

Role of Antioxidants in Oral Submucous Fibrosis

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Abstract:

The main purpose of this review article is to increase the awareness about oral submucous fibrosis. It emphasizes the role of antioxidants such as lycopene, β -carotene, α -lipoic acid, α -tocopherol, selenium, and zinc, and their combined effects in antioxidation. A combination therapy as a preventive approach and a line of the treatment regimen to be followed as after surgical or non-surgical approach with all the micronutrient combination definitely increases the antioxidation properties of various nutrient cycles.

Key Words: α -lipoic acid, α -tocopherol, β -carotene, lycopene, oral submucous fibrosis, selenium, zinc

Introduction

Oral submucous fibrosis (OSMF) is a chronic disease and potentially malignant condition of the oral cavity. It is characterized by fibrosis of the soft-tissue resulting in rigidity and progressive inability to open the mouth.

In India, 4/1000 adults in rural areas were found to have this condition. About 5 million young Indians suffer from OSMF as a result of increasing habit of pan chewing habit. Furthermore, the disease is increasing steadily over a period of time.

The OSMF begins with a burning sensation or intolerance to spicy foods. The palate presents with vesicles.

Etiology/Pathogenesis

The OSMF origin seems to be multifactorial. It may be implicated by genetic, environmental, viral infection, social and behavioral effects.

The role of diet and nutrition in prevention has attracted attention. Epidemiological studies indicate diets rich in vitamins A and C like citrus fruits, cruciferous vegetables, green and yellow fruits, and vegetables lower the risks of numerous cancers including oral cancer.¹

Some of the causative agents of OSMF:

- Consumption of chilies
- Deficiency of iron, zinc and essential vitamins²
- An autoimmune role as well as genetic predisposition²
- Areca nut, betel quid, betel nut, and pan masala.

The time to develop seems to vary with different products used. Areca nut usage usually develops OSMF in 3.5 years in younger individuals and 6.5 years in older individuals. With other products, it varies betel quid 7 years, betel nut 5 years and pan masala 4 years.

Role of Oxidative Stress

Tobacco and areca nut chewing elicit immunosuppression by generating high free radical levels. The free radicals mediate phenotypic and gene alterations leading to mutations (neoplastic effect).³

Epidemiological studies show the carcinogenic process occurs by generation of reactive oxygen species (ROS). The enhanced superoxide anions initiate lipid peroxidation (LPO). DNA damage activates pro-carcinogens that alter cellular antioxidant defense system.⁴

Antioxidant Defense Mechanism in OSMF

The antioxidant defense mechanism of the body is exacerbated. The adverse effects of ROS are inhibited by cellular antioxidant defense system.

Vitamin E can reduce oxidative damage by scavenging free radicals. The oxidative stress promotes cellular damage in tobacco users. Malondialdehyde is an end product of LPO and a biomarker of oxidative stress. Non-enzymatic antioxidants are depleted leading to alteration in biochemical parameters. The supplementation of antioxidants may prevent oxidative damage in tobacco users.

Principles of Management

This includes reducing signs and symptoms like:

- Decreasing burning
- Increasing mouth opening
- Increasing tolerance to foods
- Decreasing malignancy.

Management Protocol

The treatment protocol is divided into surgical, physical and medical treatments. A surgical management is an option for management in advanced cases.¹ Physical treatment helps remodeling tissues includes physiotherapy exercises, splints or localized heat by microwave diathermy.¹ Medical treatment can be given orally, topically or by submucosal injections includes:

- Dietary supplements (vitamins, antioxidants)
- Anti-inflammatory drugs (corticosteroids)
- Proteolytic agents (hyaluronidase)
- Anti-cytokines
- Local injection of placental extract 2 ml
- Lycopene (10%) 2000 mcg orally
- Methylcobalamin injection (1500 mcg) given intramuscularly every week.

Cessation of the habits alone may have a considerable effect on the symptoms of OSMF.¹

Pharmacology of Active Ingredients**Lycopene**

Lycopene is a carotenoid. They are natural pigments derived from plants. Carotenoids have anti-carcinogenic and antioxidant properties. Its profound benefits have been demonstrated with precancerous lesions such as leukoplakia.³

Mechanism of action

Lycopene shows abnormal fibroblasts inhibition in OSMF. It also regulates lymphocyte resistance to stress and suppresses inflammatory response. This is the first line of therapy to OSMF. Lycopene exhibits the highest physical quenching rate constant with singlet oxygen.³

β-Carotene

β-carotene is a precursor of vitamin A. It is an antioxidant and radical trapping agent.

Mechanism of action

β-carotene decreases free radical damage. It increases immune response that retards cancer cells development. β-carotene increases T-lymphocytes which increase mitogenic response. β-carotene administration elevates its concentration in blood enhances immunoresponse in patients thereby retards the development of cancer cells.⁵

α-Lipoic Acid (LA)

α-LA is a universal antioxidant. It can remove free radicals both in water as well as lipid medium.⁶

Mechanism of action

α-LA removes hydroxyl radicals and hypochlorous acid thereby terminated single oxygen molecule. α-LA indirectly

maintains cellular antioxidant status by enhancing synthesis of endogenous low molecular weight antioxidants or enzymes and induces their uptake. α-LA increases glutathione (GSH) which is a natural antioxidant at cellular levels. α-LA is absorbed from diet sources and accumulated in tissues.⁷

α-Tocopherol

Vitamin E is eight different forms present in plants (α, β, γ, delta-tocopherol/tocotrienols). In humans only α-tocopherol is retained.

Mechanism of action

α-tocopherol has the antioxidant ability. It inhibits cell proliferation, platelet aggregation and monocyte adhesion, reflecting specific interactions with enzymes, structural proteins, lipids and transcription factors.⁸

Selenium (Se)

Se is essential to prevent nutritional disorders and degenerative diseases. It is an anticarcinogenic agent.⁹

Mechanism of action

Se presents in active site of GSH peroxidase. It is an antioxidant nutrient inhibits unwanted cell growth by eliciting methylated Se metabolites and selenoproteins. Decreased Se concentrations were found in OSMF patients by Khanna *et al.*¹⁰

Zinc

Zinc is essential for multiple cellular functions and increased immunity.

Mechanism of action

Zinc increases immune efficiency by increasing function of cell mediating innate immunity, neutrophils, and natural killer cells. Zinc increases macrophages, phagocytosis intercellular killing and cytokines production. It is needed for DNA synthesis, RNA transcription cell division, and activation.¹¹

Zinc enhances functions of cytokines and their secretions. It functions as antioxidants and stabilizes membranes.¹¹

Zinc levels were 107.13 in OSMF cases and 119.9 in normal individuals. This indicated utilization of zinc by tumor tissues causing zinc deficiency.¹²

Rationale for the Combination

Epidemiological studies have shown carcinogenesis occurs by generation of ROS which act by initiating LPO. Prevention against LPO mediated damage is done by non-enzymatic antioxidants, especially β-carotene and vitamin E.⁶ Since, there is an increase demand for antioxidants a combination therapy of all these antioxidants is necessary (Table 1).

Table 1: Uses of nutrients.

Ingredients	Mode of action	Benefits
Lycopene	Patent anti-cariogenic activity bound to reactive oxygen species	Prevents progression toward malignancy Improves mouth opening
β -carotene	Inhibits mutagenesis Traps free radicals in areas of low oxygen concentration	Effective antioxidant in gums and palate reduces disease severity
α -tocopherol	Scavenging effect – breaks free radical chain reaction Maintains cell membrane integrity	Inhibits cancer cell growth Reduces periodontal inflammation
α -Lipoic acid	Removes the most difficult to remove free radicals Regenerates other antioxidants	Significant reduction in burning sensation
Minerals (Zinc, copper, selenium)	Enzyme activators and subunits of antioxidant defense mechanism	Enhances antioxidant activity

Conclusion

OSMF is a condition with oxidative stress. Strengthening the antioxidant system with supplements improves the signs and symptoms of OSMF. This has been demonstrated with various clinical trials. Hence, a combination of these antioxidant therapies will prevent and also supplement the tissues. The mouth opening also was improved by about 69% with an antioxidant therapy. This is a non-invasive alternative and should be used as a part of the first line of treatment.

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