# Correlation of Microelements and Bone Pathologies:

# A meta-analysis

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23 **Abstract**

24 Trace elements are mineral elements that are found in the body in very small quantities to achieve normal physiological processes. Copper, zinc and iron ensure the correct synthesis of macromolecules that form the bone structure. (Brancatella A et al 2020) Without those microelements, the formation of new bone by osteoblasts and the degradation (resorption) of old bone by the osteoclasts, will be modified and the osteoporosis can appear. It has to be a balance

between bone formation and bone resorption for the health of the bone. (Pierre D. Delmas 1993)

25 *Keywords:* osteoporosis, trace elements, diagnosis, bone density, bone metabolism

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28 **Introduction**

Osteoporosis is a pathology involving a number of diseases in the field of endocrinology, but also genetic and nutritional causes. The intake of microelements is essential as they are enzymatic cofactors for the specific enzymes of bone metabolism. (Saltman, PD, & Strause, LG 1993) Zinc, copper, fluorine, manganese, magnesium, iron and boron are part of bone microarchitecture, but if they are deficient in childhood and adolescence, they will cause much more loss of bone tissue at menopause or old age fact that leads to osteoporosis. (Zofková, I., et al 2013) Although the optimal concentration of calcium and vitamin D plays an important role in the prevention of osteoporosis, it is a major public health problem, affecting millions of people because there is a large inadequate supply of important nutrients to the bone, and this increase the risk for bone loss. The process of bone anabolism requires an adequate and constant supply of: protein, magnesium, phosphorus, potassium and fluoride. Recently microelements have been found to play an important role in bone-related metabolic processes, including manganese, copper, boron, iron, zinc. (Palacios, C. 2006)

Gabr S. et al 2016, observed that exercise and active lifestyle are essential for prevention of osteoporosis. The importance of copper in the formation of lysyloxidase and collagen-elastin bonds in the bone matrix has also been observed. Manganese is involved in the formation of chondroitin sulfate. Zinc is a microelement that is part of the structure of bone alkaline phosphatase and is a cofactor for collagenase. It converts procollagen into collagen, and the formation of hydroxyapatite is achieved by releasing phosphorus from the structure of bone alkaline phosphatase. (Gabr, S et al.2016).

Zinc is an essential microelement in bone metabolism that prevents bone resorption and promotes bone reformation, through various mechanisms such as regulating the secretion of calcitonin from the thyroid gland, promoting osteoblastic activity and alkaline phosphatase, having an anabolic role in bone tissue. The data showed that zinc is deficient in the elderly population, thus preventing bone mineralization and the formation of hydroxyapatite and collagen. This leads to osteoporosis with loss of bone structure integrity and increasing the risk of non-traumatic fracture. In osteoporosis, significant concentrations of zinc in the urine are observed, especially in menopausal women. (Colpan L., et al. 2005) It has been found that zinc is an essential microelement in the development of the skeletal bone since intrauterine life, its deficiency leading to abnormal changes in the fetus and postpartum. Zinc is part of the structure of over 200 enzymes, being an enzymatic cofactor for alkaline phosphatase, involved in the synthesis of some components of the bone matrix, ensures the normal synthesis of collagen playing an important role in bone mineralization. Studies have shown that zinc in optimal concentrations improves osteoblastic function, ensures the normal synthesis of collagen and proteoglycan, and increases bone deposits of calcium and magnesium. Positive correlations were found between zinc and copper deficiency and osteoporosis. Low serum copper concentrations have been identified in femoral head fractures. (Arikan D.C., et al 2011)

Yamaguchi states the importance of zinc in the normal development of the skeleton, especially after menopause. Zinc intervenes in the cellular apoptosis of mature osteoclasts and inhibits the synthesis of osteoclast-like cells in the bone marrow. It has an inhibitory effect on the activating receptor of nuclear factor (NF)-kB ligand (RANKL) which induces osteoclastogenesis. (Yamaguchi, M. 2009)

Bone tissue is a cellular interconnection in continuous microscopic dynamics, through the activities of resorption and formation, due to the action of osteoclasts, osteoblasts, bone lining cells and osteocytes. Bone tissue is also a repository for a number of micro and macroelements, as well as specific enzymes: alkaline phosphatase and dipeptidyl peptidase 3 (DDP3). Studies show the non-redundant role of DPP3 in maintaining bone homeostasis but suggest that DPP3 is a possible osteoimmunological factor and a marker of human osteoporotic pathology. Research on different animal models has shown a change in the structure of the bone matrix after decreasing the concentration of DDP3 by increasing the concentration of reactive oxygen species and reducing the level of nuclear transcription factor 2. (Florencio-Silva et al. 2015, Menale C et al 2019)

29 **Methods**

30 **Data sources and searches**

Web of Science, PubMed and Google Scholar databases were searched for relevant articles. References of selected articles and the most recent systematic reviews and meta-analyses on the subject related to osteoporosis, enzymes of the bone and the correlation between zinc, copper, manganese, selenium and their implication in the structure of the bone tissue. Databases were searched with the following search terms: (Osteoporosis OR Trace elements OR Intervention) AND (Bone density OR zinc OR manganese OR strontium OR copper OR selenium OR bone metabolism OR bone enzymes OR osteoblasts OR bone-specific alkaline phosphatase OR bone formation OR bone resorption). Studies published between 1993-and the date the searches were run were sought.

31 **Study selection**

Studies were included if they were (a) randomized controlled trials (RCTs) of a group or individual psychological interventions in which (b) objective measurements (medical analysis/biological assessments) were contained for (c) adults (30-60 years) with osteoporosis or low bone density were (d) published in English.

Studies were excluded if (a) the disease activity was measured only with subjective symptom scores indexes or diaries because these might be subject to inaccuracy and variation by psychological factors, (b) the interventions were educational or self-management and (c) contained incomplete statistical data.

# 32 Quality assessment and coding

33 **Data analysis**

34 We used R (Version 4.1.2; R Core Team, 2021) and the R-packages *papaja* (Version

35 0.1.0.9997; Aust & Barth, 2020), and *tinylabels* (Version 0.2.2; Barth, 2021) for all our

36 analyses.

37 **Results**

38 **Literature search results**

39 **Quality assessments results**

40 **Data analysis**

41 **Discussion**

42 **References**

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