REVIEW ARTICLE

Zinc: A precious trace element for oral health care?

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Abstract

This review will discuss the importance of Zinc in the maintenance of oral health. Zinc (Zn) is a trace element of valuable importance. In the oral cavity, it is naturally present at various sites such as dental plaque, dental hard tissues and saliva. It is proven to be effective against common prevalent oral health problems such as dental caries, gingivitis, periodontitis and malodour. It is being used in various oral health care products to control the formation of dental plaque and inhibiting the formation of dental calculus. It has the potential to sustain and maintain its elevated concentrations for a longer time particularly in the dental plaque and saliva on delivery from the mouth rinses and toothpastes. It has been reported that low concentrations of zinc have the capability to reduce dissolution and promote remineralization under caries simulating conditions. Most importantly low Zn2+ levels in the serum are useful as a tumour marker. Thus taking a note of its potentials, it can be concluded that zinc is a precious element for the maintenance of oral health.

Keywords: Zinc, Oral Healthcare, Oral Diseases.

Introduction

Like other elements zinc has proven its importance in the maintenance of human health, particularly growth and development and performs a significant role in the metabolism of many enzymes and proteins. It has been reported that human body contains approximately 2-3g zinc with high levels in eyes, liver, bones, hair and prostatic secretions. Studies have proven that human blood plasma and leukocytes contain 12-22% and 3% of zinc respectively.[1] In serum there is 100 μg of zinc per deciliter which is bound to the α-2 macroglobulin and some loosely bounded with the albumin.[1] The mechanism of zinc transfer into the plasma is still unknown, but Cotzias proposed it as a homeostatic mechanism by which it is distributed in various cells organelles within the body.[2] Zinc also influences the process of bone mineralization and osteoclastic activity.

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Content of Zinc in Saliva and Dental Plaque

Due to the abundance of zinc in the human body, some amount may occur naturally in saliva and dental plaque. Table shows the reported concentration of zinc in ppm found by different researchers in saliva and plaque.[3]

Zinc is also naturally occurring in dental plaque along with some found in the acquired salivary pellicle.

Table: Zinc concentrations (ppm) in saliva and dental plaque.

Saliva (ppm)	Plaque (ppm)
0.0135	15.2
0.055	31.6
0.127	6.41
0.080	19.5
0.17	18.6
0.112	< 40
< 0.200	15.9 (pooled sample)
0.0465	17.4
0.244	< 10.7

The values tabulated were obtained from Lynch (8).

Zinc Distribution in Oral Hard Tissues

The oral hard tissues stated here refer to the enamel, dentine and cementum. In this review, zinc content in enamel and dentine are described and reference to synthetic hydroxyapaptite is also given.

Enamel

Enamel forms the outermost layer of tooth which on comparison with other dental structures is known to be highly mineralized and an avascular tissue of the dental crown. The inorganic content of enamel comprises mainly of hydroxyapatite crystals, with various structural differences and incorporation of trace elements. The major elements in abundance are Na+, Ca++, Mg++, Cl- and PO43- with the average compositions of 37% Ca++, 0.4% Mg++, 18 % PO43-, 0.28% Cl-and 0.7% Na+. The trace elements include Zn+,Pb++, Fe++, Sr++ ,Cu++ and Mn++ which are present in the whole thickness of enamel structure. The concentration of all these trace elements except Sr++ and Mn++increases in the first layer (50µm depth) of whole enamel. This may explain why the outer layer of enamel is more caries resistant than the subsurface and the deeper surface.

The outer layer of enamel contains higher content of zinc whereas it is present in low concentration in subsurface. It exhibits the similar pattern to that of fluoride which is also present in lower concentration in deeper layers of enamel. Concentration of zinc varies from 430 to 2100 ppm depending upon the different layers of tooth. It has been reported that the zinc content in enamel increases during post-eruptive phase of the tooth suggesting that the tooth surface acquires more minerals from the oral fluids, similar to that of fluoride uptake.[4] Studies with synthetic hydroxyapatite showed that zinc is readily acquired by the apatite as it competes with calcium and can attain position on the apatite crystal making hydroxyapatite resistant to the acid dissolution.

Dentine

Dentine has different amounts of trace elements and shows less crystallinity in structure when compared with enamel.Thus it is more soluble in acidic conditions. Zinc due to its astringent properties on dentine alters the organic component in demineralization and remineralization. The zinc does play some role in preventing the dentine demineralization. Takatsuka reported that toothpaste containing zinc in the form of ZnO prevents dissolution of dentine. It was shown to inhibit the demineralization by 49% as well as being effective against bacterial growth and the formation of calculus and plaque.[5] In an in-situ study, it has been demonstrated that zinc together with fluoride in toothpaste formulation reduces the rate of demineralization remarkably and promotes remineralization and this result was not achieved with fluoride alone.[6]

Synthetic Calcium Hydroxyapatite (HAp)

Enamel is mainly composed of calcium hydroxyapatite (HAp), and can have variety of ionic and cationic substitutions (sodium, magnesium and zinc)in its structure. These substitutions can cause changes in crystallinity, morphology and stability of apatite. Zinc plays an important role in the modulation of crystallinity of the apatite crystals. Experiments performed by Bigi showed that zinc cannot substitute calcium in Hap.[7]

The solubility of carbonated and non-carbonated apatite is reduced after the incorporation of zinc. It also reduces the acid reactivity of the apatite which subsequently may reduce the crystalline disorder. Larger crystals precipitating out with very few defects may occur. The combination of fluoride and zinc proved to be more effective in reducing the structural disorder of HAp which is due to incorporation of carbonate.[8]

Antimicrobial Effect of Zinc

Zinc has been used in many oral healthcare products due to its efficiency against the microbes especially in toothpastes along with some other ingredients like triclosan having anti-calculus properties. Hanke investigated the effect of zinc on oral bacteria among varied consortia.[9] Later Finney reported the broad spectrum activity of zinc.[10] Zinc has antimicrobial properties against different bacteria such as Streptococcusmutans. Zinc is taken up by the bacteria by export and uptake systems regulated by their own regulators, among them are Resistance-Nodulation Division multi drugs efflux transporters, P-type ATPAses and cation diffusion facilitators and also peroxide activated system.

Cytoplasm and glycolytic enzymes of the bacterial cells are expected to be the common targets of zinc.[11] Phan performed various experiments on the efficacy of zinc against the Streptococcusmutans and proved its ability to inhibit the process of glycolysis.[11] Glycolysis is initiated by the bacteria during glucose fermentation in which acid is produced causing a major drop in the salivary pH leading to demineralization of enamel. When zinc was used in lower amounts (0.010mM), the glycolytic process was not significantly affected. Upon increasing the zinc concentration to 0.015mM the glycolytic process was found to slow down. When increased further, zinc at 0.025mM completely stopped the glycolysis along with significant change in the pH. So it was suggested that it affects both acidogenesis and the acid tolerance. When the acid tolerance of the Streptococcusmutans is reduced by zinc, the activity of F-ATPase, one of the major components which controls the acid tolerance in bacteria is blocked. The inhibition of F-ATPase causes an increased permeability of the cell towards protons. Thus, when acid is being produced, the protons can pass through the membrane and change the metabolism inside the bacterial cell.

Zinc is used in various forms of salts such as zin coxide, zinc chloride, zinc citrate and zinc sulfate and zinc lactate in mouth rinses and toothpastes. The inhibitory property of zinc salts on microbial glycolysis is pH dependent and bacteria specific, the inhibition is more at pH7 as demonstrated by Streptococcussobrinus and Streptococcussalivarius. The zinc salts also inhibit the production of volatile sulphur compounds (VSC) thus assisting in minimizing halitosis.[12] Zn2+ is a sulfhydryl reactive agent and its reaction is thought to have an antimicrobial effect.[13]

Many in vivo and in vitro studies have proven that zinc has an ability to inhibit and limit the acid production in dental plaque.[14] Under normal pH of saliva, zinc has the capability of inhibiting the acid production by Streptococcusmutans upto 50% whereas when used along with fluoride it proves to be bactericidal. Streptococcusmutans being aciduric is the most cariogenic bacteria. Zinc also efficiently inhibits the production of glucosyl transferases in the bacteria and this will affect the colonization of bacterial pathogens and subsequent development and accumulation of dental plaque.

Zinc in higher concentration has an inhibitory effect towards various glycolytic enzymes like pyruvate kinase along with aldolase and glyceraldehyde-3-P dehydrogenase and this effect has been shown in Streptococcussobrinus. Zinc also stops alkali production from the plaque urea. Zinc constrains the catabolic enzymes of Streptococcusrattus like arginine deaminase and also blocks the arginolysis process in the bacterial cell.

Zinc also blocks the synthesis of ATP along with F-ATPase. ATP is a catabolic byproduct of bacteria and its blockade will affect the bacterial growth. Phospho transferase system (PTS) of Streptococci is also sensitive to zinc especially to zinc citrate.[13] The mechanism by which zinc limits the PTS activity is not clear but it is suggested that it might be due to Zn cations which compete with Mg cations required by PTS for activity.[13]

There are several studies which show the effect of zinc on the plaque- and caries-forming bacteria but relatively some researches have been done to prove zinc as an anti-gingivitis agent. Moore proposed that zinc is effective against Fusobacterium Nucleatum and Prevotellaintermedia which cause gingivitis.[15] Fusobacteriumnucleatum provides attachment for the other plaque forming species; therefore any agent that inhibits its growth also constrains the growth of other bacteria involved in the plaque formation. Fusobacteriumnucleatum catabolizes glutamate whereas zinc inhibits this catabolic reaction and causes inhibition of growth; along with this it also prevents the growth of Prevotellaintermedia by inhibiting the catabolism of aspartyl-aspartate and aspartate. Thus, it causes reduction in the inflammatory and cytotoxic potential of microbiota causing gingivitis. Zinc also inhibits tryps in like proteases produced by Porphyromonasgingivalis.

Zinc as an Anti-oxidant

It is an efficient antioxidant as it reduces the production of toxic agents such as hydrogen peroxide (H_2O_2) which has noxious effects against the host cells. Zinc deters the respiration in Fusobacteriumnucleatum and other oral microflora to stop the production of reactive oxygen.

Zinc, a marker in oral sub-mucous fibrosis and oral squamous cell carcinoma

Low level of serum Zn is related as a biomarker of cancer e.g. lung; breast, gall bladder, colon and oral cavity.[16,17] Cancer cells have unregulated amount of Zn importers. Zn levels in whole blood, serum and saliva from oral cancer patients cannot indisputably establish a significant increase.[18,19] Therefore, it can be suggested that increased Zn level encourages immune cells survival and tumour apoptosis.[16,17]

Uses of Zinc in Dentistry

In mouth rinses

Zinc is used in mouth rinses as an anti-bacterial agent which serves as an agent to control the development of dental plaque, calculus, malodour and bleeding gums. An in vivo study carried out has shown that zinc citrate possesses inhibitory effect on the development of dental plaque.[20]

Nano-Therapeutics

The field of Nano-therapeutics has lately evoked its interest in controlling the development of oral biofilms by using biocidal nanoparticles (NPs). Sometimes treatment with conventional medications like antibiotics is considered as inadequate, and leads to chronic oral infections, which subsequently results in tooth extractions or implant removal, requiring costly restoration or regenerative procedures and treatments.[21]

The antibacterial influence of zinc oxide nanoparticles (ZnO-NPs) was explored against Campylobacter jejuni. It was found that Campylobacter jejuni was extremely sensitive to zinc oxide nanoparticles. The MIC of zinc oxide nanoparticles for this bacteria was 0.05 to 0.025 mg/ml.[22] Therefore it can be suggested that the antibacterial mechanism of zinc oxide nanoparticles causes disruption of the cell membrane and oxidative stress in Campylobacter sp.

Zinc oxide nanoparticles have been proven to have a wide range of antibacterial activities against Gram-positive as well as Gram-negative bacteria, including foremost foodborne pathogens like Escherichia coli O157:H7, Listeria monocytogenes, Salmonella typhii and Staphylococcus aureus.[23,24]

Zinc in Toothpastes

Zinc is used in toothpastes as an effective antibacterial agent where it helps to control the plaque and calculus formation. The delivery of zinc depends on the type of zinc salt, dose and rinsing regime of the tooth paste. Usually zinc is used as zinc citrate or zinc oxide (ZnO) or zinc chloride in toothpastes along with fluoride and triclosan. It has been reported that 15-40% zinc is retained in the mouth after its delivery.[25]

Gilbert and Ingram confirmed that zinc has good oral substantivity and reported that about 30% is retained after tooth brushing of which 5.7% of it was removed after rinsing three times.[26]

Zinc concentration in saliva drops within 30-60 min after its delivery because saliva clears zinc bi-modally, and the low concentrations remain in saliva for many hours.[14] Therefore it shows that loosely bound zinc is cleared rapidly whereas tightly bound zinc has slower release. In plaque, high level of zinc persists for an extended period of time and displays a build-up effect after repeating applications.

Chesters did a clinical trial with a silica based-tooth paste containing fluoride and zinc citrate trihydrate against calculus formation and showed that there was 30% calculus reduction by zinc containing toothpaste as compared to the control toothpaste in a 13 week period.[27] There were no side effects observed during the study thus proving the role of zinc as an anti-calculus agent.

Zinc in Dental Restorative Materials

Amalgamating small amounts of ZnO-NPs into the composite resin may boost its mechanical properties. Earlier studies have shown that fusion of various NPs into resin composite would result in mechanical improvement up to a threshold beyond which there will be no further improvement.[28] The incorporation of ZnO-NPs into composite resin would significantly constrain the Streptococcusmutans growth.[29]

Significance of zinc in Immuno-compromised individuals

Patients undergoing chemotherapy for haematological forms of malignancy with high dose of regime are more prone to have oral mucositis. As a prophylaxis there is no defined treatment and chlorohexidinegluconate has been used to decrease severity of the condition.

Recently it has been shown that chlorohexidine is not an appropriate agent to be used for treating oral mucositis particularly in immuno-compromised patients. Zinc in the form of zinc sulfate was found to be a good option especially in individuals who are subjected to high dose of chemo treatments (chemotherapy or radiotherapy or both).[30]

Lichen planus is a muco-cutaneous ailment affecting particularly the immuno-compromised individuals.[31] It is reported that zinc plays a significant role in the growth of epithelium. Its deficiency is concomitant with immunity and impaired wound healing results in the inhibition of lymphocytes, particularly T-lymphocytes which are of main concern in immunologic-based disorders like Lichen Planus.[32]

In another clinical study, fluocinolone containing zinc mouth rinse compared to the mouthrinse without zinc was found to be more effective in the treatment of oral Lichen planus by reducing the surface area of the wound and also the concomitant ache (pain).[33,34]

It is also reported that zinc helps to lessen soreness(inflammation) and possibly will be clinically useful as an anti-inflammatory agent for management of Recurrent Aphthous Stomatitis (RAS).[35]

Other Commercial Uses of Zinc

Zinc oxide is most commonly used in the fortification of cereal-based diets. Because of its antimicrobial properties, it has been incorporated into the linings of cans for the packaging of various food stuffs like fish, meat, peas, corn, and beans to prevent their spoilage. Nano-sized particles of zinc oxide have more distinct antimicrobial property than the large particles, as the small size (less than 100 nm) and high surface-to-volume ratio of the nanoparticle permits better interaction with bacteria. Current researches have revealed that these nanoparticles have selective toxicity to microbes but they display minimal effects on human cells.

Conclusion

Based on the discussion above, it can be concluded that zinc has a potential to provide a new era of interest in developing economical as well as valuable products for oral healthcare. It has efficiency in inhibiting dissolution and promoting remineralisation of the dental hard tissues. It has been suggested that zinc is of key importance in the treatment of imuno-compromised individuals suffering from oral diseases, undergoing chemo- or radio-therapies.

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