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**THE RELATIONSHIP OF MICRONUTRIENTS AND ORAL MUCOSA DISEASES:  
 A SYSTEMATIC REVIEW**

Desi Elvhira Rosa<sup>1)</sup>, Nanan Nur'aeny<sup>2)</sup>

<sup>1)</sup>Oral Medicine Specialist Program, Faculty of Dentistry, Padjadjaran University, Indonesia

<sup>2)</sup>Department of Oral Medicine, Faculty of Dentistry, Padjadjaran University, Indonesia

**ABSTRACT**

**Background:** The association between micronutrients and oral mucosa diseases have been studied for a long time by many researchers. Nutritional deficiency can significantly interfere the function of the oral cavity. Various diseases in the oral cavity can occur due to nutritional deficiencies, especially micronutrient deficiencies. **Purpose:** This study aimed to systematically evaluate recently studies that investigating micronutrient level in patients with oral mucosa diseases to determine the relationship of micronutrients and oral mucosa diseases. **Method:** Electronic databases were searched from January 2011 to June 2021 for studies that measured the micronutrients level in patients with oral mucosa diseases. Only case-control studies in human reporting serum, salivary and urine level of micronutrients in oral mucosa diseases were included. The quality of case-control studies was assessed using the quality assessment tool developed by the National Heart, Lung and Blood Institute and Research Triangle Institute International. **Results:** There were 23 case-controlled studies were included in this study. Three studies investigated micronutrients level in recurrent aphthous stomatitis, 5 studies in oral submucous fibrosis, 8 studies in oral lichen planus, 6 studies in oral potentially malignant disorders and oral cancer and 1 study in another oral mucosa diseases. Overall, only 1 (4,35%) was assessed as poor-quality rating. Based on this review, there was a positive association between malnutrition (excess and low) of micronutrients and oral mucosa diseases. **Conclusion:** There is a relationship between malnutrition, either excess or lack of micronutrients on oral mucosal diseases.

**Keywords:** Malnutrition, micronutrients, oral mucosa diseases

**Correspondence:** Desi Elvhira Rosa; Oral Medicine Specialist Program, Faculty of Dentistry, Universitas Padjadjaran, Jl. Sekeloa Selatan No. 1, Bandung, Indonesia; Email: [desi20004@mail.unpad.ac.id](mailto:desi20004@mail.unpad.ac.id)

**INTRODUCTION**

Micronutrients are essential substances for human health contained in foods and are required only in small amounts. They consist of vitamins and essential trace minerals. Micronutrient malnutrition occurs when intakes of micronutrients are too low to meet requirements. It affects 1/3 to 1/2 of population in the world.<sup>1</sup>

The early signs of nutritional deficiencies appear in the soft tissues in the form of thinning, inflammation and ulceration. Nutritional status and oral health reciprocally related and affect each other, nutritional deficiencies have an impairs oral function. Although micronutrients are needed only in small amounts for the human body to function properly, their deficiency leads to critical health problems.<sup>2</sup>

**MATERIALS AND METHODS**

**Data Sources and Search Strategy**

A comprehensive literature search was conducted to identify case-controlled studies investigating the status of micronutrients in oral lesions from 2011 to June 2021. The electronic databases of PubMed, Google Scholar and

Cochrane were searched. A total of 3000 studies were extracted, using the MeSH terms with the keywords micronutrients, trace elements, vitamins and oral lesions. Twenty studies were excluded because of duplicated, nonhuman research, not Scopus indexed. Only studies in English included in this study. Figure 1 shows the flow chart of the search strategy and the selection of articles.

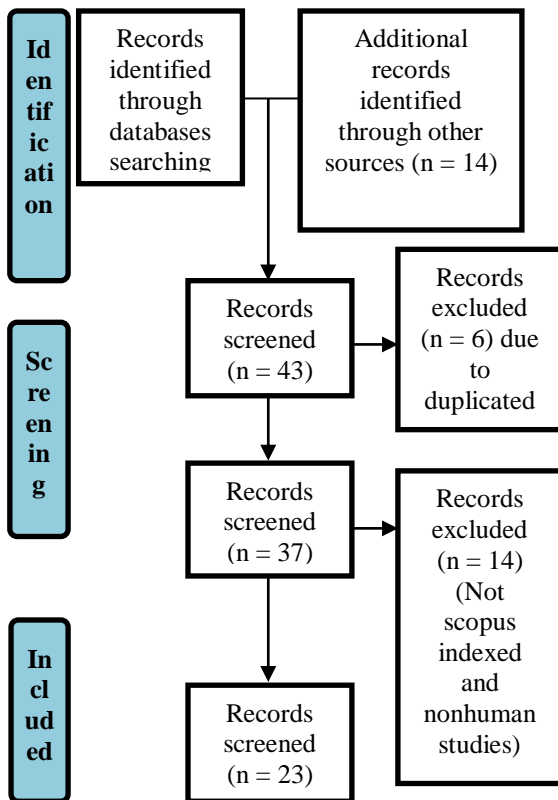
**Inclusion and Exclusion Criteria**

All relevant publications extracted were reviewed independently by two reviewers using the inclusion criteria. Inclusion criteria were cross-sectional studies in human measuring laboratory value of micronutrients in both healthy controls and patients with oral lesions. Only studies in English and Scopus indexed were recruited into this study. Exclusion criteria were studies with nonhuman research. Duplicate experiments were removed, studies not in English and not Scopus indexed also excluded in this study.

**Quality assessment: risk of bias**

The risk of bias assessment was conducted by two authors. The methodological was scored according to the quality assessment tools developed by the National Heart, Lung and Blood Institute and Research Triangle Institute International for Cross-

Sectional. The tools included items for evaluating potential flaws in study methods or implementation, including sources of bias (e.g., patient selection, performance, attrition and study analysis), confounding. Each questions scored with “yes,” “no,” or “cannot determine/not reported/not applicable”. Each study was finally scored as “good” when it has the least risk of bias, “fair” if it is susceptible to some bias and “poor” when high risk of bias is conceivable. There were nine studies assessed as good, thirteen fair and one poor.



**Figure 1.** Flow chart of the search strategy and the selection of articles.

## RESULTS AND DISCUSSION

Based on inclusion and exclusion criteria, there were twenty-three case-control studies were included. Three of these measured the micronutrients level in recurrent aphthous stomatitis (RAS) patients and controls. Five studies measured micronutrients level in oral submucous fibrous, eight studies in oral lichen planus, five studies measured micronutrients level in oral potentially malignant disorders and oral cancer and one study investigated the level of micronutrient in RAS, burning mouth syndrome, oral lichen planus atrophic glossitis and xerostomia. Measurements of micronutrients level were taken directly in different samples such as serum, saliva and urine. The statistical level of micronutrients in oral mucosal

disease patients comparing to controls served in table 1.

### Micronutrients and Recurrent Aphthous Stomatitis

The study of Ozturk, et al<sup>3</sup> found that Selenium (Se), Copper (Cu) and Zinc (Zn) level in patients with RAS lower than the controls. Low of Zn levels in the study probably due to the increased consumption of Zn, ulcer healing continuous process, free radical scavenger of Zinc because of its antioxidant activity, existence of completion in intestinal absorption and the inverse relationship between Cu and Zn concentration. In contradiction, however, copper is highly toxic. Cells have the ability to maintain intracellular copper concentrations. Disturbance of this balance causes excess Cu can induce oxidative stress that could lead to chronic inflammation.

The increase in Cu level in this study may be related to increased intestinal absorption of Cu due to Zn deficiency. Increased plasma Cu concentrations may also arise from the inflammatory tissue damage that release Cu. Contradictive with the study of Slebioda et al<sup>4</sup> that showed insignificant differences in serum zinc levels between RAS patients and generally healthy control subjects, Zinc concentrations in both groups were within the normal range. Sun et al<sup>5</sup> found that RAS patients had a significantly higher frequency of hemoglobin, iron, vitamin B12 or folic acid deficiency and abnormally elevated blood homocysteine level than healthy control subjects. These findings show a significant association of deficiencies of Hb, iron, vitamin B12 and folic acid level with RAS. This is in line with the effect that occurs on the oral mucosa with folic acid deficiency. It plays a critical role in erythropoiesis, pregnancy, cardiovascular system and mucosa health. Folic acid deficiency is seen in decreased epithelial integrity and barrier function accompanied by staining of the basal cells with degeneration and widening of the intracellular spaces in the spinous layer. This condition of the epithelium in the process of maturation and keratinization predisposes to infection and ulceration of the oral mucosa.<sup>6</sup> Another study that investigate micronutrient level in RAS was the study by Bao, et al.<sup>7</sup> In this study, there was a significant difference between Zinc deficiency in RAS than healthy controls.

### Micronutrients and Oral Submucous Fibrosis (OSMF)

The study from Guruprasad<sup>8</sup> and Karthik<sup>9</sup> showed significantly lower levels in OSMF than healthy controls. Serum Iron can be a predictor for the progression of OSMF. Guruprasad<sup>8</sup> also evaluated the correlation between serum Vitamin C levels in OSMF individuals. They found that OSMF group showed significant lower levels of serum Vitamin C. OSMF is basically a disorder of

collagen metabolism where Vitamin C gets utilized in conversion of proline into hydroxyproline. This hydroxylation reaction requires ferrous Iron and Vitamin C.

Study from Arakeri<sup>10</sup> investigated the concentration of copper ions in drinking water and assess whether copper has a role in the pathogenesis of OSMF. They found that the mean (SD) concentration of copper in the home drinking water of patients with OSMF was significantly higher than in the controls. Patients with OSMF also showed significant higher copper concentrations in serum, saliva and serum ceruloplasmin than controls.

### **Micronutrients and Oral Lichen Planus (OLP)**

There were eight studies investigate relationship between micronutrients and oral lichen planus. According to Bao<sup>11</sup>, the frequencies of serum ferritin and vitamin B12 deficiency in OLP patients were both significantly higher than those of the healthy controls. Rezazadeh<sup>12</sup> in Southwest Iran found that vitamin B12 and D3 were higher in the OLP group but the difference was not significant. They also measure vitamin A, C and E levels in OLP patients and controls but did not have a significant difference in OLP patients and healthy groups. It did not show a significant difference. Vitamin A is necessary to sustain cellular differentiation, uphold epithelial integrity, production of red blood cells and reproductions, as well as develop resistance against infections. Vitamin C is a cofactor including various collagen synthesis reactions.<sup>13</sup> Vitamin E plays a role in increasing immunity, controlling free radicals mediated cell disturbances, maintaining membrane integrity and inhibiting cancer cell growth, cytotoxicity.<sup>13</sup>

In other study, Rezazadeh<sup>14</sup> investigated the plasma levels of magnesium (Mg), calcium (Ca), zinc (Zn), copper (Cu) and iron (Fe) in oral lichen planus. Only calcium level was significantly higher in patients than in healthy control participants. The results were different with another study by Rezazadeh<sup>12</sup> investigated salivary concentrations of Magnesium (Mg), Calcium (Ca), Iron (Fe), Zinc (Zn) and Copper (Cu). They found only mean Magnesium level was significantly lower in patients than healthy control subjects.

Chang found in their study<sup>15</sup> that OLP patients had significantly lower mean Hb (for both men and women), iron (for women only), vitamin B12 and folic acid levels than healthy control participants. Chen<sup>16</sup> assessed serum level of iron, vitamin B12 and folic acid then found that patients with OLP underwent deficiencies of iron, vitamin B12 and folic acid significantly different. But only mean concentration of iron in women and vitamin B12 had significantly different. However, there were no significant differences in the blood levels of Hb,

iron, vitamin B12, and folic acid between MjEOLP (Major Erosive Lichen Planus) and MiEOLP (Minor Erosive Lichen Planus) or NEOLP (Non-Erosive Lichen Planus). The study of Zinc, Copper, Iron and Magnesium salivary and serum level by Chuykin<sup>17</sup> found that the healthy controls have serum and salivary level of trace elements mention above significantly higher except the serum level of Magnesium. It is known that zinc is one of the most important trace elements which is involved in the growth and development of the epithelium. The change of zinc content in different biological fluids was demonstrated in patients with lichen planus.

Nicolae's<sup>18</sup> measured the level of ascorbic acid in urine. This study analysed the status of ascorbic acid in patients with LP (Cutaneous Lichen Planus/ CLP and Oral Lichen Planus/ OLP). The results showed a statistically significant reduction in urinary levels of ascorbic acid in patients with LP (CLP and OLP) compared to controls. Bao<sup>11</sup> in another study found that patients with OLP had significantly lower serum Zinc level and also had significantly proportion of Zinc deficiencies.

### **Micronutrients and Oral Potentially Malignant Disorders (OPMD) and Oral Cancer**

There were six studies investigated the level of micronutrients in patients with OPMD and oral cancer. Shetty<sup>19</sup> found there was a significant increase the levels of Cu in the OSMF group when compared to controls. The Cu levels were significantly elevated in the OL and OSCC groups when compared to healthy controls. However, there was no statistically significant difference when the groups OL and OSCC were compared. There was reduction in the salivary Zn levels in three study groups (OSMF, OL and OSCC) and statistically different when compared to healthy controls. There was no significant difference in the mean zinc levels between the OL and OSMF groups. Zinc has the ability to induce an intrinsic protein-based enzyme (lysyl-oxidase) in the connective tissue that cross links collagen and elastin which is an important factor in etiopathogenesis of OSMF.<sup>19</sup>

The study of serum and salivary level of ascorbic acid in patients with oral potentially malignant disorders by Bhat<sup>20</sup> showed significantly higher level in healthy control than OPMD, healthy control than oral cancer and OPMD than oral cancer. Vitamin C is the major water-soluble antioxidant. Vitamin C can act as primary line of defense against free radicals in whole blood and plasma. Epidemiological studies have suggested that the risk of certain cancers has been inversely proportional to the fruit and vegetable consumption containing essential antioxidant micronutrients, other essential micronutrients along with phytochemicals and fiber.

Ayinampudi<sup>21</sup> investigate salivary level of zinc and copper in patients with OPMD (OSMF, OLP

and OL). They found that salivary level of copper was significantly higher in OPMD than in controls and significantly higher in OSCC than in OPMD. However, there was not significantly higher in OSCC comparing to OPMD. Salivary level of Zinc in OPMD significantly higher than in healthy controls.

As well as salivary level of Zinc, there were significantly higher in OPMD than in controls and significantly higher level in OSCC than controls. The same result also seen in significantly higher salivary level of OSCC and OPMD. Zinc is essential for regulation of cell cycle and cell division and also essential for DNA polymerase activity. It is also particularly important for rapid cell proliferation encountered in growing tumors. In early stages, copper plays an important role in tumor angiogenesis. Copper is needed in activation of endothelial cell as it stimulates their proliferation and activation. The level of ceruloplasmin, the principal copper transporting protein, increases malignant progression that affect tumors become palpable.<sup>21</sup>

Tiwari study<sup>22</sup> that comparing serum level of copper and iron in OPMD, OSCC and healthy control showed that copper level significantly higher in OSCC then in OPMD and OPMD higher than healthy controls. While the iron level significantly lower in OSCC than OPMD and OPMD lower than healthy controls. The lower level of iron appears to be the effect of the disease process rather than its cause. Serum iron levels are one of the biochemical indicators for nutritional assessment because iron is essential in our body. The cancer cells need iron in the same amounts as the normal cells. They express their transferrin receptors to get iron which may explain depletion of iron in our body. Hypoferremia can be seen in association with carcinogenesis and that is why iron levels can be a prognostic indicator. However, excess iron is also known to aid carcinogenesis by provoking DNA damage. Iron and oxygen together has a biologically damaging effect due to increased formation of free radicals.<sup>22</sup>

From the study by Kaur<sup>23</sup>, we found levels of vitamins C and E were significantly lower followed by those in advanced stages of precancer relative to those in the early stages of disease. The levels of vitamins C and E were significantly lower in oral leukoplakia, submucous fibrosis and lichen planus. There is a complex process in development of cancer in humans. This involves molecular actions and cellular alterations which in turn contribute to cancer development. The generation of reactive oxygen species (ROS) is a different type of endogenous and exogenous stimulation mediated the overall process of cancer development. ROS has been reported not only initiates but also promotes multistep of carcinogenesis. Animal and cell culture studies have shown that Vitamin E,

Vitamin C, beta-carotene and the mineral selenium prevent the transformation of normal cells to cancer. Vitamin E as an antioxidant helps to prevent and slow the growth of head and neck cancer, enhance the effect of chemotherapy and diminish the side effect from both chemotherapy and radiation therapy for cancer patients. Vitamin-E has an antioxidant effect by acting as a lipid-soluble free radical molecule in cell membranes. Another anti-carcinogenic effects of vitamin E are inhibiting nitrites in some foods to form carcinogenic chemical nitrosamine and promoting the function of immune system.<sup>13</sup>

Serum level of copper studied by Khanna<sup>24</sup> showed significantly higher in oral cancer comparing to OPMD and OPMD were higher than healthy controls. As well as copper, serum zinc level was higher in OSCC than in OPMD and OPMD higher than controls. While serum molybdenum and selenium showed the significantly lower in OSCC comparing to OPMD and OPMD were lower than controls. The Cu/Zn ratio has been proposed as a reliable tool in the diagnosis and prognosis as an indicator of the disease but in this study the ratio obtained in the OSMF, OSCC and normal group were found to be not significant. The increase in serum Cu can be occurred due to high Cu in areca nut, a major etiological factor in pathogenesis of OSMF. It initiates fibrogenesis by increasing the regulation of lysyl oxidase that cause inhibition of collagen degradation. On the other hand, Se acts as the enzyme glutathione peroxidase. Se is also known as an antioxidant nutrient. Se has a complex role of immune modulation and anti-proliferative properties by making immune cells more resistant to oxidative stress.<sup>24</sup>

### **Micronutrients and Other Oral Mucosa Disease**

According to Bao<sup>7</sup> in their study of serum Zinc level in oral mucosa disease (OMD) including RAS, OLP, burning mouth syndrome (BMS), atrophic glossitis (AG) and xerostomia, the mean serum zinc levels in the healthy control group was higher than the levels of all other groups and statistically differences. The mean serum zinc levels of all patients with any OMD were significantly lower than the control group although still in normative range. The zinc deficiency rate was significantly difference in oral mucosa diseases (OMD) group (all patients with OMD).<sup>7</sup> Zinc, in the oral cavity can be found in saliva, dental plaque and in the hard tissues. It contributes to healthy teeth formation. Since taste buds are known to contain various zinc containing enzymes, zinc deficiency will cause taste disorders. Decreased of taste sensation and lingual trigeminal nerve sensitivities as well as reduced salivary flow has been associated with zinc deficiency.<sup>25</sup> From this study, we can conclude that there is a relationship between malnutrition, either excess or lack of micronutrients

on oral mucosal diseases. Deficiency or excess levels of micronutrients can cause oral mucosa disease. We can monitor patients' nutritional intake by suspecting certain micronutrient deficiencies. In

the future, it is hoped that research on micronutrients administration in oral mucosa diseases can be carried out.

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