**Micronutrient zinc deficiency aggravates Periodontal diseases**

**in Type 2 Diabetes Mellitus**

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**Abstract**

A complex inflammatory condition linked to bacterial infection, periodontitis causes the breakdown of tooth-supporting tissues and ultimately leads to tooth loss. Both zinc and metallothionein may be essential for the onset and advancement of periodontal disorders due to their roles in inflammation and infection. More precisely, zinc and metallothionein play a significant role in immune function regulation, bacterial infection control, inflammatory response balancing, and oxidative stress reduction—all of which are linked to the aetiology of periodontal disorders. The physiological roles of zinc will be examined in this review study, along with the idea that dysregulation may have a detrimental effect on periodontal health and result in Type 2 diabetes. Together, these deficiencies cause inefficient necrosis, increase gingival epithelial permeability, and interfere with the humoral immune response, all of which exacerbate periodontal disorders. Furthermore, in zinc-deficient environments, LPS promotes M1 macrophage polarisation and dendritic cell maturation while also suppressing regulatory T cells' anti-inflammatory function. All of these findings may theoretically contribute to the chronic inflammation associated with periodontal diseases, and the disturbed homeostasis of zinc and metallothionein is anticipated to have a negative effect on periodontal health and aid in the onset and advancement of periodontal diseases in people with Type 2 diabetes mellitus. In order to better understand the complex interaction and mechanisms underlying the role of zinc deficiency in exacerbating periodontal diseases in people with type 2 diabetes, this chapter draws on both established literature and recent research findings.

**Keywords:** Micronutrients, Zinc, Antioxidants, Free radical scavenging, Periodontitis, Type 2 Diabetes Mellitus.

**1.Introduction**

Periodontitis is a common, hereditary condition that affects the tissues underneath and next to teeth. It is characterized by resorption of alveolar bone, loss of attachment, swelling gingival tissue, and bleeding. Adult tooth loss is caused by more severe or advanced forms of periodontitis. As per the global estimate in 2021, the disease showed high pevalance rate affecting nearly 1.07 billion individuals, worldwide. The disease involves complex dynamic interactions among specific bacterial pathogens and destructive immune responses. Clinically it presents with an array of varied features such as bleeding, swollen gingiva, loss of attachment, and resorption of alveolar bone. More severe or advanced form of periodontitis might lead to tooth loss in adults. Periodontitis has been linked over the past years, to several medical conditions such as Diabetes Mellitus, Cardiovascular problems, Respiratory disorders, Pre term low birth weight etc. Although the exact relationship between diabetes mellitus and periodontitis still remains unclear, diabetes mellitus has long been considered a risk factor for the development of periodontal disease and vice versa.

A systemically impacting chronic inflammatory disease, periodontitis, is associated with other diseases such as type 2 diabetes mellitus (T2DM). Increased blood sugar levels lead to periodontal diseases, which in turn can disrupt the body’s glucose metabolism if gingival inflammation persists. This interdependent relationship grants periodontitis the distinction of being termed as the “the sixth complication” of diabetes. Diabetes mellitus has long been regarded as a risk factor for the development of periodontal disease, even if the precise association between the two conditions is still unknown (Sundaram et al.,2017). The state of the mouth, teeth, and orofacial structures that permits people to carry out basic tasks like eating, breathing, and speaking is known as oral health, according to the World Health Organisation. It also includes psychosocial aspects like self-esteem, wellbeing, and the capacity to interact with others and work without experiencing pain, discomfort, or embarrassment.

A person's general health and quality of life can be determined by their oral health. If left untreated, periodontal disease—an inflammatory reaction to bacteria in the gum tissue next to the teeth—can cause gum recession, bone resorption, tooth loosening, and ultimately tooth loss (Cesalie et al.,2024).This condition is under diagnosed worldwide and is thought to put people at higher risk for type 2 diabetes mellitus. Diabetes mellitus is a systemic condition that has a number of serious side effects that shorten and degrade life expectancy. The metabolic syndrome known as type 2 diabetes mellitus is linked to obesity, dyslipidaemia, hyperglycemia, insulin resistance, and hyperinsulinemia. An increased risk and severity of infections, particularly periodontitis, are linked to uncontrolled or inadequately managed diabetes. Diabetes mellitus does not produce gingivitis or periodontitis, as is the case with other systemic illnesses linked to periodontitis. However, there is evidence that it accelerates bone loss by changing how the periodontal tissues react to local circumstances.

Micro nutrients encompass Vitamins and Minerals that are needed in small quantities for both development and functioning of the human body. Zinc is one such essential micronutrient that is readily available in foods such as meat, nuts, diary products, whole grains or through supplements. It plays a significant role in the proper functioning of the immune system concreting its importance in inflammatory diseases such as Periodontitis.  Zinc deficiency is known to hamper immune cell function and increase oxidative stress, potentially worsening periodontitis. Several studies have reported that adequate zinc levels, including through supplementation, can improve clinical parameters and reduce salivary MMP-8 levels in periodontitis patients. Therefore, a possible link and plausible explanation on the role of Zinc in Type 2 Diabetes Mellitus patients with Periodontitits needs to be studied in detail.

1. **Type 2 Diabetes mellitus**

The incident although type 2 diabetes mellitus (T2DM) is a concerning global health issue, China, India, the United States, Brazil, the Russian Federation, Mexico, and Indonesia have the highest estimated rates of diabetes cases. The 11th edition of the Diabetes Atlas states that 589 million people worldwide will have T2DM in 2024 and 2050, with China having the biggest patient population . The disease is growing at an alarming rate. Insulin resistance and pancreatic β-cell dysfunction were two characteristics of diabetes. Firm suppression of insulin and glucose production was linked to T2DM. Additionally, elevated glucose levels exacerbate diabetes. Globally, the number of people with diabetes mellitus has been rising quickly, placing a significant health burden on both industrialised and developing nations (IDF Atlas, 11th Edition).

 At the moment, diabetes is more common in Asia. Changes in lifestyle and environmental exposures are the main causes of its sharp rise in incidence and prevalence over the past few decades (Sacks et al.,2023). The prevalence and severity of periodontal diseases were considerably higher in T2DM Indian natives than in non-diabetic controls. India is thought to account for 174.8 million cases of diabetes in adults worldwide, or 45.8% of all cases. In many communities, individuals with diabetes or hyperglycemia have a roughly 50% higher chance of developing periodontitis than the overall population. Small amounts of micronutrients are necessary for certain bodily processes. An important antioxidant trace element that aids in the control of gene expression is zinc . It is yet unknown how zinc contributes to the inflammation of periodontitis in T2DM, however research has shown that diabetes mellitus is associated with a lower zinc status.

Dysregulation of lipid and carbohydrate metabolism, which results in decreased insulin secretion, action, or both, is a hallmark of type 2 diabetes (MA Atieh etal.,2014). The cause of this dysregulation is pancreatic beta cell failure, which lowers insulin responses in tissues that are sensitive to insulin, including the liver, skeletal muscle, and visceral adipose tissue. Insulin resistance, sometimes referred to as diminished insulin sensitivity, is the inability of insulin to bring target tissues' blood glucose levels down to normal plasma insulin levels. Pancreatic β-cells try to compensate for insulin resistance by secreting more insulin in an effort to keep glucose levels stable. As a result, fasting plasma insulin levels increase, hyperinsulinemia subsequently arises, and β-cell failure ultimately leads to hyperglycemia (Zheng etal.,2008 & Seeta., 2011).

1. **Periodontal Disease, Diabetes Mellitus and Zinc**

The increasing breakdown of tooth-supporting structures, such as the epithelium, connective tissue, alveolar bone, and periodontal ligament fibres, is a hallmark of periodontitis, a chronic inflammatory illness linked to a dysbiotic microbial biofilm. Deeper periodontal pockets, loss of periodontal attachment, and bleeding on probing are clinical indicators of periodontitis (Ramadan etal.,2020). More than 700 million individuals, or around 11% of the world's population, suffer from this illness. Gingival inflammation is the result of bacterial challenges in this slowly progressing illness. Over the past "Vicennial" several studies have assessed the association between periodontitis and T2DM. The most plausible mehanism for the increased risk of periodontitis in T2DM patients.might be associated with elevated levels of [oxidative stress](https://www.sciencedirect.com/topics/medicine-and-dentistry/oxidative-stress%22%20%5Co%20%22Learn%20more%20about%20oxidative%20stress%20from%20ScienceDirect%27s%20AI-generated%20Topic%20Pages) and inflammation due to [hyperglycemia](https://www.sciencedirect.com/topics/medicine-and-dentistry/hyperglycemia%22%20%5Co%20%22Learn%20more%20about%20hyperglycemia%20from%20ScienceDirect%27s%20AI-generated%20Topic%20Pages) leading to damage of periodontal tissues. In patients with T2DM, advanced glycation end-products (AGEs) and their receptors (RAGEs) are interacted and deposited in the periodontal tissues activating the local inflammation. This interaction increased the release of pro-inflammatory cytokines by monocytes/macrophages and [endothelial cells](https://www.sciencedirect.com/topics/medicine-and-dentistry/endothelial-cell%22%20%5Co%20%22Learn%20more%20about%20endothelial%20cells%20from%20ScienceDirect%27s%20AI-generated%20Topic%20Pages), such as IL-1β, IL-6, and tumor necrosis factor (TNF)-α (Lalla etal 2001). This exacerbated inflammation may further increase the periodontal inflammation resulting in attachment, and [bone loss](https://www.sciencedirect.com/topics/medicine-and-dentistry/osteolysis%22%20%5Co%20%22Learn%20more%20about%20bone%20loss%20from%20ScienceDirect%27s%20AI-generated%20Topic%20Pages) ( Yan etal, 2010).

The role of Zinc in maintaining periodontal health is attributed to its anti - oxidant property and its role in inflammation.  Zn deficiency may increase the susceptibility to infection through increasing the permeability of gingival epithelium for bacteria, as well as impair [neutrophils](https://www.sciencedirect.com/topics/medicine-and-dentistry/neutrophil%22%20%5Co%20%22Learn%20more%20about%20neutrophils%20from%20ScienceDirect%27s%20AI-generated%20Topic%20Pages) and [macrophages functions](https://www.sciencedirect.com/topics/medicine-and-dentistry/macrophage-function%22%20%5Co%20%22Learn%20more%20about%20macrophages%20functions%20from%20ScienceDirect%27s%20AI-generated%20Topic%20Pages) and stimulate them to interleukin-1 (IL-1) production. Therefore adequate Zn intake in  T2DM patients, reduces the risk of developing periodontitis by neutralizing bacterial toxins and inflammation. Multiple factors come into play in the development of periodontitis in T2DM patients, such as increased production of advanced glycation end products (AGEs), immunological alterations, and heightened inflammation (Saito et al., 2018; Tervonen et al., 2019). Increased sugar levels can cause the body to accumulate AGEs, resulting in inflammation and destruction of periodontal pathologies (Sundaram et al., 2017). In addition to this, diabetes increases one’s susceptibility to infections by weakening their immune response, which puts them at a greater risk for periodontal diseases (Mealey & Oates, 2006).

The principal causes of periodontitis are not isolated bacteria. A subgingival microenvironment that is more selective for particular microbes is typically found in people with an elevated pro-inflammatory response. Therefore, the balance is shifted from homeostasis to damaging inflammation by genetic, environmental, and systemic influences as well as local tissue and microbial components. This unbalanced community keeps expanding in an inflammatory environment, which exacerbates the inflammation. Tissue destruction and the advancement of disease are largely caused by inflammatory mediators such as cytokines (e.g., TNF-α, IL-1β, IL-6) and signalling pathways (e.g., NF-κB)( M.A. Godoi etal.,).Periodontitis will arise as a result of the disease's progression and alterations in microbes. Diabetes mellitus is a common chronic illness, and in recent years, patients with the condition have experienced a variety of oral health issues. The majority of tooth loss instances are caused by untreated chronic periodontitis (Leite, et al., 2022).

Globally, inflammatory periodontal diseases have been linked. Bacterial-derived virulence factors increase TNF-α levels in periodontitis, a devastating inflammation-related disease. Because of the interplay between dangerous bacteria, their byproducts, and the heightened host defence response, it is an infectious disease that causes irreversible damage to the cells that maintain teeth (Y.A. AlJehani., 2014). One of the most common oral disorders, periodontal disease is characterised by the breakdown of soft tissues, alveolar bone, and other dentition-supporting components, which ultimately results in tooth loss. Soft tissue pockets or deeper fissures between the gingiva and tooth root were the outcome. Periodontitis is underdiagnosed worldwide and is thought to enhance a person's chance of developing T2DM. Impaired neutrophil chemotactic responses, a heightened monocyte response to dental plaque antigens, and poor wound healing are all linked to diabetes and can increase local tissue damage. Diabetes and cigarette smoking are major risk factors, and there is a reciprocal relationship between the two conditions and periodontal disease (Abdullameer et al., 2023) .

**4.Periodontitis and T2DM**

 When compared to people without or with well-controlled type 2 diabetes, people with poorly managed type 2 diabetes usually exhibit more severe periodontitis symptoms, such as bleeding on probing, clinical attachment loss, and marginal bone loss in radiological pictures.One known contributing factor to the development or progression of type 2 diabetes is hyperglycemia. Furthermore, a complex link between hyperglycemia and periodontal tissues is revealed, leading to a greater build-up of advanced glycation end products (AGEs) in these tissues. In the periodontium, AGEs lead to tissue damage, increased amounts of inflammatory mediators, protein cross-linking, and oxidative stress. As a result, insulin resistance is made worse by inflammation, and the two conditions feed off one another in a vicious cycle. In addition to accelerating the development of periodontitis, this mutual relationship makes managing diabetes more difficult.The effect of type 2 diabetes on resident cells and those linked to both innate and adaptive immune responses drawn to the periodontitis lesion is responsible for the elevated inflammatory activity in periodontal tissues (Nicchio et al.,2021). The interaction of several cells, including leukocytes, vascular cells, mesenchymal cells, fibroblasts, and osteoblasts, results in an exacerbated inflammatory response. Increased AGE and glucose levels in periodontal tissues exacerbate the activation of transcription factors linked to inflammation, including NF-κB.This mechanism causes a deeper infiltration of pro-inflammatory cells in periodontal tissues by upregulating the levels of TNF-α, IL-1β (interleukin-1-beta), IL-6, IL-17 (interleukin 17), and IL-23 (interleukin 23)( Battancs et al.,2020).

Additionally, TNF-α influences the inflammation of periodontal tissues both directly and indirectly by promoting the decrease of transforming growth factor-beta (TGF-β) and anti-inflammatory cytokines like IL-4 (interleukin 4) and IL-10 (interleukin 10) (A. Mirzaei et al.,). Given that a higher glycaemic level is associated with more severe periodontitis, it has been hypothesised that there may be a proportionate relationship between glycaemic control and these cytokines. In addition to cytokines, T2DM is linked to the expression of several other proinflammatory substances, including chemokines, metalloproteinases, and other transcription factors (J.J. Taylor et al.,). T2DM patients with inadequate glucose control had increased levels of matrix metalloproteinase-14 (MMP-14) expression in their periodontal tissues. Furthermore, individuals with diabetes have been shown to exhibit an imbalance favouring a decreased M2 macrophage population, which promotes repair and reduces inflammation, and an increased M1 macrophage population, which may exacerbate the inflammatory process if recruited or activated. According to results from other diabetic problems, diabetes may increase M1 macrophage polarisation, making people more vulnerable to severe periodontal disease.

**5.Zinc and Insulin**

All of the human body's growing cells depend on zinc (Zn), an essential mineral. More than 300 distinct enzymes, over 3000 Zn-dependent transcription factors, and other protein domains have been found to include zinc, making this micronutrient crucial for a variety of intracellular functions ( Kato et al.,2017). By stabilising the regulation of the structural and well-organised reliability of eukaryotic cells and tissues, it serves as a crucial prerequisite for the proper development of several internal organs. Zinc is essential for apoptosis, differentiation, and proliferation at the cellular level. It has been demonstrated in recent decades that the development and progression of type 2 diabetes are impeded by the altered metabolism of zinc. Zn availability and Zn transporters of the SLC30 and SLC39 gene families, which together regulate intracellular circulation, are regulated by metallothioneins (Hwang, et al.,2016). Although the exact involvement of zinc ions in insulin secretion and diabetes pathogenesis is unknown, pancreatic islet cells' zinc levels are strictly controlled. Numerous research have raised awareness and provided fresh information about zinc's known insulin-mimetic properties. While the amount of zinc is partially present, the amount of insulin in the pancreas of persons with T2DM is found to be one-fourth that of healthy individuals. Zn is packed with insulin in the secretory granules of the pancreatic β-cell. When compared to other cell types, pancreatic cells have a very high zinc content, and crystallographic experiments have verified that zinc is present in insulin crystals. Because zinc depletion alters the antigenic determinants of insulin, it can reduce the immunological effect of insulin. Glycaemic regulation and insulin synthesis, storage, and secretion may be impacted by disruptions in zinc metabolism. Periodontitis affected Zn homeostasis in T2DM individuals, according to several human investigations (Pushparani., 2015).

Antioxidants act as protectors against damage caused by free radicals mediated by metals. Zn reduces oxidative stress by acting as an antioxidant. Serum Zn concentration is typically used to assess its status; however, stress and actual Zn shortage both cause a fall in serum Zn concentration. Serum Zn is transferred into the liver during times of stress. Zinc's capacity to unite and fortify cellular membranes against lipid peroxidation and disintegration may be the cause of its protective actions against elevated rates of lipid peroxidation. The potential of metallothionein to release Zn for binding at membrane surface locations, dislodging adventitious iron and preventing lipid peroxidation, is another likely protective mechanism (Ben-Eltriki, M., et al., 2024).

The ability of Zn to trigger metallothionein production could represent an alternative protective mechanism. Metallothionein's high sulfhydryl concentration makes it an effective oxyradical scavenger. Moreover, the SH-residue in many functional proteins may be preserved by the proposed effect of Zn on the formation of SH-rich metallothionein. Zn may thereby preserve the structural and functional integrity of the enzymes that are dependent on SH, such as those that control the metabolism of glucose. Studies using crystallography have shown that Zn is present in the insulin crystal. There are a number of reasons to believe that the pathophysiology of diabetes mellitus and some of its consequences may be related to aberrant zinc metabolism. Insulin synthesis as well as its storage and secretion is directly linked to zinc. It is needed for the stabilization of insulin hexamers, thus helping with the release of insulin into circulation (Maret, 2013).In managing T2DM, the imbalance of zinc metabolism leads to a relative zinc deficiency on a cellular level, because of insufficient absorption and enhanced renal excretion (Sundaram et al., 2017). Zinc deficiency has other implications as well like reduced insulin sensitivity which may promote hyperglycemia, making the management of diabetes more difficult.

The signal transduction response to insulin and the production of cytokines, which cause beta-cell death during the pancreatic inflammatory process, may be impacted by a Zn homeostasis deficiency. Under typical circumstances, Zn is distributed throughout the pancreas and plays a crucial role in the crystalline structure of insulin, stabilizing the insulin granule by making it less soluble. Zinc affects taste, smell, appetite control, and food intake in addition to the general metabolism of protein, carbohydrate, and fat. These hormones are closely related to bone metabolism, and this micronutrient plays a role in their synthesis as well as their activities. According to in vitro research, Zn promotes the growth of osteoblastic bone.

The structure and function of many enzymes involved in a wide range of metabolic processes are closely related to the fundamental mechanisms of action of this trace element. Accordingly, when Zn particularly affects cartilage formation, it is a multifactorial event because it is engaged in several enzymatic activities. By reducing the generation of free radicals at the ligand-binding site and by its involvement in the Cu–Zn superoxide dismutase enzyme, Zn may lessen the severity of oxidative damage. Although these animals are not zinc deficient, Zn supplementation lowers increased blood glucose in genetically obese mice and lessens the degree of lipid peroxidation and atherosclerotic plaques in rabbits fed a high-cholesterol diet.It is unknown how human serum zinc levels and glycaemic indicators interact (Jazli Azi et al., 2021).

1. **Zinc deficiency and Type 2 Diabetes mellitus with Periodontitis**

In both of these inflammatory conditions, there is a process that occurs between the periodontopathogenic bacteria and the host response. Matrix metalloproteinases (MMPs) also play a role in this process (Gasner & Schure, 2023). MMPs are a family of zinc-containing proteolytic enzymes that play a role in many physiological and pathological conditions (Li et al., 2023). MMPs can degrade extracellular matrix and non-matrix proteins (Luchian et al., 2022). Due to these properties, when activated by periodontopathogenic bacteria, they cause tissue destruction in periodontitis. Because it is a catalytic component, Zn is an essential element for growth development, puberty, and wound healing. Zinc deficiency affects the body’s oxidative balance and chronic inflammation is a hallmark of both periodontal disease and diabetes (Wang et al., 2020).Much of this stems from zinc deficiency and the resulting oxidative stress—a condition characterized by an excess of reactive oxygen species—can further slow the healing processes imparted by zinc, resulting in a vicious cycle of inflammation and tissue damage (Ekuni et al., 2020).

Zinc deficiency is known to have a variety of structural and biological roles in a wide range of proteins, peptides, and hormones. It has also been linked to reactivity and poor wound healing in individuals with diabetes. Scalp hair was another biological indicator of Zn status that was assessed. A few clinical research have found significantly reduced Zn levels in T2DM patients' scalp hair when compared to healthy controls. It was found that people with diabetes consume less zinc, which results in an intracellular deficiency. Some consequences from diabetes would result from the altered metabolism of Zn. The kidneys, liver, intestinal mucosa, and pancreas are the main organs that maintain Zn homeostasis. Metallothionein plays a crucial function in gluconeogenesis and lipogenesis by facilitating metal exchange with Zn metalloenzymes and shielding cells and tissues from free radicals that induce oxidative stress. By lowering cytokine production, Zn, a structural element, aids in the synthesis, storage, and release of insulin. Increased vulnerability to diabetes mellitus and metabolic syndrome may result from changes in insulin metabolism and oxidative stress brought on by an aberrant Zn level.

Increased levels of metallothionein in the cytosol are caused by Zn accumulation in the liver cells. However, it is quite unlikely that Zn that is consumed by liver cells will attach to subcellular organelles and impact the metabolic processes of the cells. Zn interferes with taste, smell, appetite control, and food ingestion via interacting with protein, carbohydrates, and fats. This micronutrient plays a role in the production and control of hormones, which are eventually connected to the metabolism of bones. Zn promotes osteoblastic bone growth, according to in vitro research. Decreased immunological response and decreased tissue regeneration and healing following traumatic shocks are signs of Zn deficiency, but Zn helped to prevent oxidative stress-induced damage in diabetes. Zn has been demonstrated to favourably affect the transcription of the insulin genes, which produce insulin. It has recently been discovered that animals lacking ZnT8 have reduced granular zinc content in the β-cell, which adversely impacts proinsulin processing enzyme activity and raises the blood's proinsulin to insulin ratio.

1. **Mechanisms Linking Zinc Deficiency, Periodontal Disease, and Diabetes**

Minerals are essential to the human body's metabolic processes. Many theories have been put out to explain how hyperglycemia causes the long-term problems of diabetes mellitus, such as the polyol and hexosamine pathways and the production of AGEs. In addition to causing other kinds of biological harm, the free radicals produced during the glucose autoxidation process will oxidatively harm proteins, lipids, and nucleic acids]. Zinc deficiency, periodontal disease and T2DM are interrelated through multiple mechanisms. Zinc has an important impact on the immune system, especially its deficiency, leads to a shift in pro and anti-inflammatory cytokines balance (Prasad, 2008; Ghosh et al., 2018). Such changes may intensify impactful periodontal inflammation, tissue breakdown especially in diabetic patients that have a blunted immune response (Mealey & Oates, 2006).

Zinc deficiency leads to higher concentration of free radicals which is a hallmark of oxidative stress referred to as the silent killer. This phenomenon has been previously and widely recognized as a risk factor for periodontal disease and complications for diabetes (Kumar et al., 2013; Tervonen et al., 2019). Additionally, free radical reactions and diabetic cardiovascular problems are linked to trace elements, specifically copper and Zn. The non-enzymatic byproducts of AGEs are the results of hyperglycemia. Numerous pieces of evidence point to reactive oxygen species as the origin of damage and the production of age-modified molecules. The effects of Zn levels in T2DM patients with periodontitis were investigated in this review. Zn levels were lower in T2DM patients with periodontitis than in those without the condition. Comparing T2DM without periodontitis and non-diabetes mellitus with periodontitis to control, it was discovered that the serum Zn levels were noticeably higher (DS.Pushparani, 2016., Fig 1). Zinc, insulin, and diabetes mellitus have a complex interaction that frequently shows a decline in Zn level. This would hinder insulin's ability to initiate and distribute its normal series of actions for hyperglycemia caused by alloxan. Because it contributes to the structure of metalloenzymes and possesses catalytic and regulatory properties, Zn has a known effect on them. It was thought to be a legitimate cause of ageing. Consequently, it seems that a homeostatic balance in the extracellular and intracellular concentration of Zn ions is required.



**Fig 1: Hypothesis to link Zinc deficiency and Type 2 diabetes mellitus with Periodontitis**

 Enzymes involved in extracellular matrix remodelling, LDL modification, and numerous other proinflammatory activities and biological processes are abundant in periodontitis plaques. T2DM without periodontitis and non-DM with periodontitis had higher serum Zn levels, although their levels of triglycerides, LDL-c, and total cholesterol did not differ significantly (Tervonen, T., et al. 2018). This indicates that additional problems arise as a result of these people' decreased serum Zn levels. Zn may protect the metallothionein production pathway. This review has provided a convincing explanation of the connection between Zn and the regulatory function in diabetes with periodontitis. Additionally, it implies that variations in serum Zn levels are not as suggestive of periodontitis as they are of certain metabolic problems of T2DM.

 This indicates that additional problems arise as a result of these people decreased serum Zn levels. It may protect the metallothionein production pathway. Additionally, it implies that variations in serum Zn levels are not as suggestive of periodontitis as they are of certain metabolic problems of T2DM. Reduced intake, excessive loss, or an inherent disruption in Zn metabolism could be the cause of the reduced serum Zn content in those with T2DM who also had periodontitis. According to the analysis, persons with T2DM who also have periodontitis may have decreased dietary bioavailability as a result of low Zn levels (Sinha, S., & Sen, 2014).

1. **Future Directions**

Exploring the intricacies of the association between zinc deficiency, periodontal disease, and T2DM has important implications for further research. It is of paramount importance to ascertain the effects of zinc supplementation on maintaining periodontal health as well as on managing diabetes. Also, the role of other micronutrients in conjunction with zinc dietetic supplementation needs scrutiny for the development of evidence-based clinical protocols.

1. **Conclusion**

Individuals with metabolically uncontrolled diabetes are more likely to have abnormal zinc and cholesterol levels. In patients with type 2 diabetes, these lipid abnormalities have a major role in the development of periodontitis problems. The body produces physiologically significant low serum zinc levels when hyperglycemia from either type of diabetes mellitus is combined with periodontitis. In T2DM with periodontitis, poor wound healing and insulin resistance may likely be caused by a low serum zinc level. To track the progress in a definitive way, more study on the effects of zinc in diabetes with periodontitis may be helpful. The relationship between zinc deficiency, periodontal disease, and type 2 diabetes mellitus highlights the contribution of inappropriate intake of dietary micronutrients in disrupting oral and systemic homeostasis. Zinc deficiencies can negatively impact immune systems, inflammation control, and tissue health. These factors are critical when considering the onset and management of periodontal disease, particularly in diabetics. Improving zinc status through dietary modification or supplementation may strategically improve periodontal and overall diabetes control in this demographic. Zinc deficiency causes lysosomal enzymes to become more permeable, which raises blood D glucuronidase levels and compromises the stability of the lysosomal membrane. Subjects with T2DM and periodontitis would then experience more issues as a result of these conditions.

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