Trace Elements in Oral Biology and Dental Practice: Molecular Mechanism and Clinical Applications

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ABSTRACT

In oral biology, trace elements are crucial because they affect the host immune system, microbial ecology, salivary function, and the structural integrity of tooth tissues. Fluoride, zinc, copper, selenium, iron, manganese, and other elements are involved in the mineralization of dentin, the development of enamel, antioxidant defense systems, and enzymatic control. These micronutrients influence the onset and course of dental caries, periodontal diseases, and disorders of the oral mucosa by modifying signaling pathways, gene expression, collagen formation, and oxidative stress responses at the molecular level. While fluoride encourages remineralization and inhibits demineralization by producing fluorapatite, zinc and copper boost antibacterial activity and matrix metalloproteinase regulation. Manganese and selenium protect oral tissues from damage from reactive oxygen species because they are cofactors for antioxidant enzymes. Both an excess and a deficit of trace elements can disrupt oral homeostasis, which can lead to reduced enamel, delayed wound healing, altered salivary composition, and increased susceptibility to infection. Trace elements are used in clinical practice for a variety of prophylactic and therapeutic purposes, including dental implants, bioactive restorative materials, fluoride products, and adjunctive periodontal therapy. Recent research shows their potential in nanotechnology-based drug delivery systems and regenerative dentistry. This review covers the most recent studies on the molecular mechanisms and clinical applications of trace elements in dentistry, with an emphasis on their dual role in maintaining dental health and causing disease when out of balance. Understanding these linkages is the foundation for developing targeted therapeutic and preventive approaches in modern dentistry.

Keywords: Trace elements, Dentistry, Oral biology, Dental practice

INTRODUCTION

Knowledge about the human body's components that is under a century old. [1] Nine nonmetallic elements and the four major electrolytes—calcium, magnesium, potassium, and sodium—are thought to make up 98% of the human body mass. These make up around 1.89% of the total, with the remaining 0.02%.[1] Nevertheless, this small portion has a significant impact on every bodily function. By serving as a cofactor or catalyst for several enzymes, the majority of them mediate numerous important metabolic reactions.[2] They also act as centers of building stabilizing structures of enzyme and proteins. A different mechanism that could result in the disorders could be triggered by the buildup of metals or their lack.[2]

Classification: Twenty nine different types of elements including metallic and non metals in an adult human body.These are broadly classified into five major groups they are as follows:[2]

Table 1: Classifications of trace elements

Group	Trace elements	Examples
Group I	Macromolecules	Carbon , Hydrogen , Oxygen , Nitrogen
Group II	Nutritional minerals	Sodium,Potassium,Chloride,Calcium,Phosphorous, Magnesium

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Group III (Minor elements)	Essential elements	Copper , Iron , Zinc , Chromium , Cobalt , Iodine , Magnesia, Molybdenum and Selenium
Group IV	Additional trace elements	Cadmium , Nickel , Silica, Tin , Vanadium and Aluminum
Group V	Functional elements	Gold , Mercury, Cyanide, Lead

Minor elements that are necessary for daily tasks and whose daily requirements are less than 100 mg may not interfere with appropriate development, but their activity may be replaced by that of another metal. [3]

The trace elements in human enzyme system:

Micronutrients, sometimes referred to as trace elements, are vital minerals needed in trace levels for the human body to operate properly. Because they frequently function as cofactors or components of enzymes, facilitating biochemical reactions vital to life, these elements are important to enzyme systems.

Copper:

Copper is an essential element that the human body need in trace levels. Numerous metabolic and physiological processes depend on it. The body needs only 1-2 milligrams of copper every day, but it plays a vital role in maintaining health. Copper is mostly absorbed in the stomach and small intestine, and it is transported to the tissues by proteins like ceruloplasmin. About 2 to 5 mg are needed daily, of which 50% are absorbed through the gastrointestinal tract. The kidney and bile eliminate the remainder. More copper builds up in the kidney, liver, and brain than in the rest of the body. Cervloplasmin is linked to more than 90% of plasma copper, and superoxide dismutase is attached to 60% of red blood cells.[2] Copperis very essential for synthesis and function in Hemoglobin synthesis, connective tissue metabolism and bone development. Synthesis of tryptophan is done in the presence of copper.[5]

Conditions like myocardial infarction, leukemia, solid tumors, liver cirrhosis, hemochromatosis, thyrotoxicosis, and certain connective tissue disorders will cause copper levels to rise, while Nephritic syndrome, Kwashinikar and Wilson's diseases, and severe diarrhea and vomiting conditions will cause copper levels to fall.[4] Copper is released some enzymes and which are essential for proper function. (Table 2)

Table 2: Enzymes required for proper function of cooper**[5]**

Enzymes	**Role of the enzyme**
Superoxide Dismutase (SOD)	Neutralizes superoxide radicals, protecting cells from oxidative damage.
Cytochrome c Oxidase	A key enzyme in the mitochondrial electron transport chain, necessary for energy (ATP) production
Lysyl Oxidase	Involved in the cross-linking of collagen and elastin, critical for connective tissue strength and elasticity.
Dopamine β-Hydroxylase	Converts dopamine to norepinephrine, essential for neurotransmitter synthesis

Copper is a critical trace element with diverse roles in the human body, including energy production, antioxidant defense, iron metabolism, and connective tissue formation. A copper deficiency can cause anemia, growth retardation, improper keratinization and coloring of hair, hypothermia, mental retardation, survey-like skeletal deformities, and degenerative changes in aortic elastin.[6] Consuming too much copper from food or other sources can cause nausea, vomiting, diarrhea, excessive sweating, and renal failure. Extremely delayed acquisition of Cu levels causes cirrhosis, hepatitis, tremors, mental impairments, kayser-fleshier rings, hemolytic anemia, and GIT hemorrhage.Congenital disorders like Wilson's disease, Menki's syndrome, and idiopathic lung fibrosis have all been connected to Cu.[6] Lung diseases in vineyard sprayers are a work-related risk because of the intake of copper by aerosol, which is 75% in the blood.[7]

Iron:

For many physiological and biochemical processes in the human body, iron is a necessary trace mineral. Its main functions are energy production, oxygen transport, and cellular functions. Large avantitiles of iron, mostly derived from plants, are found all throughout the crust of the globe.[11] Iron is more soluble in the food chain as ferric or ferrous ions in an acidic environment. The total amount of iron in the body is between 3 and 5 grams,

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of which 75% is found in the blood and the remaining portion is found in the muscles, liver, and bone marrow. The main element that contains iron is heme. Myoglobin, or Hb, contains it.[12]

Enzymes associated with iron include cytochrome 450, catalases, xanthine oxidases, succinate dehydrogenase, cytochrome C reeducate, tryptophan pyrrolose, and glycerophospahatase dehydrogenate.[13] Ferritin is the transport form of iron, which is taken up from meals as needed. Because phytase and oxalate restrict the absorption of iron in the GIT, the typical daily need is 1-2 mg/dl, which must be provided as 20 mg of iron in meals.[13,12] Hemosiderin is a golden brown material seen in reticulo endothelial cells that have denatured ferritin.2,3 Serious ailments will arise from a deficiency of these essential trace metals. The most common of these is iron deficiency anemia.[11] Deficits over time might be fatal. Increased iron levels can cause nausea, vomiting, diarrhea, and liver damage. Long-term or chronic iron accumulation in the body causes peripheral neuropathy, diabetes, hepatic failure, testicular atrophy, arthritis, cardiomyopathy, and hyperpigmentation[11]

Iron deficiency anemia:

- Microcytic hypo chromic anemia
- Plummer Vinson syndrome
- Blocking oxidative reaction
- Reduced energy production
- Multiple lipids per oxidation and Reduces O2 supplies to all organs.**[11]**

Zinc:

Ionizing in either acidic or alkaline soil allows zinc, an omnipotent metal with an amphoteric nature, to enter the food chain. The zinc content is between two and three. The body of a typical adult contains two to three GMs of zinc. 99 percent of it is intracellular, while the remaining portion is in plasma. Plasma zinc serves as a zinc reserve.[6] The typical daily need is between 15 and 20 mg. Zinc competes with calcium, phosphates, and copper for absorption from the small intestine, and phytotates weaken fibers. The pancreas and digestive system eliminate two to five milligrams every day.[6] Reduced plasma zinc levels are caused by acute myocardial infarction, infections, cancer, blood loss, fluid loss, oral contraceptive use, and pregnancy.[4] Zinc is associated with enzymes that impact the neurological, immunological, reproductive, dermatological, and gastrointestinal systems, and metalloproteinase is required for zinc to function in cells and tissue. It is necessary for appropriate spermatogenesis and maturation, sperm genomic integrity, normal organogenesis, neurotransmitter function, thymus development, wound healing epithelialization, taste perception, and pancreatic secretion.[13] The most crucial enzymes for zinc are alkaline phosphates, alcohol dehydrogenases, carbohydrates, glutamate and lactose dehydrogenates, and RNA polymerases. Impaired energy metabolism, alcohol intoxication, acidosis, suppression of protein synthesis, and a transmutation mechanism that stops superoxide radicals from killing cells are all signs of deficiency.[13] Growth retardation, dermatitis, alopecia, immunological dysfunction, psychiatric disorders, gonadal atrophy, defective spermatogenesis, fetal deformity, keratogenesis, taste issues, and delayed wound healing are all consequences of zinc deficiency.[11] Increased salivation brought on by acute zinc overload in humans can result in mental fume fever or brass chills. Lung fibrosis, respiratory conditions, nausea, vomiting, fever, lethargy, anemia, pancreatitis, and stomach ulcers are all brought on by persistently high zinc levels. One of the genetic diseases associated with zinc metabolism is aerodermatitis antipathy, an autosomal recessive disorder marked by an incapacity to absorb zinc.[4]

Chromium:

The total amount of chromium in an average adult is about 0.006 grams. The dosage is roughly 0.005 milligrams per day.4 Chromium has hexavalent and trivalent atoms. The synthesis of the glucose tolerance factor depends critically on chromium. A lack of chromium can lower glucose tolerance, which can lead to toxicities such lung cancer, dermatitis, and renal failure.[13]

Cobalt:

The average person possesses 1.1 gms, but an adult human needs 0.0001 mg each day.[4] It is a component of the complex of vitamin B12. It stops the thyroid from absorbing iodine and induces erythropoiesis. By controlling transferee enzymes such homocyteine methyl transfers, it contributes to the metabolism of methioinine. Deficits produce polycythemia, thyroid enlargement, pericardial effusion, cardiomyopathy, and congestive heart failure.[13]

Manganese:

There are about 15 mg of magnase in the typical adult human body. Nucleic acid is most frequently seen. Two to five milligrams are required each day. How much of the ingested manganese is absorbed. [4] Manganese is an enzyme activator and a part of metalloenzymes. They participate in the urea cycle, oxidative phosphorylation, mucopolysaccharide metabolism, and the metabolism of fatty acids and cholesterol.[14] Enzymes required for manganese include arginase, glutamine synthetase, phosphogluco mutates, succinate dehydrogenate, pyruvate carboxylate, diamine oxides, and superoxide dismutase. Long-term accumulation results in anorexia, lethargy, headache, impotence, leg cramps, speech disorder, encephalitis-like syndrome, and parkinsonian-like syndrome; deficiency, on the other hand, increases prothrombin time and causes bleeding problems.[15]

Molybdenum:

The average adult's body has 0.005 mg of molybdenum. This metal appears to be a common source of pollution based on its abundance in industrial areas. In alkaline soil, these ions have a higher chance of making their way into the food chain.Six The typical daily need is about 100 milligrams. The metal facilitates xanthine oxidative, xanthine dehydrogenases, aldehyde oxides, sulfite oxides, format dehydrogenases, nitrate reeducates, and nitrogenase. While too much molybdenum can lead to conditions like molybdonosis, too little molybdenum may prevent formation. This will lead to anemia and growth retardation, mostly from a copper shortage. Another reason for the shortage is esophageal cancer.[16]

Selenium:

The usual range for selenium levels is 80–120 micrograms per liter. A daily dosage of 0.05 to 0.2 milligrams is advised. primarily absorbed by the duodenum. typically found as a selenoprotein or in bound form. It is believed to be an antioxidant that controls the glutathione peroxide enzyme, which is involved in lipid peroxidation and O2 metabolism.16. Cirrhosis, liver necrosis, striated muscle degeneration, cardiomyopathy, and congenital heart failure are the outcomes of the deficiency.[17] Conversely, excessive selenium accumulation causes breath and stomach odor issues, emotional instability, baldness, and abnormal nails. It has the opposite effect in minute gravity and induces cancer in large gravity.[18]

Iodine:

Iodine the sole non-metal; the body has between 25 and 39 mg of iodine, but the daily requirement is between 150 and 200 mg.[19] Thyroid hormone production is the primary use of iodine.20Normal cell growth and differentiation, as well as all vital metabolisms, depend on thyroid hormones. Thyroid level distribution might be lethal.Since their deficiencies are not readily apparent, the other trace elements—silicon, arsenic, nickel, tin, and vanadium—are not well understood.[20]

Role of Trace elements in Dentistry:

The mottled teeth were attributed to drinking water at the Taxas Dental Society conference in El Paso in 1908. After looking into the source, scientists concluded that oral diseases could be the source of trace elements.[21] More than 41 trace elements are required for tooth development, according to numerous studies. The quantity of each component represented the process's surroundings. Once the hard dental tissue has formed, it can only be slightly altered. After an eruption, trace element uptake is limited to the surface and after restoration is finished.[22]

Trace elements of teeth:

The concentrations of the elements Na, Cl, and Mg are more than 1000 parts per million. The amounts of potassium, sulfur, zinc, silicone, and flouride range from 100 to 1000 parts per million. The concentrations of iron, aluminum, lead, boron, and barium range from 10 to 100 parts per million. Copper, molybdenum, cadmium, iodine, titanium, chromium, and magnesium are found in the range of 1–10 ppm, whereas nickel, lithium, silver, selenium, and cobalt are found in the range of 0.1–0.9 ppm.[23]

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Trace elements in saliva:

Trace elements are typically absent from saliva. Metal may be eliminated through saliva if it is present in excess. Water, pollution, and diet can all reflect this. They may therefore have an impact on the development of plaque. the concentration of metals in saliva and the volume of saliva secreted.[24]

Trace elements in dental caries:

Saliva is devoid of trace elements, if too much metal is present, it may be expelled through the saliva. This could be seen in the water, food, or pollution. They may therefore have an impact on plaque formation. the quantity of saliva released and the level of metals in it.[24]

Role of Trace elements in Oral submucousfibrosis :

According to World Health Organization defined as "An insidious chronic diseases epithelial inflammatory reaction followed by fibroelastic changes of lamina propria with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and inability to eat".[26] In many chronic diseases, this thick, fibrous tissue is deposited in the oral submucosa and surrounding tissues. It is typified by varying degrees of mucosal rigidity caused by the fibroelastic transformation of the submucosa, which prevents the cheek and tongue from moving or being eaten. Therefore, mouth opening affects tongue projection and cheek flexibility. [27] It is a collagen disease characterized by a decrease in more soluble procollagen types III and IV and an increase in high crosslinked insoluble collagen type I. In many fibrotic illnesses, the formation and progression of fibrosis are significantly influenced by the cross-linking of collagen and the enzyme LOX, which is responsible for this process.[28] The nut containsarecoline as the active ingredients along with polyphenols or tannins. Arecolin is a potent parasympathetic mimetic drug which stimulates secretion of saliva, is found in large quantities. Among tannins (11.4-26.0%) gallotannic acid (18.03%) and D- catechol (0.4%) are important chemicals. The components such as arecadine ,Isoguvanine, arecolidine and guvacoline are present in minute quantities. Arecoline, arecadine and tannins are said to be carcinogens.[28]

The dry weight of copper in areca nuts was determined to be 302 nmol/gm, of which 11.3% to 11.6% dissolve in human saliva. The amount of copper in the tissues of oral submucous fibrosis has increased to a threefold level. Patients with submucous fibrosis had 6.57 µg/gram of tissue, compared to 2 µg/gram of normal tissue. The serum copper levels layer on the upper end of the normal range. [29] Zinc and Iron in oral tissues were studied and compared with oral submucous fibrosis patients and reported that the netalcontant can be regarded as an alternative indicator of the precancerous nature of Oral sub mucous fibrosis. [30] In another study , a decrease of serum iron patients and an extended study revealed decreased levels of iron, cerbroplasmin copper and zinc in serum[25,26].The total binding capacity of iron , in sub mucous fibrosis is of not normal pattern due to decrease in value of serum iron.[31]

Metal interaction with Lysyloxidase :

Copper is a crucial metal for lysyl oxidase because it functions as a cofactor. It is therefore a member of the cupro protein class.[6] The copper concentration of the rats' liver and plasma was shown to decrease when they were fed an upper-deficient diet, while the copper content of their skin remained same. This suggests that lysyl oxidase has a great affinity for copper.[32] It was shown that cyclohexamide hindered the incorporation of copper into lysyl oxidase, and that around 5% of the oral copper consumed was integrated into the skin for lysyl oxidase. This is due to the rapid activation of lysyl oxidase caused by copper absorption into the aorta.It is stipulated that variations in plasma copper levels or the concentration of the copper-delivering vehicle that raises skin parse levels more significantly disrupt the enzyme's functional functioning. However, skin copper levels did not decrease when exposed to copper deprivation.[33] It has been reported that the functional activity is the changeable factor, but the levels of mRNA for lysyl oxidase expression are the same in rats fed copperdeficient and copper-adequate diets. Deprivation of copper reduces the activity of lysyl oxidase. This frequently results in numerous bone and skin disorders, aortic aneurysms, and pulmonary illnesses.[27] The formation of lysine tyriosy quinine in the active site of lysyl oxidase it is believed to be caused by coppermediated direct catalysis.[10] The integration of copper into prolysyl oxidase was examined. Protein synthesis is necessary for the process, and findings indicate that lysyl oxidase is connected to the majority of protein-bound copper produced by skin fibroblasts. Lysyl oxidase does not need to be glycosylated in order for copper to be incorporated into it or secreted from it.

Between 0.1 and 0.3% of the protein made in the skin is lysyl oxidase, which is also connected to other proteins that are bound to copper. The enzyme that converts pro-lysyl oxidase to lysyloxidase is called precollagen C peptidase. It is a glycoprotein that extracellularly cleaves the C terminal polypeptide of type I, II, and III collagens. Copper incorporation was unaffected by prolysyl oxidase glycosylation or inhibition of this enzyme.[29] The enzyme's copper binding domains span amino acids 278–295 or 326–399, respectively. Either in the endoplasmic reticulum or during protein trafficking via golgi bodies, copper is incorporated into lysyl oxidase. The carrier was proposed to be a P type copper ATPase, a eukaryotic copper transporter. This protein is found in the membranes of trans-golgi vesicles within cells. Secretary proteins are delivered to the cell membrane by vesicles made by budding and fusing with subcellular membranes via the golgi apparatus. It is hypothesized that copper secretion requires the same vesicular processes as lysyl oxidase secretion.[28]

Techniques used for detection of trace elements:

- Atomic absorption spectrometry
- Emission spectroscopic methods
- Neutron activation analysis
- Isotope dilution mass spectrometry
- Atomic X ray fluorescence spectroscopy.[2]

CONCLUSION

Copper and other trace elements may play a crucial role in lysyl oxidase and submucous fibrosis, making it unable to use enzyme inhibitors as antifibrotic medications. Lysyl oxidase's capacity to act as a ras recession gene product may explain why cancer rather than sarcoma arises from connective tissue abnormalities. The reversible serum levels may interact with the increased copper and decreased zinc and iron levels in oral submucous fibrosis when compared to normal. Anemia, a constant finding with the disorders, can then be linked to them.Therefore, once the function of trace elements and metal interactions in lysyl oxidase are understood, it will be possible to comprehend the etiopathogenesis and offer a quick diagnostic tool as well as a therapeutic approach.

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