# Correlation of Microelements and Bone Pathologies:

# A meta-analysis

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23 **Abstract**

24 Osteoporosis is a condition caused by bone loss that affects people around the world. Studies show that the spine is most prone to fractures. The mature bone matrix is a complex mineralized tissue, with a structural framework composed mainly of collagen and containing a small number of proteins and non-collagenous glycoproteins, calcium phosphates but also microelements. The bone matrix is composed not only of calcium, phosphorus, magnesium, elements that have been studied so much, but also of a series of microelements such as manganese, strontium, chromium, copper, zinc. Strause L. et all. 1994 Studies of the white population show that over 50% of women and about 20% of men above the age of 60 will suffer a non-traumatic fracture of the hip, vertebral body, proximal humerus and distal forearm during the rest of their lives. There are 3.5 million new cases of osteoporosis each year in the European Union. It is desired to diagnose the disease early by specific tests for osteoporosis prevention. Grigorie, D et al. 2013

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.

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) Studies have shown that strontium can replace calcium, which is chemically very similar to calcium. (Pierre D. Delmas 1993 and Pemmer, B. et al. 2013)

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 and the correlation between trace elements (zinc, copper, manganese). Databases were searched with the following search terms: Osteoporosis AND trace elements AND densitometry. We found studies at PubMed published between 1970 - and the date the searches were run were sought in number of 39. On Google Scholar we found 3640 studies using the same search criteria.

31 **Study selection**

Studies were included if they were (a) randomized controlled trials (RCTs) of a group in which (b) objective measurements (medical analysis/biological assessments) were contained for (c) adults (50-90 years) with osteoporosis or low bone density, or women with postmenopausal osteoporosis, or bone density deficit (diagnosed), were (d) published in English.

Studies were excluded if (a) the disease activity was measured only with subjective symptom scores indexes or the presence of other associated conditions, therapy with drugs that influence the level of microelements, or that can induce changes in bone metabolism (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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