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**Review Article**

# Iron in Oral Health and Disease

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## ABSTRACT

Certain essential elements are required by the metabolically active cells and tissues for the maintenance of health of human body. Iron is one of the essential elements for life and is needed for a number of highly complex processes that continuously take place at molecular level and that are indispensable to human life. It is necessary for oxygen transport, electron transport, cellular differentiation, and functioning of many enzymes. Concentration of iron in body tissues must be tightly regulated because excessive iron leads to tissue damage whereas iron deficiency encompasses a broad spectrum of diseases with diverse clinical manifestations. Iron levels affect the integrity of oral mucosa alongwith the development and progression of many oral lesions. Also, iron levels could act as a prognostic indicator for many oral lesions.

## INTRODUCTION

Certain essential elements are required by human body in small quantities and their absence or excess may result in severe malfunctioning of the body processes.[1] The levels of trace elements in human body could act as very accurate and sensitive indicator which signals the onset of pathological changes as their appropriate levels reflect the homeostatic status of the body.[2] Iron is a vital trace element for the survival of almost all organisms and is toxic in excess. Iron homeostasis in mammals must be fine-tuned to avoid iron deficiency as well as iron excess. Due to the unique nature of iron metabolism, iron homeostasis is achieved by integrated specialized mechanisms that operate at the cellular and molecular level.[3-4] In iron deficiency, oral epithelium exhibits significant alterations alongwith some structural, histochemical, and clinical changes that may occur before significant alterations in red cell morphology or haemoglobin level are noted.[5] Thus, this review highlights the importance of iron in oral health and disease.

## Iron Metabolism

Iron is the most abundant essential micronutrient in the human body.[1] About 60-70% of total body iron is present in the form of hemoglobin in circulating erythrocytes and 10% is present in the form of myoglobin, cytochromes, and iron containing enzymes. The remaining 20-30% of iron is stored as ferritin and hemosiderin in hepatocytes and reticuloendothelial macrophages.[6] Dietary iron occurs in two forms i.e heme and nonheme. The primary sources of heme iron are hemoglobin and myoglobin from animal sources whereas nonheme iron is obtained from both plant and animal sources.[7] Iron is recycled and thus conserved by the body.[8] To maintain iron balance, the sum of these losses plus the iron required for growth in infants, children, adolescents and during pregnancy must be provided by the diet.[7] Dietary requirement of iron is 10 mg/day, 18 mg/day, and 40 mg/day for an adult man, menstruating woman, pregnant and lactating woman, respectively.[9] Iron is absorbed in the gut (stomach and duodenum) from diet which allows the intake of appropriate quantities of iron to balance small daily losses.[1,5] The factors promoting iron absorption are citrate, acidity, fructose, alcohol, cysteine, and ascorbic acid. Iron is mostly found in food in the ferric form bound to proteins or organic acids and is released from the food in the presence of an acidic medium. The ascorbic acid and cysteine reduce ferric ion to ferrous ion by forming soluble complexes and thus enhancing its absorption. The factors inhibiting iron absorption includes phytic acids, polyphenols, and calcium.[7-9] Iron is delivered to tissues by circulating transferrin, a transporter that captures iron released into the plasma mainly from intestinal enterocytes or reticuloendothelial macrophages.[8] Its excretion is not actively controlled and main mechanism responsible for its excretion is through skin desquamation

which accounts for about1-2 mg per day.[10] The homeostasis in iron levels of human body is maintained by regulating the absorption and never the excretion.[1]

## Role of Iron in Health

Iron is essential for many vital functions of the body. The main functions of iron include:

**Oxygen transport:** Iron is one of the major elements required for the oxygen transport as heme is the major iron containing substance in ferrous or ferric state which is present in hemoglobin, myoglobin, and cytochrome. Heme forms covalent bonds with the globin protein to form hemoglobin which is the major oxygen carrying pigment in RBCs of mammals.[1,11-12]

**Biological oxidation, electron transport, and redox-reaction:** Iron plays an important role in biological oxidation, electron transport, and redox-reactions as cyto-chromes (iron containing hemeproteins) and certain non-heme proteins are necessary for electron transport and oxidative phosphorylation. Iron participates in oxidation reduction reaction called as Fenton reaction. It exists in both ferrous and ferric state and thus it is capable of accepting as well as donating electron.[12] Although most iron in the body is present in forms that are not readily available to catalyze this reaction but it is still an important mechanism for the formation of the hydroxyl radical in-vivo. Under most circumstances, iron remains tightly bound to proteins, however, a small iron pool will be maintained as complexes with a variety of small molecules, such as nucleotides and citrate within the cytoplasm and few subcellular organelles. This pool is probably capable of catalyzing an iron driven Fenton reaction in-vivo. However, iron is released from binding proteins in an acidic pH and thus in conditions like active inflammation and ischaemia reperfusion injury, iron is released and hydroxyl radicals are produced resulting in tissue injury.[13]

**Enzymes:** Iron is the key component of many cellular enzymes like oxidases, catalases, tryptophan pyrrolase, ribonucleotide reductases, xanthine oxidases, aconitases, cytochromes, peroxidases, nitric oxide synthases, cyto-chrome a-c, cytochrome p-450, and succinate dehydro-genase by acting as co-factor for these enzymes.[1,12]

**Synthetic:** Iron is required by many enzymes which are responsible for synthesis of DNA, RNA, protein, steroid hormones, and bile acids. Iron is necessary for the formation of myelin and neuronal dendritic tree. Iron containing enzymes are responsible for signal controlling of some neurotransmitters such as dopamine and serotonin in the brain.[1,12]

**Detoxification:** Iron containing enzymes (cytochrome p 450) are also associated with detoxification of foreign substances in the liver.[11]

**Cellular differentiation:** Iron is critical for the growth and differentiation of all cells. Iron regulates the transcription of three mammalian genes: protein kinase Cβ, tartrate-resistant acid phosphatase, and p21 which are associated with cell differentiation.[12]

**Vasculature:** Iron ions are actively involved in the formation of the vascular bed and its deficiency leads to the increased vascular permeability and reduced vascularization of tissues.[2]

**Immunity:** Iron serves as a cofactor in many enzyme systems such as peroxide generating enzymes and nitrous oxide-generating enzymes that are critical for immune cells to function normally.[14] Iron also helps in the synthesis of antibodies. It has been stated that hepicidin (peptide) produced by liver and adipose tissue is a key regulator of iron homeostasis and its expression increases in chronic inflammation which may contribute to increased prevalence of iron deficiency.[7] Decreased resistance to infection in iron deficiency can be attributed to deficient bactericidal activity of polymorphonuclear leukocytes, suppression of the T-cell response by hyper-segmented neutrophils, impaired cellular immunity, inadequate antibody response, abnormalities in epithelium and decreased bactericidal properties of myeloperoxidase enzyme due to its inhibition.[15-19]

## Effect of Iron on Oral Health

**Effect on epithelium /Oral mucosa:** Iron is essential for the normal functioning of oral epithelial cells. In iron deficiency, turnover rate of oral epithelial cells increases resulting into an atrophic or immature mucosa.[20,21] This atrophy of epithelium in iron deficiency is also attributed to the low levels of iron dependent cytochrome oxidase which is required for normal maturation of epithelium.[22] It has been suggested that decrease in the thickness of epithelium was because of the reduction in the thickness of middle cell layer of epithelium (maturation compartment).[23] A decrease in cell diameter, increase in nuclear diameter, altered nucleocytoplasmic ratio,

increased number of nucleoli and increased number of binucleated cells in iron deficiency state has been reported.[24]

**Effect on periodontium:** It has been established that iron plays an important role in maintaining the healthy periodontium by affecting the action of enzyme superoxide dismutase.[25] Enzyme superoxide dismutase has an antioxidant activity and catalyses the dismutation of superoxide to hydrogen peroxide and this hydrogen peroxide is further removed by catalase or glutathione peroxidase.[13] Chakraborty et al[25] reported that iron deficiency anemia patients with chronic periodontitis have more periodontal breakdown than chronic periodontitis patients. They also suggested that iron-deficiency anemia is associated with decrease in antioxidant activity of superoxide dismutase, resulting in an increased oxidative stress and worsening of periodontal diseases. Other researchers have also endorsed the decreased activity of superoxide dismutase, in patients with iron deficiency anemia.[26-28]

**Effect on salivary glands:** Iron plays an important role in maintaining the function of salivary gland. Malnutrition, such as iron deficiency, often impairs salivary gland function causing reduced salivary secretion, and low buffering capacity.[29] Mahantesha et al[30] reported an improve in levels of serum ferritin, salivary pH, and buffering capacity after the treatment of iron deficiency anemia suggesting that iron deficiency has a significant relationship with salivary pH**.** Buffering capacity of saliva and salivary pH has been identified as one of the many factors that may affect an individual's caries risk.[31-32] It has been reported that children with severe early childhood caries were nearly twice as likely to have low ferritin levels and were over six times more likely to have iron deficiency anemia than caries-free controls.[33]

## Role of Iron in Oral Diseases

Maintenance of iron levels in human body is essential for the proper functioning of the human body as any alteration in its levels has a deleterious effect on the body. The deleterious effect of iron is attributed to the generation of reactive oxygen species by Fenton reaction resulting in DNA damage, altered cell proliferation, impaired synthesis of membrane lipids, proteins, and carbohydrates (Figure 1). Also, free iron directly reacts with unsaturated fatty acids, impairs cellular integrity, and ultimately results in cell death. This destructive potential of iron gives an indication that it plays an important role in development of many oral lesions.[12,34-35]

**Iron deficiency anemia**: It is the most common type of anemia frequently seen in women. Patients with iron deficiency anemia presents with specific systemic symptoms like lightheadedness, fatigue, weakness, shortness of breath, and palpitations. Oral manifestations include atrophic glossitis (smooth, red painful tongue with atrophy of filiform papilla and fungiform papilla), generalized oral mucosal atrophy, and tenderness or burning

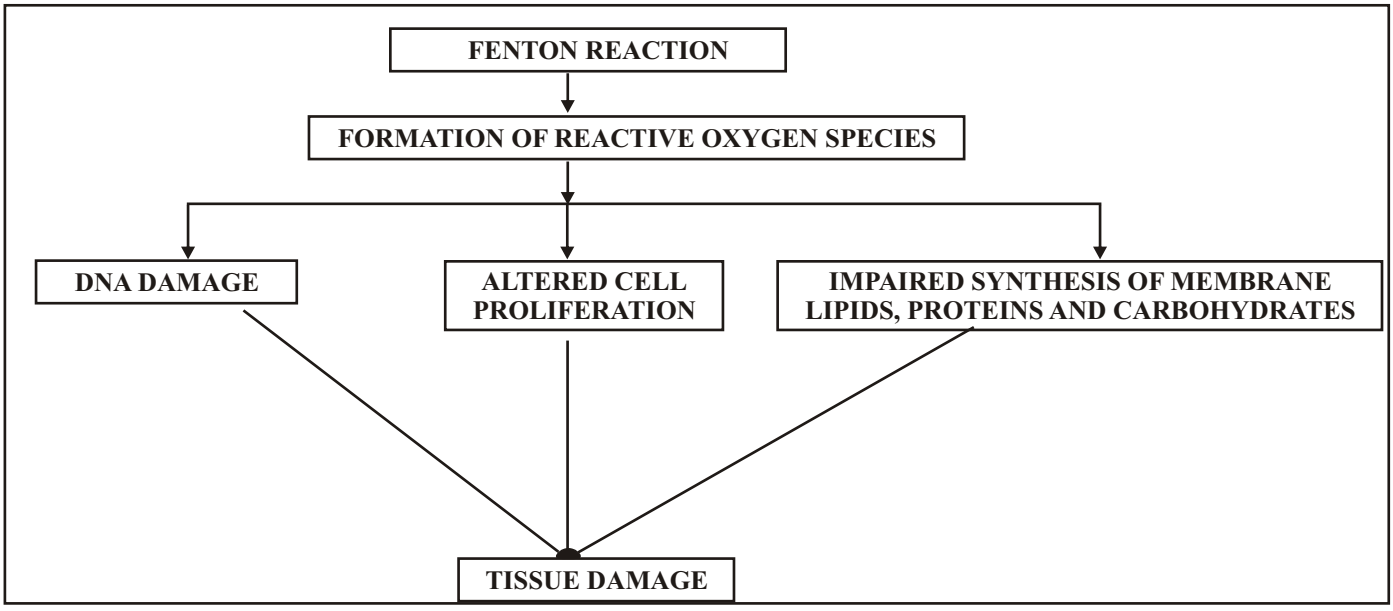


**Figure 1: Mechanism for deleterious effect of iron on tissues.**

sensation of oral mucosa.[20] In another study, oral manifestations in iron deficiency anemia patients were burning sensation of oral mucosa (76.0%), lingual varicosity (56.0%), dry mouth (49.3%), oral lichen planus (33.3%), atrophic glossitis (26.7%), recurrent apthous ulcers (25.3%), numbness of oral mucosa (21.3%), and dysfunction of taste (12.0%).[21]

**Plummer Vinson syndrome/ Paterson-Kelly syndrome/ Sideropenic Dysphagia:** This is characterized by classical triad including post-cricoid dysphagia, iron-deficiency anemia, and esophageal webs. The dysphagia is mostly painless and sometimes associated with weight loss. Other symptoms include glossitis, angular cheilitis, koilonychia (spoon-shaped finger nails), enlargement of spleen and thyroid. Many studies also considered it as a risk factor for developing squamous cell carcinoma of the upper gastrointestinal tract.[36-37]

**Candidiasis:** Lu et al[14] observed that iron deficiency predisposes patients to a high incidence of candida infection. They reported that patients with iron deficiency manifest various clinical forms of candida like pseudomembranous candidiasis, erythematous candidiasis, median rhomboid glossitis, chronic mucocutaneous candidiasis, papillary hyperplastic candidiasis, or cheilo-candidiasis. They stated that iron deficiency should always be considered in every case of oral candidiasis when no obvious cause is found. Alteration in immune response due to iron deficiency results in an inadequate host response towards infection. Impaired lymphocyte transformation and a reduced delayed hypersensitivity reaction is associated with persistence of infection.[5,15]

**Recurrent aphthous ulcer:** These are characterized by recurrent, small, round or ovoid ulcers often multiple with circumscribed margins, erythematous halo and yellow to grey floors. Various factors that contribute to occurrence of recurrent aphthous ulcer include systemic, genetic, immunological, local, and infectious. However, role of nutrition in its association with aphthous is still a controversial subject. A significant decrease in levels of iron and copper in the recurrent aphthous ulcer patients indicates that copper and iron deficiencies play a crucial role in the etiopathogenesis of recurrent aphthous ulcer.[22]

**Oral lichen planus**: It is a chronic mucocutaneous disease affecting oral mucosa first. Frequency of hematinic deficiency is significantly higher in oral lichen planus patients than in healthy control participants, but this hematinic deficiency is probably not the main etiology causing the oral lichen planus.[38] Low iron levels in the oral fluids affect the course of the inflammatory process, contributing to the transition of oral lichen planus to more severe forms. A significant decrease in oral fluid levels of zinc, copper, iron with increase in the severity of the clinical course has been reported. This decrease in levels in turn aggravates the severity of oral lichen planus.[2]

**Potentially malignant disorders:** Serum iron levels in the potentially malignant disorder and oral cancer group were studied. A statistically significant reduction was observed. A lowered level of iron appears to be the effect of the disease process rather than its cause and thus iron levels can serve as prognostic indicator for carcinogenesis.[39,40] Shetty et al[41] found that salivary iron was decreased in oral submucous fibrosis, oral leukoplakia and oral cancer patients.

**Oral submucous fibrosis:** It is a chronic disease and a potentially malignant disorder affecting the oral mucosa. Various factors have been associated with the development of oral submucous fibrosis, of which most important is use of areca nut and chillies. Various studies have emphasized on the importance of deficiency of nutritional factors primarily iron and vitamins in the development of oral submucous fibrosis.[18,42-43] Patients with oral submucous fibrosis exhibit significantly lower levels of hemoglobin and serum iron.[18] Kumar et al[42] in their study observed that mean serum iron level decreases with increase in severity of diseases. It is attributed to the utilization of iron for collagen synthesis during the hydroxylation of proline and lysine.[44-45] It was also found in literature that lack of iron in tissues leads to decrease in vascularity which in turn facilitates percolation of arecoline which causes increase in proliferation of fibroblasts and collagen formation.[43]

**Oral cancer:** Iron insufficiency could lead to oral cancer by affecting the enzymes and enzymatic antioxidation resulting in oxidative stress. This reaction can cause serious damage to cells and DNA by producing excessive free radicals or decreasing the antioxidant defense or both.[46] A decrease in serum iron levels has been reported in patients with oral cancer. This may be attributed to the utilization of iron in collagen synthesis resulting in decrease serum iron levels in patients with oral cancer.[46]

On the other hand, it has also been reported that iron overload could lead to carcinogenesis by provoking DNA damage. Iron induced oxidative stress causes redox regulation failure leading to lipid peroxidation, DNA and protein damage. Iron binding sites on macromolecules serve as centers for repeated production of hydroxyl radicals generated via the Fenton reaction.[47-48]

## CONCLUSION

Iron is the one of the crucial micro element required for human body. Both its deficiency and excess have detrimental effects on tissues especially on oral tissues. Alteration in levels of iron not only act as a causative factor for many disorders but it is also the effect of many diseases thus indicating that iron levels could act as an indicator for the development of certain diseases. Therefore, it is important that homeostasis of iron must be maintained in the body.

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