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An Evaluation of Estimation of Salivary Copper and Zinc Levels in Oral Cancer Patients of Middle Age Range: An Original Research Study

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KEYWORDS

Oral Squamous Cell Carcinoma, Pre-Malignant, Zinc, Copper, Oral Leucoplakia, Submucous Fibrosis

ABSTRACT:

Aim: This study aims to analyze Salivary Copper and Zinc Levels in middle-aged patients with oral cancer.

Materials and Methods: This study involved 60 patients, aged 30-55, with sore or ulcer lasting over 3 weeks and mucosal patches, seeking treatment. The participants were divided into three groups: Group 1 had 20 patients with confirmed oral squamous cell carcinoma; Group 2 had 20 patients with pre-malignant lesions, specifically oral submucous fibrosis; and Group 3 included 20 healthy individuals. Salivary copper and zinc levels were measured by collecting 2-5 ml of resting saliva, centrifuging it, and analyzing it using the ERBA CHEM 5 semi-auto analyzer. SPSS software was used for statistical comparison of means using Student's t-test or ANOVA.

Statistical Analysis and Results: The study observed markedly elevated copper levels in individuals diagnosed with oral squamous cell carcinoma, with a mean concentration of 250.50±62.4 µg/dl. In contrast, when examining premalignant conditions, the average copper level was significantly lower at 190.98±18.4 µg/dL. Healthy individuals exhibited the lowest copper levels, at 120.67±18.2 µg/dl. On the other hand, zinc levels presented a different trend. The zinc concentration was notably reduced in those with oral squamous cell carcinoma, recorded at 85.15±16.85 µg/dl. In individuals with premalignant lesions, the zinc levels were slightly higher at 86.19±12.56 µg/dl, while healthy individuals had the highest zinc levels among the groups, measuring 87.56±18.5 µg/dl.

Conclusion: This study found that cancer patients often have elevated serum copper levels and decreased serum zinc levels; higher copper is linked to disease progression and poor prognosis, while lower zinc is associated with greater disease severity.

Introduction

Oral cancer is a grave condition that often reveals itself through persistent lesions within the oral cavity. These lesions may appear as conspicuous red or white patches, painful ulcers, or noticeable masses on the lips, inside the mouth, or in the throat. This type of cancer

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predominantly originates in the squamous cells that form the lining of these vital areas. Several key risk factors play a significant role in the development of oral cancer. Notably, the use of tobacco, whether through smoking or smokeless forms, poses a major threat, as does excessive consumption of alcohol.[1,2] Additionally, infection with human papillomavirus type 16 (HPV-16) has been identified as a crucial factor, particularly affecting younger individuals who appear to be especially vulnerable. The prognosis for patients diagnosed with early-stage oral cancer (Stages I and II) is remarkably optimistic. Those in these stages experience a high success rate in treatment, with survival rates soaring between 80% and 90%.[3,4] However, a diagnosis at more advanced stages leads to a disheartening decline in survival rates, plummeting to between 50% and 60%. Among the various forms of oral cancer, Oral Squamous Cell Carcinoma (OSCC) is the most prevalent, accounting for more than 90% of diagnosed malignancies within the oral cavity. OSCC is notorious for its aggressive nature and typically arises from critical areas, such as the tongue or the floor of the mouth. The primary factors contributing to the onset of this formidable cancer include tobacco usage, alcohol intake, and HPV infection, underscoring the importance of awareness and early detection in improving outcomes.[5,6] Clinically, it presents as persistent ulcers, white or red patches, or lumps that do not heal. Treatment protocols often involve surgical intervention, frequently accompanied by radiotherapy to eradicate tumour cells and prevent recurrence. Another condition of concern in the oral cavity is Oral Submucous Fibrosis (OSF/OSMF), a chronic and progressive disease that is particularly notable for being premalignant. Characterised by juxta-epithelial inflammation and gradual fibrosis, OSF is predominantly driven by the habitual chewing of areca nut.[7,8] This condition leads to considerable stiffening of the oral mucosa, resulting in severe burning sensations and restricted mouth opening, known as trismus, which can significantly impair quality of life. Recent research has highlighted the role of biomarkers in assessing and diagnosing oral cancer. In patients diagnosed with Oral Squamous Cell Carcinoma, salivary copper levels are significantly elevated, with mean concentrations ranging approximately from 163 to 249 µg/dL.[9,10] In contrast, healthy individuals show much lower levels of around 103 ± 123 µg/dL. This increase in copper is not only indicative of the presence of OSCC but also correlates with disease progression and cytomorphological changes observed in the affected tissues. An analysis of zinc (Zn) levels has demonstrated consistently lower concentrations in both serum and saliva of OSCC patients compared to healthy controls. This deficiency is often related to tumour progression, increased invasiveness, and compromised nutritional health. Specifically, serum zinc levels below 104.9 ± 11.1 µg/dL are recognised as a significant predisposing factor for the development of malignancies in the oral cavity.[11,12] For laboratory diagnostics, the Erba Chem 5X is a highly compact and efficient semi-automated clinical chemistry analyser. It is purposefully designed to facilitate routine laboratory testing and is particularly adept at handling electrolytes and immunoturbidimetric assays. Its widespread use in small to medium-sized laboratories can be attributed to its affordability and an extensive menu of tests, making it an invaluable tool in the clinical setting.[13] This study aims to analyse Salivary Copper and Zinc Levels in middle-aged patients with oral cancer.

Materials and Methods

This study focused on a cohort of 60 patients who presented to the clinic with a primary complaint of sore lesions or ulcers in the oral cavity that had persisted for over three weeks. These patients exhibited distinctive symptoms, including mucosal patches, unexplained dental loosening not related to periodontal disease, and significant changes in the texture or colour of their mucosal tissues. Following a meticulous clinical examination and subsequent histological assessment, a confirmed diagnosis of primary oral squamous cell carcinoma (OSCC) was established in 20 of the participants. Moreover, 20 patients were identified as having premalignant lesions, while the remaining 20 individuals were deemed healthy and served as a control group. The study encompassed both male and female participants aged between 30 and 55 years, ensuring a diverse demographic within this age range. The inclusion criteria were carefully defined, selecting patients who not only had a biopsy-confirmed diagnosis of primary oral squamous cell carcinoma but also had completed their clinical and pathological records. These individuals typically exhibited signs of suspected malignant lesions and had documented histories of tobacco, alcohol, or betel quid use, all of which are

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known risk factors for oral malignancies. In contrast, the exclusion criteria were stringent, eliminating patients who had previously undergone chemotherapy or radiotherapy for any diagnosis of head and neck cancer. Additionally, individuals with incomplete medical records, a prior history of oral cancer or recurrent disease, significant immune disorders such as HIV or hepatitis, as well as those suffering from severe systemic diseases or distant metastases involving the head and neck were also excluded from the study. Informed consent was meticulously obtained from all participants prior to their involvement; ensuring ethical standards were upheld throughout the research. The participants were divided into three distinct groups, each comprising 20 individuals. Group 1 included those diagnosed with oral squamous cell carcinoma, where the evaluation of salivary levels of copper and zinc was conducted using the ERBA Chem 5 semi-automated analyzer, followed by comprehensive statistical analyses to interpret the findings. Group 2 consisted of patients presenting with premalignant oral submucous fibrosis, whose salivary copper and zinc levels were assessed using the same methodology, ensuring consistency across the evaluation. Group 3 comprised healthy individuals, whose salivary copper and zinc levels were similarly analyzed, serving as a baseline comparison for the other groups. To facilitate the analysis, a blood sample of 5 ml was meticulously collected under strict aseptic conditions and transferred into acid-washed test tubes. This blood sample was then centrifuged at 2500 revolutions per minute for 15 minutes to separate the serum, which was preserved in a frozen state until further analysis could be conducted. The serum levels of zinc and copper were evaluated using specific reagents provided alongside the ERBA Chem 5 semi-automated analyzer. The primary aim of this research was to compare and analyze the salivary levels of these essential trace metals in middle-aged patients diagnosed with oral cancer, with the intention of elucidating potential correlations between the concentrations of copper and zinc and the presence of oral malignancies. This investigation holds promise for enhancing the understanding of the biochemical underpinnings associated with oral cancer and could potentially guide further research and clinical approaches in managing this condition.

Statistical Analysis and Results

In this research, we employed SPSS version 31.0 software to perform all statistical analyses. This comprehensive tool allowed us to rigorously analyse our data and draw meaningful conclusions from our findings. To assess the significance of our findings, we employed the chi-square test, effective for comparing proportions across groups. This method enabled us to rigorously analyse categorical data and accurately reflect trends within the dataset.

Results

This study encompassed a total of 60 patients aged between 30 and 55 years, comprising both males and females. Table 1 presents a statistical description of the age and gender demographics of the participants, while Graph 1 illustrates the distribution of patients along with associated demographic details, revealing a cohort of 32 males and 28 females, thereby summarizing the total study group size of 60 individuals. Participants were categorized into three distinct groups, each containing 20 individuals. Group 1 included patients diagnosed with oral squamous cell carcinoma (OSCC). In this group, we evaluated the salivary levels of copper and zinc, utilizing the ERBA Chem 5 semi-automated analyzer, followed by thorough statistical analyses to interpret the results. Group 2 consisted of patients presenting with premalignant oral submucous fibrosis, in which salivary levels of copper and zinc were assessed using the same methodology to maintain uniformity in the evaluation process. Lastly, Group 3 comprised healthy individuals, whose salivary copper and zinc levels were similarly analyzed, providing a baseline comparison for the other groups involved in the study. Table 2 details the findings for Group 1 (n=20), where salivary copper levels in patients with oral squamous cell carcinoma were assessed. The results indicated an average salivary copper level of 250.50 ± 62.4 µg/dl after analysis with the ERBA Chem 5 semi-automated analyzer. The significance of these findings was evaluated using the Pearson Chi-Square test, confirming their statistical relevance. Table 3 highlights zinc levels in patients diagnosed with oral squamous cell carcinoma, where the salivary zinc levels were also assessed using the ERBA Chem 5 semi-automated analyzer. The findings showed an average salivary zinc level of 85.15 ± 16.85 µg/dl, with the significance of

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these results similarly determined through the Pearson Chi-Square test. For Group 2 (n=20), Table 4 presents the salivary copper levels in patients with oral submucous fibrosis. The analysis revealed an average level of 190.98 ± 18.4 µg/dL for salivary copper, evaluated through the ERBA Chem 5 semi-automated analyzer, with the findings' significance assessed using the Pearson Chi-Square test, reinforcing the consistency of the methodology. Table 5 discusses the salivary zinc levels in patients with oral submucous fibrosis, where the average zinc concentration was found to be 86.19 ± 12.56 µg/dl, again assessed with the ERBA Chem 5 semi-automated analyzer and subjected to Pearson Chi-Square test for statistical significance. Table 6 encompasses findings from Group 3 (n=20), which consisted of healthy individuals. The salivary copper levels recorded for this group averaged 120.67 ± 18.2 µg/dl, determined through the same analytical approach, with significance evaluated through the Pearson Chi-Square test. Similarly, Table 7 outlines the salivary zinc levels in healthy individuals, where the average level was measured at 87.56 ± 18.5 µg/dl, with analysis conducted using the ERBA Chem 5 semi-automated analyser, and the significance confirmed with the Pearson Chi-Square test. Lastly, Table 8 provides a comprehensive estimation among all studied groups, evaluated through one-way ANOVA, yielding insights into the variations in salivary copper and zinc levels across the different patient categories. This detailed statistical assessment serves to underpin the conclusions drawn from the study.

Table 1: Age & gender based statistical description of contributing patients

Age Group (Yrs)	Male	Female	Total	P value
30-35	5	6	11	0.06
36-40	6	7	13	0.50
41-45	6	5	11	0.01*
46-50	7	6	13	0.60
51-55	8	4	12	0.50
Total	32	28	60	*Significant
*p<0.05 significant				

Graph 1: Patients demographic distribution and associated details

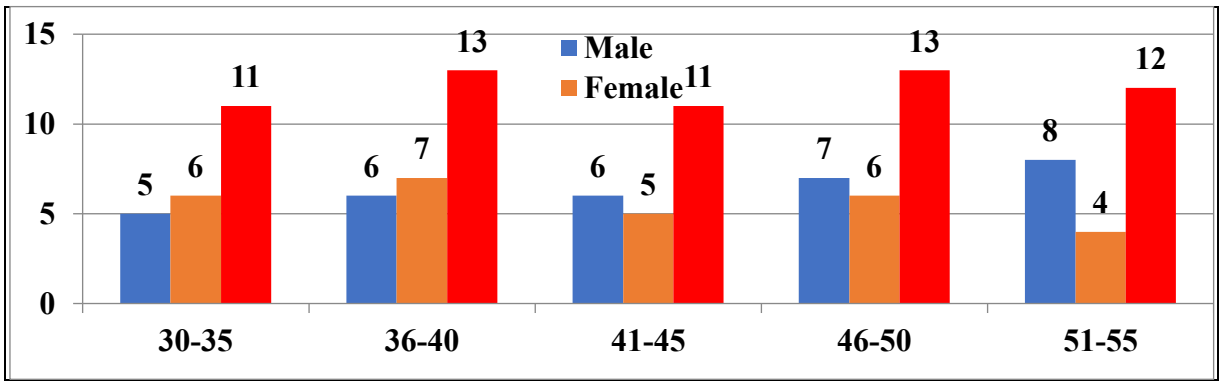

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Table 2: Group 1 (n=20) Salivary copper levels in patients with oral squamous cell carcinoma were determined using the ERBA Chem 5 semi-automated analyser and evaluated. To assess the significance of the findings, the Pearson Chi-Square test was employed

Trace metals	Mean value	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Copper levels	250.50±62.4 µg/dl	2.20	2.04	2.02	1.16	1.19	0.70
*p<0.05 significant							

Table 3: Group 1 (n=20) Zinc levels in patients with oral squamous cell carcinoma were determined using the ERBA Chem 5 semi-automated analyser and evaluated. To assess the significance of the findings, the Pearson Chi-Square test was employed

Trace metals	Mean value	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Zinc levels	85.15±16.85 µg/dl	1.09	1.13	1.34	1.14	1.19	0.08
*p<0.05 significant							

Table 4: Group 2 (n=20) Salivary copper levels in patients with premalignant lesion, oral submucous fibrosis, were determined using the ERBA Chem 5 semi-automated analyser and evaluated. To assess the significance of the findings, the Pearson Chi-Square test was employed

Trace metals	Mean value	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Copper levels	190.98±18.4 µg/dL	1.20	1.06	1.02	1.07	1.09	0.50
*p<0.05 significant							

Table 5: Group 2 (n=20) Zinc levels in patients with premalignant lesion, oral submucous fibrosis,were determined using the ERBA Chem 5 semi-automated analyser and evaluated. To assess the significance of the findings, the Pearson Chi-Square test was employed

Trace metals	Mean value	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Zinc levels	86.19±12.56 µg/dl	1.05	1.06	1.02	1.09	1.06	0.06

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*p<0.05 significant

Table 6: Group 2 (n=20) Salivary copper levels in healthy individuals were determined using the ERBA Chem 5 semi-automated analyser and evaluated. To assess the significance of the findings, the Pearson Chi-Square test was employed

Trace metals	Mean value	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Copper levels	120.67±18.2 µg/dl.	1.18	1.05	1.06	1.07	1.08	0.50
*p<0.05 significant							

Table 7: Group 2 (n=20) Zinc levels in healthy individuals were determined using the ERBA Chem 5 semi-automated analyser and evaluated. To assess the significance of the findings, the Pearson Chi-Square test was employed

Trace metals	Mean value	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Zinc levels	87.56±18.5 µg/dl	1.10	1.08	1.20	1.17	1.15	0.05*
*p<0.05 significant							

Table 8: Estimation amongst all studied groups using one-way ANOVA

Variables	Degree of Freedom	Sum of Squares ∑	Mean Sum of Squares m∑	F	Level of Sig. (p)
Between Groups	4	2.267	2.356	1.2	0.02*
Within Groups	22	2.245	2.671	_	
Cumulative	213.17	40.242	*p<0.05 significant		

Discussion

Xu C et al reviewed in their study that Oral Squamous Cell Carcinoma (OSCC) is a significant type of cancer that arises from the squamous cells located in the oral mucosa, representing a critical health challenge worldwide with over 350,000 new cases reported annually. The development of OSCC is closely associated with several key risk factors, including the use of tobacco products, heavy alcohol consumption, chewing betel quid, and infection with high-risk types of human papillomavirus (HPV), particularly type 16. Patients often present with troubling symptoms such as persistent ulcers, the presence of white or red patches in the mouth, pain during chewing and swallowing, and difficulty in swallowing. The process of diagnosing OSCC typically begins with a physical examination, which is then followed by a biopsy. This is considered the gold standard for confirming malignancy. Treatment options are often dependent on the cancer stage and commonly involve surgical resection of the tumour. In some cases, patients may also receive chemotherapy or

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radiotherapy.[14,15] Badwelan M et al included in their study that the overall prognosis shows that the five-year survival rate stands at approximately 63%, with significantly better outcomes for those diagnosed in the early stages, achieving survival rates as high as 83%. Moreover, conditions such as Oral Submucous Fibrosis (OSF) are recognised as premalignant and significantly elevate the risk of OSCC development, with the malignant transformation rate ranging between 1.5% and 15%. OSF is strongly associated with the consumption of areca nut and tobacco, leading to increased stiffness of the oral tissues. Common symptoms include a burning sensation in the mouth and whitening of the oral mucosa, which can eventually progress to restricted mouth opening. Management strategies focus on eliminating harmful habits, and may involve steroid injections, physiotherapy, or surgical intervention in more advanced cases. Early detection of these conditions is vital, as progression often leads to irreversible consequences.[16,17] Shih YH et al included in their studies that salivary copper levels are significantly elevated in individuals diagnosed with OSCC, indicating its potential role in tumour metabolism and the formation of blood vessels (angiogenesis). Given saliva's non-invasive collection method, it serves as a valuable medium for analysing trace elements like copper, particularly when assessing pre-malignant conditions and malignant lesions. Notably, higher salivary copper levels correlate with increased severity of dysplasia or cancer. Furthermore, the ratio of copper to zinc in saliva exhibits distinct patterns in OSCC, with some studies indicating an elevated copper-to-zinc ratio that enhances the sensitivity of these measurements as potential biomarkers for the disease.[18,19] Mathur A et al reviewed in their study that advanced techniques, such as inductively coupled plasma mass spectrometry (ICP-MS) are employed for the precise quantification of these trace elements. In contrast, zinc levels tend to decline in patients with OSCC, particularly in the more advanced stages of the disease, and this decrease is associated with lymph node metastasis and greater tumor aggression. The observed rise in the copper-to-zinc ratio suggests a potential metabolic imbalance, as low zinc levels can foster cancer proliferation and impair immune responses.[20,21] Kudva AK et al showed un their study that nutritional deficiencies, especially concerning serum zinc, are often linked to poor nutritional status in cancer patients. As a result, serum and salivary copper/zinc ratios, along with levels of Zinc-alpha 2 glycoprotein (ZAG), are emerging as promising early-stage OSCC biomarkers. Additionally, ongoing research is exploring metallo-immunotherapy as a means to manipulate zinc levels for tumour suppression.[22,23] Formigari A et al reviewed in their study that while the trend of decreased zinc levels in OSCC patients is well-documented, some studies have highlighted nutritional factors that may influence zinc levels, underscoring the necessity for further investigation. In the realm of diagnostics, the Erba Chem 5X stands out as a compact clinical chemistry analyser, recognised for its affordability and advanced capabilities in performing routine assays, further enhancing the diagnostic landscape for conditions such as OSCC. Similar and somewhat contrasting findings were advocated by several other researchers.[24,25,26]

Conclusion

In the context of their study, the authors conducted a thorough examination of salivary copper and zinc levels in patients with oral cancer, specifically focusing on individuals in the middle age range. The results of their analysis concluded a significant finding: serum copper levels were notably elevated in cancer patients, while there was a corresponding decrease in serum zinc levels. This imbalance resulted into a heightened copper to zinc (Cu/Zn) ratio, a factor that has been associated with tumor progression, advanced stages of the disease, and an increased risk of mortality among patients. This study underscores the potential role of these trace elements in the pathophysiology of oral cancer.

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