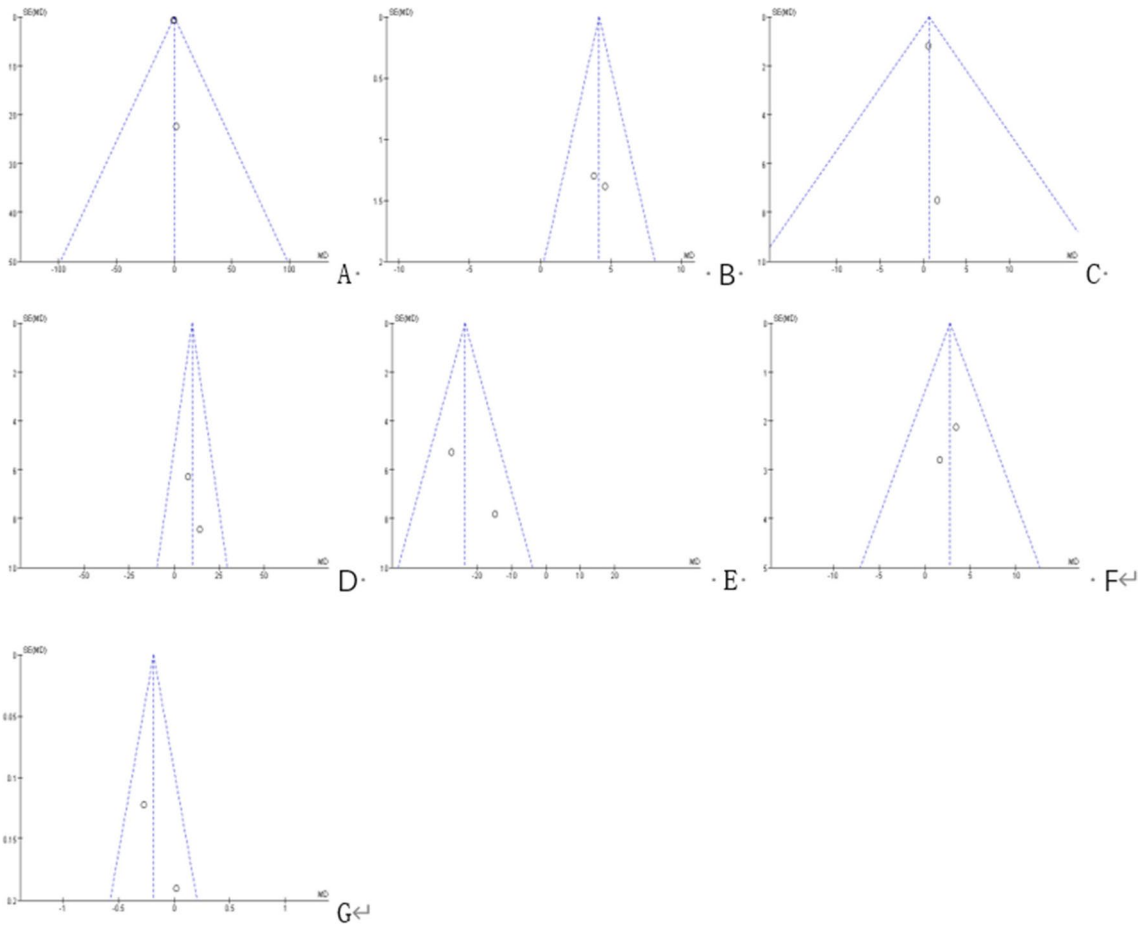

Fig. 7 Funnel plots detecting publication bias. **A** Funnel plots of serum Zn levels in OA and CO. **B** Funnel plots of serum Cu levels in OA and CO. **C** Funnel plots of plasma Zn levels in OA and RA. **D** Funnel plots of plasma Cu levels in OA and CO. **E** Funnel plots of plasma Cu levels in OA and RA. **F** Funnel plots of bone tissue Zn levels in OA. **G** Funnel plots of bone tissue Cu levels in OA

the cytoplasm, whereas ZnT transporter proteins promote the outward movement of Zn into the extracellular space or sequester cytoplasmic Zn into the intracellular compartment [44]. When inflammation occurs, it triggers an acute phase reaction, which results in a decrease in Zn in the blood; however, no significant difference was found in this study. From Tables 3 and 4, we found that most of the OA group had a slight decrease in blood Zn levels compared to the CO group, but it was not statistically significant. In addition, there was also a study on the rise of Zn in serum, which is contrary to the results obtained from many previous literature. More studies with a better study design and a larger sample size are needed to properly address these issues.

Cu is essential for bone health, promoting the regeneration of articular cartilage, enhancing chondrogenic differentiation, and regulating cellular and humoral immunity [13]. Cu plays an important role in regulating bone growth and development by inducing lysine cross-link formation in collagen and elastin through lysyl oxidase activation [45]. As a cofactor for antioxidant enzymes, Cu scavenges bone free radicals and inhibits osteoclast activation [46]. Cu directly inhibits osteoclastic bone resorption, which can enhance bone strength and help maintain an optimal state of bone quality. It promotes angiogenesis and osteogenesis and has antimicrobial properties [10]. In addition, Cu is widely used in the development of bone graft materials [47]. Cu can promote regeneration of articular cartilage and subchondral bone through activation of the cartilage immune response. The underlying mechanism may be related to Cu-mediated activation of hypoxia-inducible factor, which then further increases macrophage conversion to the macrophage 2 phenotype, thereby enhancing the secretion of anti-inflammatory cytokines with beneficial effects on OA.

Interestingly, however, the outcome of this study found that Cu levels in OA patients tend to increase in serum, plasma, and synovial fluid. It has been proposed that this may be due to Cu-mediated oxidation and collagen degradation in the presence of excess free Cu, which results in elevated levels of elemental Cu in the body [48]. Although Cu acts as a strong antioxidant, eliminating oxygen free radicals and preventing cell damage [49], high concentrations of Cu have an oxidizing capacity that exceeds its antioxidant capacity, leading to potential oxidative stress through pro-inflammatory effects. Additionally, high concentrations of Cu can catalyze the production of ROS by reducing the concentration of glutathione, a potent cellular antioxidant. This reduction leads to the release of highly reactive hydroxyl radicals after the reduction of Cu ions (Cu^{2+}) to cuprous ions (Cu^{+}). This may activate activator protein-1, hypoxia-inducible factor-1 α, and nuclear factor-κ B signaling pathways, which upregulate pro-inflammatory cytokines and chemokines, resulting in inflammation [50]. Oxidative stress results in alterations to both the intra- and extracellular environments. This, in turn, triggers the infiltration of inflammatory cells and the release of inflammatory mediators. During inflammation in OA, certain inflammatory biomarkers, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α), upregulate the synthesis and secretion of cuprocyanin in hepatocytes. Subsequently, cuprocyanin is transferred from hepatocytes to the bloodstream, leading to an increase in the concentration of Cu [51]. The resulting inflammatory response further increases the production of oxygen free radicals and other reactive oxygen species, thereby exacerbating the degree and duration of oxidative stress [52]. Therefore, maintaining Cu homeostasis is crucial for the health of OA patients. The elemental content of ligaments and menisci is critical for maintaining joint strength, elasticity, and normal function, and increased levels of Cu inevitably exacerbate the pathogenesis and progression of OA, and the related sites need to be further investigated.

Previous meta-analysis results showed an increased level of serum Cu and a decreased level of serum Zn in RA patients [53]. Similarly, Wang et al. also found blood Cu level was significantly higher in RA patients, while Zn levels were decreased [54]. The trend of Cu element changes is consistent with that of this study. In the available data, the group of RA patients had significantly higher plasma concentrations of Cu compared to OA patients and healthy subjects. However, the variation pattern of Zn element still needs further clarification. RA is a chronic inflammatory autoimmune disease manifested by immune dysfunction, autoantibody production, synovitis, cartilage, and symmetric joint damage [55]. There are significant differences in the pathomechanisms of OA and RA, but it is sometimes difficult to distinguish between them due to their similar clinical symptoms [56]. In the future, it is necessary to clarify the diagnosis and differentiation between OA and RA, and then test the differences in Zn and Cu content in different organs to further explore the mechanisms of these two elements in OA and RA.

Genome-wide phenotypic association studies aim to identify regions of genes associated with specific diseases or traits by comparing genetic variation between individuals. This approach enables the screening of target genes to determine associations between OA and Zn and Cu. Identified variants can be analyzed to determine their association with specific phenotypes. The genome-wide analysis indicated that high Zn and Cu status were positively associated with OA [14]. Further study found that the expression of five cuproptosis-related genes (FDX1, LIPT1, PDHA1, PDHB, and CDKN2A) was significantly increased in the OA synovium [15]. Zn and Cu are both essential trace elements for the growth, development, and maintenance of healthy bone, and both have been strongly implicated in OA. Rył A suggests that serum and bone Zn/Cu ratios may have a significant positive effect on total BMD and BMC [57]. However, the positive or negative effects of trace elements are decided by a very narrow concentration range. More clinical data needs to be analyzed to find the relationship between Cu and Zn with OA.

Our study had some limitations, including the small number of subjects involved in the study and the lack of analyses

of the relationship between Cu and OA in different organizations with OA. Additionally, the order of occurrence of Cu and OA needs to be further clarified. Further studies should focus on overcoming these limitations through a large sample size and clarifying the staging of OA.

In conclusion, this meta-analysis demonstrates that the Cu levels in the serum, plasma, and synovial fluid significantly increased in patients with OA, and further studies of higher quality may lead to more solid conclusions.

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Author contributions Haowei Zhou was responsible for the conceptualization and design of this study. He contributed to the acquisition, analysis and interpretation of the data, as well as the writing and revision of the article. Yuchen Zhang was responsible for the production of pictures and tables, and analyzed and interpreted the data. Tian Tian and Zhang Bingqian were responsible for collecting, organizing, and summarizing the data. Yalei Pan finally critically revised the important intellectual content and finally approved the published version. All authors reviewed the manuscript.

Data Availability All data supporting the findings of this study are available within the paper and its Supplementary information.

Declarations

Competing interests The authors declare no competing interests.

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