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A Comparison of Copper, Zinc, and Iron in the Serum of Chronic Cigarette Smokers versus Non-Smokers.

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ABSTRACT

The importance of trace elements is gaining popularity worldwide and hence there is a paradigm shift to co-relate the levels of these elements with the habits which are implicated as the cause for carcinogenesis. The objective of this study is to evaluate the effect of smoking on trace elements required for normal functioning of body and assess the deleterious effects of this habit on the homeostasis of the body.Serum levels of copper, zinc and iron were estimated in 200 age-matched subjects in 3rd and 5th decade of life. These subjects were grouped into two groups of, one control group comprising of healthy individuals without habits and the other case group comprising of individuals who were chronic smokers. The levels of copper, zinc and iron was found to be significantly elevated in case group when compared to control group.Copper, Zinc and Iron is significantly elevated in case group indicating the toxic effect of constituents of cigarette smoke and the desperate attempt of the body to limit the effect of this onslaught on its normal homeostasis.
Keywords: Copper; Zinc; Iron; Angiogenesis; Antioxidants; Smoking

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INTRODUCTION

The tumour markers are gaining popularity in diagnosis and assessing prognosis of pre-malignant and malignant lesions.Hence there is a paradigm shift to co-relate these tumour markers with the habits which are most commonly implicated as the cause for occurrence of these pre-malignant and malignant lesions.

Tobacco use leads most commonly to diseases affecting the heart and lungs, with smoking being a major risk factor for heart attacks, strokes, chronic obstructive pulmonary disease, emphysema, and cancer (particularly lung cancer, cancers of the larynx and mouth, and pancreatic cancer).Smoke contains several carcinogenic pyrolytic products that bind to DNA and cause many genetic mutations. Smoke contains several carcinogenic pyrolytic products that bind to DNA and cause genetic mutations. Particularly potent carcinogens are polynuclear aromatic hydrocarbons (benzopyrene,acrolein,crotonaldehyde) and Nitrosamines, which are toxicated to mutagenicepoxides which are electrophilicalkylating agents.

Essential elements copper (Cu), zinc (Zn) & iron (Fe) havea role in many biochemical reactions as a micro-source [1]. Recently there is high evidence that tumour evoked angiogenesis has a high requirement of copper. Tumour growth is dependent on angiogenesis which is dependent upon release of growth factors which are dependent on copper status.Zn stimulates gene transcriptions andcell multiplication. Increased Zn concentration levelsmight help multiplication of tumor cells [2].While Cu and Zn are necessary for activation ofRNA and DNA polymerase enzymes, they also havea role as co-factors of antioxidant enzymes. Inaddition, Zn is necessary for the optimum performanceof the immune system [3, 4]. Iron is a critical nutritional element that is essential for avariety of important biological processes including cellgrowth and differentiation, electron transfer reactions,and oxygen transport, activation, and detoxification [5].Iron also has a major effect on neoplastic cell growth dueto its catalytic effect on the formation of hydroxyl radicals,its suppression of the activity of host defense cells, and itsrole in the promotion of cancer cell multiplication [6,7].

International Agency for Research on Cancer (IARC) conducts focused research on cancer etiology and prevention. Thus providing evidence on global cancer incidence, prevalence, the causes of cancer, mechanisms of carcinogenesis and the most effective strategies for cancer prevention and early detection. In this regard trace elements have been extensively studied in recent years to assess whether they have any modifying effects in the etiology of cancer [8,9].

MATERIAL AND METHODS

The material for the present study comprised a total of 200 subjects reported to various hospitals in and around Mangalore.All these individual were age-matched in range of 3rd and 5th decade of life. These subjects were grouped into two groups:

Group 1 (Control Group)→ 100 healthy subjects in control group without any habit and oral lesions.

Group 2 (Case Group)→ 100 patients who were chronic smokers without any other habit and oral lesions.

Inclusion criteria:

1. Smokers with frequency of more than 15 cigarettes per day and duration of 10 or more years
2. Patients are males in age group in range of 3rd and 5th decade of life.
3. Patients with absolutely no other habits other than smoking.
4. Patients who are otherwise healthy with no evidence of oral or systemic diseases.

Exclusion criteria:

1. Patients who have any other habits other than smoking.
2. Patients who have any evidence of oral or systemic diseases.
3. Patients with metabolic disorders either congenital or acquired.

5ml of venous blood was drawn and was centrifuged, serum separated and transferred into vaccutainers for transport to laboratory for analysis.
Estimation of serum copper and zinc was done using Atomic Absorption Spectrophotometry. Estimation of serum iron was done using Bathophenanthroline Methodand photometrically determined.

RESULTS AND OBSERVATIONS

In the present study, descriptive statistics of copper, zinc and iron was done for both the groups and this includes mean and standard deviation. Also the results were analyzed using Students Unpairedtest for zinc, iron as well as Mann-Whitney 'U' test for copper and assessed for significance.

TABLE 1: Descriptive Statistics of Serum Copper (*µg/Dl)* in Case and Control Group

Case	Control	Z	p
Mean + SD	Mean + SD		
35.51+ 12.81	32.45 + 4.46	2.26	.025 sig

TABLE 2: Descriptive Statistics of Serum Zinc (*µg/Dl)* in Case and Control Group

Case	Control	t	p
Mean + SD	Mean + SD		
170.6+45.88	125.3+67.22	4.87	<.001 vhs

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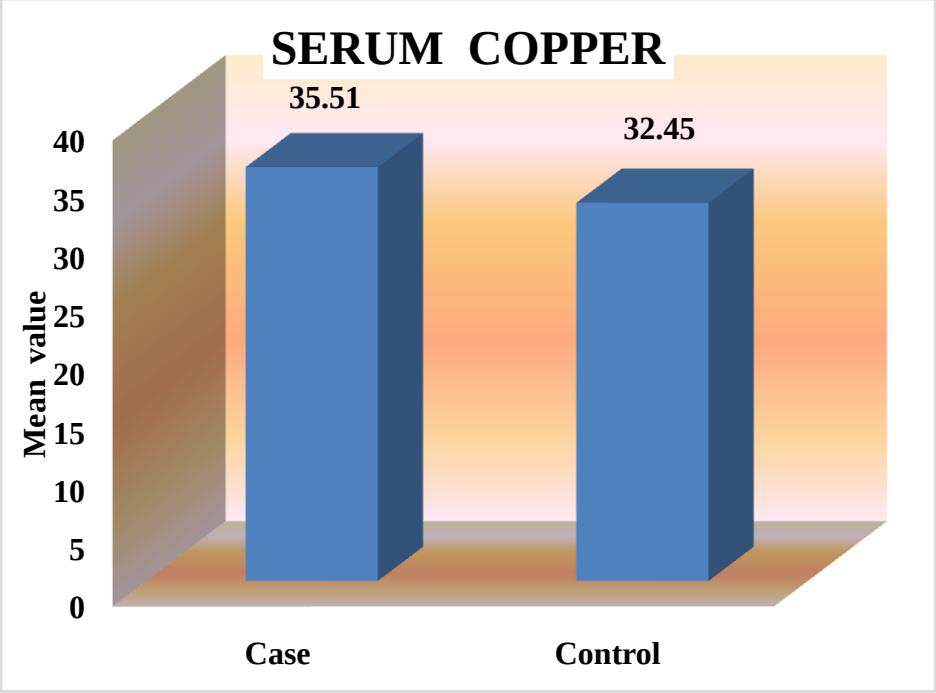
TABLE 3: Descriptive Statistics of Serum Iron (*µg/Dl*) in Case and Control Group

Case	Control	t	p
Mean + SD	Mean + SD		
139.4+57.9	116.1+55.97	2.844	0.005 HS

In the present study, when inter-group comparison was done for serum copper levels between control (Group 1) and case (Group 2) using Mann-Whitney 'U' test for significance, it was found to be significant with increased serum copper level in Group 2 (p=0.025). Likewise when inter-group comparison was done for serum zinc levels between control (Group 1) and case (Group 2) using Students Unpaired test for significance, it was found to be very highly significant with increased serum zinc level in Group 2 (p=<0.001). Also when inter-group comparison was done for serum iron levels between control (Group 1) and case (Group 2) using Students Unpaired test for significance, it was found to behighly significant with increased serum iron level in Group 2 (p=0.005).

An increase was seen in the mean serum copper value in Group 2 (mean=35.51) on comparison with Group 1 (mean=32.45). Likewise an increase was also seen in the mean serum zinc value in Group 2 (mean=170.6) on comparison with Group 1 (mean=125.3). Also increase was seen in the mean serum iron value in Group 2 (mean=139.4) on comparison with Group 1 (mean=116.1).



BAR DIAGRAM 1: COMPARISON OF MEAN SERUM COPPER (*µg/Dl*) AMONG CONTROL AND CASE GROUPS

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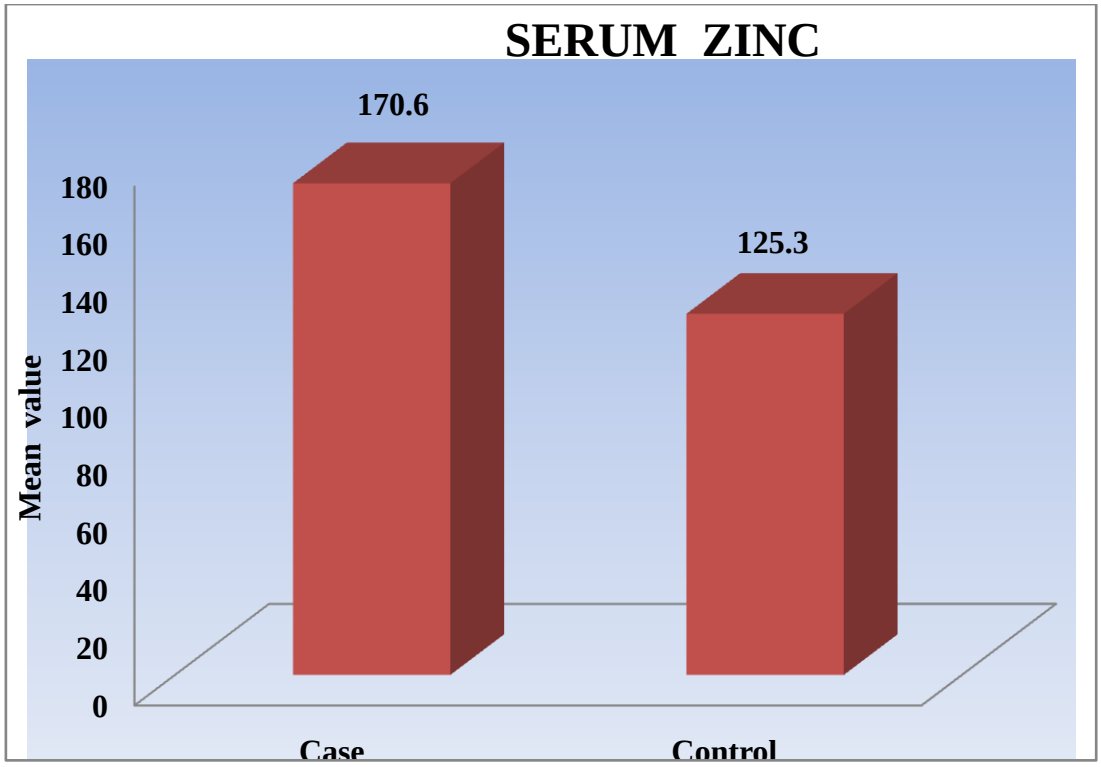
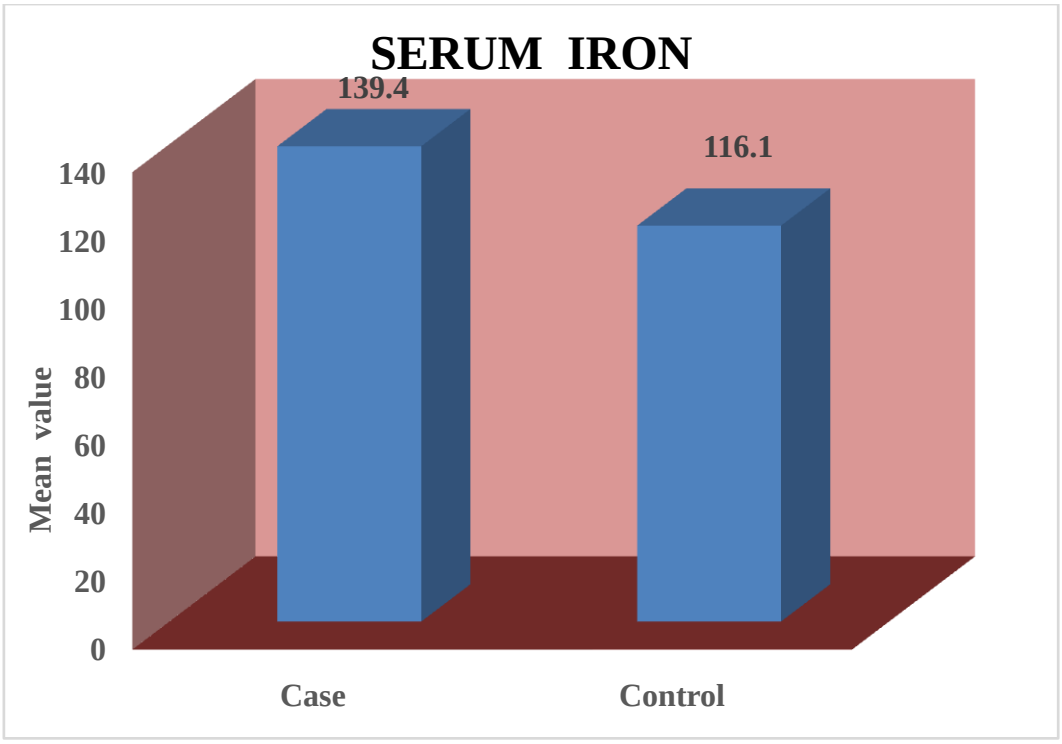


BAR DIAGRAM 2: COMPARISON OF MEAN SERUM ZINC (*µg/Dl*) AMONG CONTROL AND CASE GROUPS



BAR DIAGRAM 3: COMPARISON OF MEAN SERUM IRON (*µg/Dl*) AMONG CONTROL AND CASE GROUPS

DISCUSSION

Copper is an essential trace element. Copper plays an important role in tumour angiogenesis, especially at its early stages. Copper seems to be necessary for endothelial cell

activation as it stimulates their proliferation and migration. Several angiogenic factors, e.g. VEGF, basic fibroblast growth factor (bFGF), tumour necrosis factor alpha (TNF-a) and interleukin (IL) 1 have been found to be copper activated. It effects activity of many enzymes [copper/zinc-superoxide dismutase, ceruloplasmin, cytochrome oxidase, tyrosinase, dopamine hydroxylase and lysine oxidase] both as a cofactor and as an allosteric component [10,11]. These enzymes are essential for cellular respiration, defense against free radicals, melanin synthesis, formation of connective tissue and for iron metabolism.Copper metabolism is profoundly altered in neoplastic disease. It has been found that serum copper concentration correlates with tumour incidence, malignant progression and recurrence in a variety of human cancers. The cellular deposition of copper is also altered in tumour tissues from cytoplasm in normal tissue to intranuclear and perinuclear zones in tumour[12].

Increase in copper concentration correlates with tissue hyperplasia and neoplasia, tumour incidence, malignant progression and recurrence in a variety of human cancers. Zinc is a essential trace element which has a critical role in body's defense against oxidative stress caused by excessive smoking. It acts as a free radical scavenger in view of their ability to scavenge OH, O-2, and NO radicals [13]. Zinc is an essential element integral to many proteins and transcription factors which regulate key cellular functions such as the response to oxidative stress, DNA replication, DNA damage repair, cell cycle progression, and apoptosis. Zinc has been ascribed roles in the metabolism and interaction of malignant cells, particularly in apoptosis. Zinc is involved in structural stabilization and activation of the p53 that appears to be an important component of the apoptotic process and also in activation of certain members of the caspase family of proteases[14].Zinc is known to be an essential component of DNA-binding proteins with zinc fingers, as well as copper/zinc superoxide dismutase and several proteins involved in DNA repair. Thus, zinc plays an important role in the functions of transcription factor, antioxidant defense system and DNA repair[14, 15].

In chronic smokers zinc levels are increased and are part of a defense mechanism by the body to fight the deleterious effects of smoking. Since free radicals play an essential part in carcinogenesis by damaging the cellular material hence transforming the normal cells to malignant cells, the body expresses antioxidants and scavengers to limit the effect of these carcinogens and destroy these free radicals to reduce the reactive oxygen intermediates.

The association of iron loading with initiation and proliferation of neoplasms is well established [16]. Iron is carcinogenic because of its catalytic effect on the formation of hydroxyl radicals, suppression of the activity of host defense cells, and promotion of cancer cell multiplication. In both animal models and in humans, primary neoplasms develop at tissue sites of excessive iron deposition [17].Mechanism by which iron can provoke DNA damage and lead to carcinogenesis is because of ironbinding sites on macromolecules which serve as centers for repeated production of hydroxyl radicals generated via the Fenton reaction as well as also iron and oxygen together constitute a biologically highly damaging mixture due to increased formation of free radicals.Normally, chances of these are reduced by sequestration in storage or transport proteins and action of 'acute-phase' proteins such as ceruloplasmin, haptoglobins, etc., involved in iron metabolism for the following reasons 1.Iron promotes cancer cell growth, 2. Hosts attempt to withhold or

withdraw iron from cancer cells, 3. Iron is a factor in prevention and in therapy of neoplastic disease.

But in chronic smokers iron levels are increased and this iron loading can occur because of inhalation of the metal contained in tobacco smoke, asbestos, and urban air particulates [16, 18]. Moreover, iron can be released from its normal body compartments by hemolysis or by destruction of nonerythrocytic cells that contain iron deposits because of deleterious effects of chronic smoking[19].

Increase in copper concentration correlates with tissue hyperplasia and neoplasia, tumour incidence, malignant progression and recurrence in a variety of human cancers. The results of the present study strongly suggest the deleterious effects of smoking in oxidative stress and subsequently in carcinogenesis. Serum zinc has been shown to be a powerful scavenger and antioxidant of free radicals and superoxide ions, hence in present study there is a highly significant increase in its level in chronic smokers indicating the deleterious effects of smoking on the cellular metabolism of the body. The explanation for this appears to be an increase in serum zinc consequent to increased compensatory antioxidant defenses in serum, to combat the deleterious carcinogenic effects of smoking.

Serum iron levels are increased in chronic smokers in the present study indicating the toxic effects of smoking as well accentuating thehemolysis caused by its deleterious effects of such habits on normal body compartments.

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