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Research Article

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Alteration in serum levels of copper, iron, zinc, vitamin C and lipid profile in patients with oral cancer and oral sub-mucous fibrosis

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ABSTRACT

In human race the most prevalent oro-dental diseases include; dental caries, pulpal and peri-apical inflammation, periodontal problems and many more conditions. Among these conditions cancer of the oral cavity in India has the uncertainly peculiarity among the world. Cancer of the oral cavity secures first rank among all cancers in male patients in India. Globally, Cancer of the oral cavity is 3rd most common cancer in males and 4th in females. Timely recognition of oral cancers and pre-cancers improves quality of life for affected patients. Aim of this study is to evaluate Serum levels of lipids, copper, iron, Zinc, vitamin C in patients with oral Cancer (Squamous cell carcinoma) and oral sub-mucous fibrosis (OSMF) associated with habit of tobacco consumption in any form and its comparison patients with oral habit of tobacco consumption in any form but without any lesion and with the patients among control group i.e. without any habit / lesion and in the patients having habit of tobacco but no lesion. After obtaining ethical clearance from the Institution and informed written consent from participants, 30 individuals with physical status ASA I and ASA II are included in this study. It can be concluded from the present study that levels of trace elements and lipids could be used as a prospective prognostic and diagnostic markers in patients with oral cancer / pre-cancerous lesions.

Keywords: Serum levels of Copper, Iron, Zinc, Vitamin C, Lipid profile, oral cancer, OSMF

INTRODUCTION

Oral health is an important as well as an essential constituent of complete general health all through life. Dental diseases are not merely toothache; it can be the source for more serious problems. The sternness of dental diseases ranges from just a common cavity of tooth or small traumatic ulcer up to lethal oral cancer [1]. In human race the most prevalent oro-dental diseases include; dental caries, pulpal and peri-apical inflammation, periodontal problems and many more conditions. Among these conditions cancer of the oral cavity in India has the uncertainly peculiarity among the world. Cancer of the oral cavity secures first rank among all cancers in male patients in India [2]. Globally, Cancer of the oral cavity is 3rd most common cancer in males and 4th in females [3]. Oral cancer, pre-cancerous lesions/conditions has multifactorial etiology and is appreciably allied with peril factors of the individual's lifestyle, mostly, use of tobacco, spicy food, alcohol and smoking [4].

Timely recognition of oral cancers and pre-cancers improves quality of life for affected patients. At this time affirmation of pre-cancer and cancer is by histopathology. Therefore, there is a call for development of susceptible, precise and quicker tests as abet in the early diagnosis of the primary tumor and its recurrence or malignant conversion in premalignant states [5]. Hence, detection of trace elements which can forecast disease succession is obligatory for better management of these disorders. Lately, trace elements are gaining much consideration in the detection of oral cancer and pre-cancer as their levels are significantly changed in head and neck, lung and breast

carcinomas and they also have an imperative role in carcinogenesis [5]. Hence a comprehensive study has been carried out to estimate changes in Serum levels of Copper, Iron, Zinc, Vitamin C and Lipid Profile in patients with oral Cancer and oral sub-mucous fibrosis (OSMF).

Aim & Objectives

- To evaluate Serum levels of lipids, copper, iron, Zinc, vitamin C in patients with oral Cancer (Squamous cell carcinoma) and oral sub-mucous fibrosis (OSMF) associated with habit of tobacco consumption in any form and its comparison with the patients among control group i.e. without any habit / lesion and in the patients having habit of tobacco but no lesion.
- To evaluate Serum levels of lipids, copper, iron, Zinc, vitamin C in patients with oral habit of tobacco consumption in any form but without any lesion and its comparison with the patients among control group.
- To assess whether such altered levels, if any could be used as a bio-chemical marker for oral cancer and oral sub-mucous fibrosis (OSMF).

EXPERIMENTAL SECTION

Ethical Approval – Ethical approval was taken by Ethical committee of "Kothiwal Dental College & Research Centre, Moradabad, Uttar Pradesh, India".

After obtaining ethical clearance from the Institution and informed written consent from participants, 30 individuals with physical status ASA I and ASA II are included in this study. The patients were equally and randomly allocated to one of the below mentioned groups without any bias for the purpose of this study.

Group 1: patients with oral Cancer (Squamous cell carcinoma) and oral sub-mucous fibrosis (OSMF) associated with habit of tobacco consumption in any form
Group 2: patients with oral habit of tobacco consumption in any form but without any lesion
Group 3: control group i.e. without any habit / lesion

Exclusion Criteria:

Patients with known cardiac disease, pulmonary disease, metabolic disease, disease affecting fluid and electrolyte balance of the body, taking anti-oxidants /multivitamin preparations, taking lipid lowering drugs, women on oral contraceptives and patients who were not willing to be a part of study, were excluded from the study.

Collection of Sample:

Taking aseptic precautions, approximately 10 ml of blood samples were collected, from in appropriate sterile vials by venous arm puncture after overnight fasting and kept standing for 30 minutes at room temperature. Then the serum was separated by centrifugation at 3000 rpm for 10-15 minutes. Precautions were taken to prevent the contamination of samples by other elements. After separation of serum lipid profile was analyzed, Serum iron, copper and zinc were detected by colorimetric method; Estimation of Vitamin C was done by 2-4 dinitrophenylhydrazine method.

RESULTS AND DISCUSSION

Variables of study groups were shown in Table 1. Study subjects were composed of 25 male (83.3%) and 05 (16.6%) female individuals. The results were expressed as Mean ± SD values. The mean, standard deviation and P value of copper, iron, Vitamin C, Zinc, triglyceride, cholesterol, HDL, LDL and VLDL levels in the groups were calculated and compared. Mean age of patients in group I, group II and group III is 50 ± 13.37 years, 36.5 ± 10.2 years and 42 ± 11.57 years respectively (table 1) which is statistically not significant. There was a significantly increased level of mean serum copper and decreased level of iron was found in group I and II as compared to the controls ($P < 0.001$) (table 1), significantly decreased level of vitamin C was found in group I and II as compared to the controls ($P = 0.002$) (table 1) and a significantly decreased level of zinc was found in group I and II as compared to the controls ($P < 0.001$) (table 1). The levels of serum triglycerides, low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were statistically significant lower in patients of group I when compared with the levels of patients in group III ($P < 0.001$) (table 1). The level of high density lipoprotein (HDL) was statistically significant higher in patients of group I and II when compared with the levels of patients in group III ($P < 0.001$).

Life style and factors play a significant function in the pathogenesis of oral cancer. Studies have shown a clear relationship between tobacco chewing and smoking and oral squamous cell carcinoma. Researches from corner to corner of the globe attempted to clarify possible liaison of trace elements with the peril of cancer in humans.

Attempts of clinical association were also made by several scientists in this regard to set up an underlying mechanism of malignancy inflicted by deficit or surplus of trace elements [4].

Widespread biochemical studies have been conducted on tumor tissue and peripheral blood to look at the cause of cancers and to found tumor markers as an add-on for instituting the diagnosis and prognosis of disease [6]. Chemical processes liable for malignancy can be better understood with the help of biochemical changes occurring in the tissues. Taking this into consideration, many studies [7-10] have shown serum alkaline phosphate, serum amylase, serum lactate dehydrogenase, CEA, serum calcium, serum magnesium, serum copper, serum zinc, and the copper/zinc ratio in various malignancies as promising diagnostic and prognostic biochemical markers.

Table 1: variables of study groups

	Group I (n=10)		Group II (n=10)		Group III (n=10)		Statistical sig.	
Male:Female							χ^2	p
	4:1		4.5:1		4:1		0.480	0.787 (NS)
	Mean	SD	Mean	SD	Mean	SD	F	p
Age	50.00	13.37	36.50	10.20	42.00	11.57	3.318	0.051
Copper (mcg/dl)	131.56	7.00	114.03	6.13	100.51	7.79	49.391	<0.001
Iron (mcg/dl)	95.03	12.24	107.59	6.24	117.46	10.50	12.675	<0.001
Vitamin C (mg/dl)	0.66	0.26	0.83	0.15	1.02	0.18	7.895	0.002
Zinc (mcg/dl)	72.52	9.91	85.62	8.85	98.66	7.19	22.463	<0.001
Triglyceride (mg/dl)	104.46	8.29	138.99	5.02	127.52	6.64	67.228	<0.001
Cholesterol (mg/dl)	148.30	22.13	140.26	5.95	141.48	6.27	0.998	0.382
HDL (mg/dl)	42.32	1.63	44.89	1.86	39.95	1.20	24.212	<0.001
LDL (mg/dl)	97.55	3.97	91.64	2.74	104.64	5.09	25.826	<0.001
VLDL (mg/dl)	19.03	1.73	24.04	1.07	21.72	3.35	12.273	<0.001

Significant
Group I: Habit + Lesion
Group II: Habit + No lesion
Group III: Control

Trace elements participate, directly or indirectly, an imperative function in various physiological metabolic activities in humans. In the literature there are various classifications proposed by many authors on elements — both major as well as the trace elements, regarded as crucial for the usual development and growth. Frieden (1981) [11] proposed a classification of elements in which he divided the elements into micro, trace, and ultra-trace elements based on the quantity found in tissues:

1. Essential trace elements: Boron, cobalt, copper, iodine, iron, manganese, molybdenum, and zinc.
2. Probable essential trace elements: Chromium, fluorine, nickel, selenium, and vanadium.
3. Physically promotive trace elements: Bromine, lithium, silicon, tin, and titanium.

Copper plays a very significant role in our metabolism as it allows many important enzymes to do their task appropriately [12]. Mainly copper is present in the liver, shellfish, dried fruit, milk and milk products, sunflower seeds, oysters, sesame seeds, tahini, and sun dried tomatoes [13]. In human blood, copper is primarily dispersed between the erythrocytes and in the plasma. In erythrocytes, 60% of copper present as the copper-zinc metallo-enzyme superoxide dismutase, the remaining 40% is loosely bound to other proteins and amino acids [14]. Copper plays an important role in hemoglobin (Hb) synthesis, connective tissue metabolism, and bone development, also copper is needed for the synthesis of tryptophan. Moreover, in the form of ceruloplasmin, copper aids in the transport of iron to cells [15]. Copper is also known for its anti-carcinogenic activity, and is a part of a range of enzymes such as tyrosinase, uricase, and cytochrome oxidase, which are primarily concerned with oxidation reaction [16]. In our study a significantly increased level of copper was found in group I as compared to the controls may be explained on the basis that because areca nut in any form has high level of soluble copper in them, and also because of deficient oxidative mechanism there is increase in copper levels in oral malignant and pre-malignant lesions i.e. OSMF. In group II also there is marked increase in levels of copper than controls and the probable reason is that, copper has been associated in tissue fibrinogenesis via the copper –dependent enzyme lysyl oxidase, which has a essential role in the cross linking of collagen and elastin [19].

The metal zinc is an invincible metal that has amphoteric nature. Zinc is implicated in proteolysis (carboxy peptidase, leucine amino peptidase, etc.) [17]. Bio-elements like Copper (Cu) and Zn are involved in essential biochemical activities like different redox and free radical formation and in maintaining cellular proton homeostasis [18]. Zinc is also necessary for regulation of cell cycle and cell division and also crucial for DNA polymerase activity and is predominantly significant for swift cell proliferation came across in growing tumors [20]. In our study a significantly decreased level of zinc was found in group I and II as compared to the controls may be explained on

the basis that dysplastic cells and tissue have increased metabolic requisite of Zn which result in an increased uptake.

In the present study, decrease in Serum Vitamin C levels in group I and II which is in accordance with the studies conducted by other authors [21, 22].They ascribed poor nutritional status [23] and oxidative stress in cancerous / precancerous lesions and conditions were accountable for reduction in vitamin C levels. In OSMF patients, production of highly cross linked insoluble collagen type I is increased, and also there is increase in loss of more soluble pro-collagen type III and collagen type VI. The cross linking of collagen due to the up-regulation of lysyl oxidase, plays a decisive role in the advancement and progression of the condition from stage I to stage II [24]. Vitamin C level reduces possibly because of its utilization in collagen synthesis [25].

This study showed significant reduction in serum iron levels when compared with the values of the control group which is in accordance with the other studies reported in the literature [23, 26]. Iron deficiency is very common in oral cancer. Iron is also necessary for collagen production by enzymes in hydroxylation of proline and lysine. Proline hydroxylase and peptidyl lysine hydroxylase respectively catalyze hydroxylation of proline and lysine [27]. Peptidyl proline hydroxylase requires molecular oxygen, ferrous Iron, Alpha-ketoglutarate and Vitamin C as co-factors [28]. Thus in OSMF individual's Serum Iron level is decreased which can be ultimately allied with decreased Vitamin C level.

Significant changes have been reported in the levels of phospholipids and cholesterol in certain type of malignancies. Thus, the progression of carcinogenesis could be liable for decreased levels of phospholipids and cholesterol in proliferating tissues and in blood compartments [29]. Fu-chuan chao et.al [30] conducted study and stated that hypolipidemia in patients with malignancies is because of direct lipid lowering effects of tumor cells because neoplastic cells itself utilizes cholesterol for their own metabolism. In another study Min-ah choi et.al [31] concluded that hypolipidemia is because of decreased levels of serum anti-oxidative vitamins which results in increased number of free radicals and increased lipid per-oxidation. These results are strengthening by the results of present study which also shows low serum levels of lipids in patients with oral cancer when compared to controls. The results of this present study revealed an inverse relationship between decreased serum lipid profile and oral cancer. Therefore, it can be stated that lower serum lipid status may be a useful indicator, i.e. biochemical marker for initial changes occurring in neoplastic cells.

CONCLUSION

It can be concluded from the present study that levels of trace elements and lipids could be used as a prospective prognostic and diagnostic markers in patients with oral cancer / pre-cancerous lesions. Though, as there are contentious reports on the relationship of oral cancer and these trace elements future studies are expected on a larger diverse population to confirm the suggestion.

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