Assessment & Comparison Of Serum Folate & Iron Levels In Clinically Diagnosed Oral Leukoplakia Against Those Without Oral Leukoplakia In Bangalore & Kolkata Patients – A Research

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Keywords	Abstract
Cancer, Malignancy, Biochemical, Oral potentially malignant disease, Oral pre-cancer	Potentially malignant oral mucosal diseases such as oral leukoplakia, oral erythroplakia and oral submucous fibrosis have a high malignant transformation rate with tobacco, alcohol, chewing of betel quid containing areca nut being etiological agents. Early identification, diagnosis and treatment hinders progression of the disease to severe dysplasia and even carcinoma in situ and/or squamous cell carcinoma. Therefore early intervention is highly advocated to attain favorable prognosis as well as treatment outcome. **Aim:** To assess & compare the levels of serum folate & iron in patients with/without any visible Oral leukoplakia. **Materials & Methods:** This prospective research study consisted of a total of 136 patients; wherein we had 34 Oral leukoplakia patients with habit(s) & 34 patients without leukoplakia with habit(s) in Bangalore & 34 Oral leukoplakia patients with habit(s) & 34 patients without leukoplakia with habit(s) in Kolkata. Amongst them, serum folate levels were measured by chemi-luminescent immunoassay & serum iron concentration was measured by photometric method. We used student't' test and chi square test for intergroup comparison using SPSS software version 22.0, wherein p<0.05 was considered to be statistically significant. Student "t" test was used to compare the mean folate (ng/ml) and iron levels (μg/dl) between 02 groups and also different age groups within each group. Chi Square Test was used for qualitative analysis. **Results:** There was a definite male predilection with majority of the subjects found in the age group of 20-30 years. The mean folate levels in BOL, BWOL, KOL, KWOL was found to be 5.20, 5.3, 6.4 and 5.6 respectively, whereas the mean iron levels were 91.20, 105.73, 102.12 and 114.53 respectively, which was statistically insignificant **Conclusion**: The mean serum folate & iron levels were found to be high in the Kolkata population in comparison to that of the Bangalore population. A clear decline in the serum iron & folate levels in patients with clinically diagnosed leukoplakia amongst smokers as well as in tobacco chewers was seen, suggestive of a relation between serum iron & folate levels and leukoplakia patients.

INTRODUCTION

Despite being globally reckoned as the 6th most common malignancy, early intervention of Oral squamous cell carcinoma (OSCC) has not been completely accomplished till date even though it is a multiphasic progressive disease with the precursor/pre-cancerous lesion preceding OSCC.[1,2]

These precursor/pre-cancerous lesion include (but are not limited to) oral leukoplakia, oral erythroplakia and oral submucous fibrosis (OSMF) with tobacco, alcohol, chewing of betel quid containing areca nut being key etiological agents.[3]

Even though there is no uniformity in the rates of malignant transformation across these common potentially malignant oral mucosal diseases yet their rapid ascent into malignancy is a matter of concern wherein the highest malignant transformation rate is of OSMF (7-13%, over 10 years), followed by oral leukoplakia (0.13 – 17.5) higher transformation rates in non-homogenous leukoplakia than in homogenous leukoplakia.[4,5]

There are a plethora of diagnostic tests such as toluidine blue, chemiluminesence test and biopsy, for early identification and management of potentially malignant disorders; however the research for newer diagnostic tests has not been relinquished.[1,6] Trace elements such as copper, iron and selenium play an indispensable role even in such trace amounts as they not only play a role in initiation of the functions of the body but also help to regulate them.[6]

Therefore, any alterations observed in the serum levels of trace elements may act as potential biochemical markers which may be linked with the pathogenesis of oral cancer. Even though such markers may not act as standalone diagnostics, it may act as an adjuvant diagnostic for mass screening. In future, it can also be used for treatment in case of early stage detection of the disease process in an attempt to stop/slow down their progression.[3,6]

Metabolic alterations in Iron has been found to have severe impact on most of the functions of the body, therefore it is hypothesized to be one of the key trace elements responsible for the development of tumor. Similarly, serum folic acid levels might also be responsible for the development and progression of tumor as hypofolatemia is a well-reckoned risk factor for head and neck carcinogenesis.[3,6]

Henceforth, early identification, diagnosis and treatment of the potentially malignant disorders is highly advocated in order to intervene the disease process at an early stage whilst replenishing the deficiencies, all of which will help us attain the required prognosis as well as the treatment outcome.

The present study was designed to determine & compare the serum iron levels and folic acid as a potential biomarker with patients that were diagnosed with Oral Leukoplakia in comparison to those without leukoplakia in Bangalore and Kolkata, which can help add useful information to the existing data [3,6] suggestive of a relation between serum iron and folic acid levels amongst oral leukoplakia patients.

AIMS AND OBJECTIVES OF THE STUDY
❖ To assess & compare the levels of serum folate and iron in patients with/without clinically diagnosed Oral leukoplakia as well as habits in Bangalore & Kolkata patients.

MATERIALS AND METHODS
This prospective research study enrolled a total of 136 patients, which was carried out in The Oxford College of dental sciences, Bangalore & Guru Nanak Institute of Dental Sciences and research, Kolkata during October 2016- March 2022.
❖ Group A (BOL): 34 Oral leukoplakia patients with habit(s) in Bangalore
❖ Group B (BWOL): 34 patients without leukoplakia with habit(s) in Bangalore
❖ Group C (KOL): 34 Oral leukoplakia patients with habit(s) in Kolkata
❖ Group D (KWOL: 34 patients without leukoplakia with habit(s) in Kolkata
❖ Serum folate was measured by chemi-luminescent immunoassay & serum iron concentration was measured by photometric method.

Inclusion criteria:
❖ Patients with a habit history of smoking and chewing tobacco for more than a year, diagnosed with Oral Leukoplakia, aged 20-80 years with long standing habits of smoking and tobacco chewing for more than a year but without any visible oral lesions.

Exclusion criteria:
❖ Patients with nutritional disorder requiring vitamin supplementation.
❖ Patients undergoing chemotherapy.
❖ Patients with long term drug history for systemic diseases such as hypertension, diabetes, cancer

Statistical analysis
Tabulation of the results was carried out for patients with habits showing oral leukoplakia lesions and patients without oral leukoplakia. All the variables from the study were statistically analyzed by SPSS 22.
Student "t" test was used to compare the mean folate (ng/ml) and iron levels (μg/dl) between 02 groups and also different age groups within each group. Chi Square Test was used for qualitative analysis.

Results

Majority of the subjects across all the groups in either state were males & were found in the age group of 20-30 years, except for kolkata leukoplakic patients being higher in the age group of 31-40 years. (Table 1 & 2)

Amongst smokers, the mean duration in years amongst smokers in group 1, group 2, group 3 and group 4 was found to be 12.84, 7.34, 15.57 and 7.96 years respectively. (Table 3) The mean folate levels amongst smokers in group 1, group 2, group 3 and group 4 was found to be 5.51, 5.244, 7.44 and 5.77 respectively whereas mean iron levels in group 1, group 2, group 3 and group 4 was found to be 88.47, 111.88, 99.5 and 120.46 respectively. (Table 3)

Amongst tobacco chewers, the mean frequency of tobacco chewing in a day in group 1, group 2, group 3 and group 4 was found to be 4.8, 4, 5.46 and 5 times respectively with 13.35, 6.05, 21.33 and 6.03 years being the duration(in years). (Table 4)

The mean folate levels amongst tobacco chewers in group 1, group 2, group 3 and group 4 was found to be 4.50, 5.29, 4.4 and 4.96 respectively, whereas mean iron levels amongst tobacco chewers in group 1, group 2, group 3 and group 4 was found to be 91.94, 88.2, 106.92 and 98.82 respectively. (Table 4)

The mean folate levels in group 1, group 2, group 3 and group 4 was found to be 5.20, 5.3, 6.4 and 5.6 respectively, which was statistically insignificant. (Table 5) The mean iron levels in group 1, group 2, group 3 and group 4 was found to be 91.20, 105.73, 102.12 and 114.53 respectively, which was statistically insignificant (Table 6)

The mean folate & iron levels in group 1, group 2, group 3 and group 4 amongst smokers was found to progressively increase when the patients were found to have an increase in the no of smokes/day.(Table 7 & 8)

The mean folate & iron levels in group 1, group 2, group 3 and group 4 amongst tobacco chewers was found to progressively increase when the patients were found to have an increase in tobacco consumption initially, after which we found a decline in the mean levels .(Table 7 & 8)

TABLE 1: DISTRIBUTION OF SUBJECTS AS PER AGE

AGE	GROUP 1	GROUP 2	GROUP 3	GROUP 4
20-30	9 (26.47%)	21(61.76%)	1 (2.94%)	24 (70.59%)
31-40	8 (23.53%)	6 (17.65%)	12 (35.29%)	6 (17.65%)
41-50	8 (23.53%)	4 (11.76%)	7 (20.59%)	2 (5.88%)
51-60	6 (17.65%)	3 (8.82%)	10 (29.41%)	2 (5.885)
>60	3 (8.82%)	0 (0.0%)	4 (11.76%)	0 (0.0%)
TOTAL	34	34	34	34
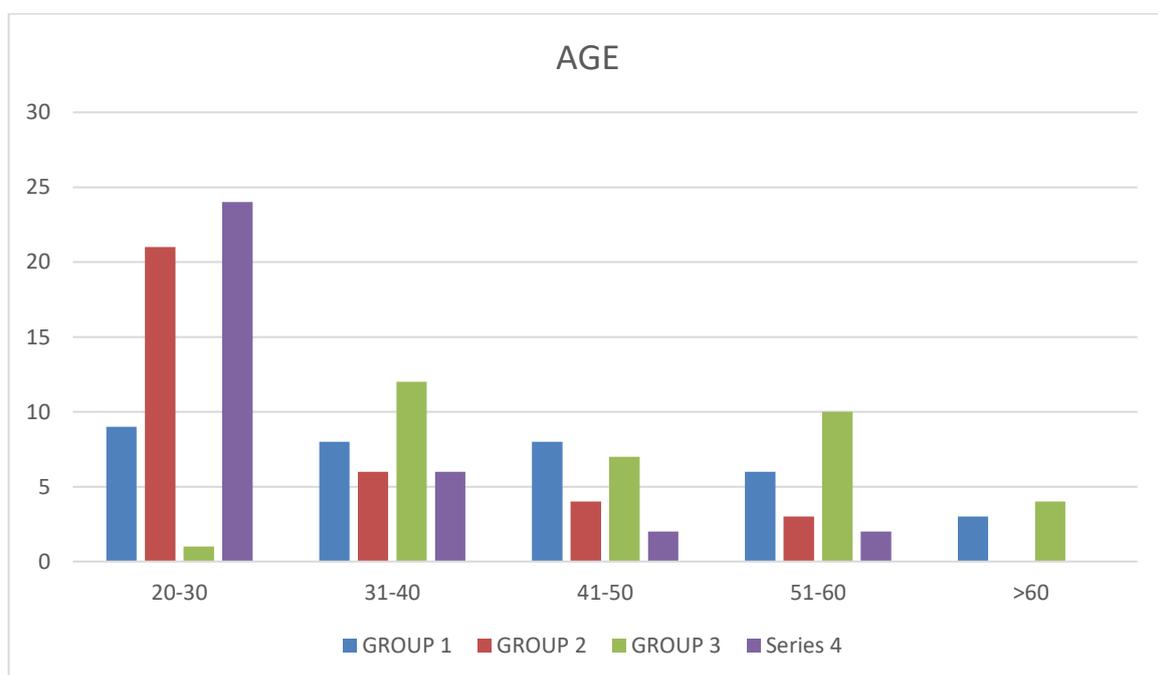
GROUP 1 – BANGALORE LEUKOPLAKIA PATIENTS

TABLE 2: DISTRIBUTION OF SUBJECTS AS PER GENDER

GENDER	GROUP 1	GROUP 2	GROUP 3	GROUP 4
MALES	28 (82.35%)	33 (97.06%)	22 (64.71%)	25 (73.53%)
FEMALES	6 (17.65%)	1 (2.94%)	12 (35.29%)	9 (26.47%)
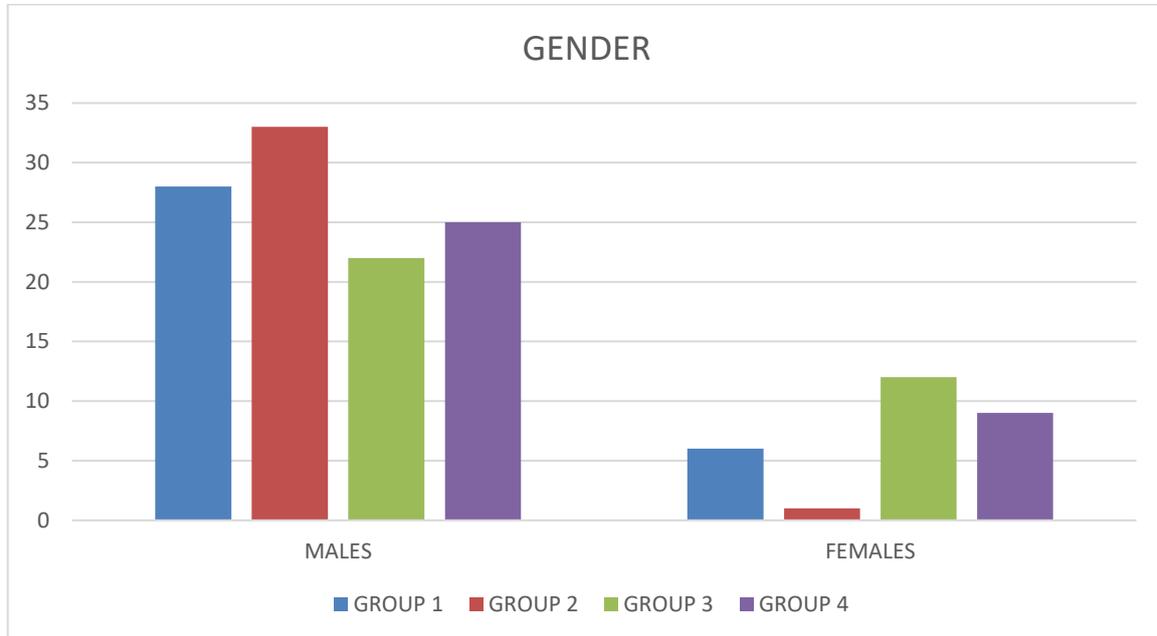
GROUP 2 – BANGALORE NON-LEUKOPLAKIA PATIENTS

**TABLE 3: DESCRIPTIVE DATA FOR SMOKERS**

FOR SMOKING	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Number OF SUBJECTS	19	25	22	24
FREQUENCY (TIMES)	5.95	4.5	8.84	4.85
DURATION (YEARS)	12.84	7.34	15.57	7.96
MEAN FOLATE (ng/ml)	5.51	5.244	7.44	5.77
MEAN IRON (µg/ml)	88.47	111.88	99.5	120.46

TABLE 4: DESCRIPTIVE DATA FOR TOBACCO CHEWERS

FOR TOBACCO CHEWERS	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Number OF SUBJECTS	17	10	12	11
FREQUENCY (TIMES)	4.8	4	5.46	5
DURATION (YEARS)	13.35	6.05	21.33	6.03
MEAN FOLATE (ng/ml)	4.50	5.29	4.4	4.96
MEAN IRON (µg/ml)	91.94	88.2	106.92	98.82

TABLE 5: Mean FOLATE levels across the groups

Mean Folate (ng/ml)	GROUP 1 (BOL)	GROUP 2 (BWOL)	GROUP 3 (KOL)	GROUP 4 (KWOL)
Mean	5.20	5.3	6.4	5.6
S.D	2.71	2.10	2.78	2.06
	P = 0.179585			
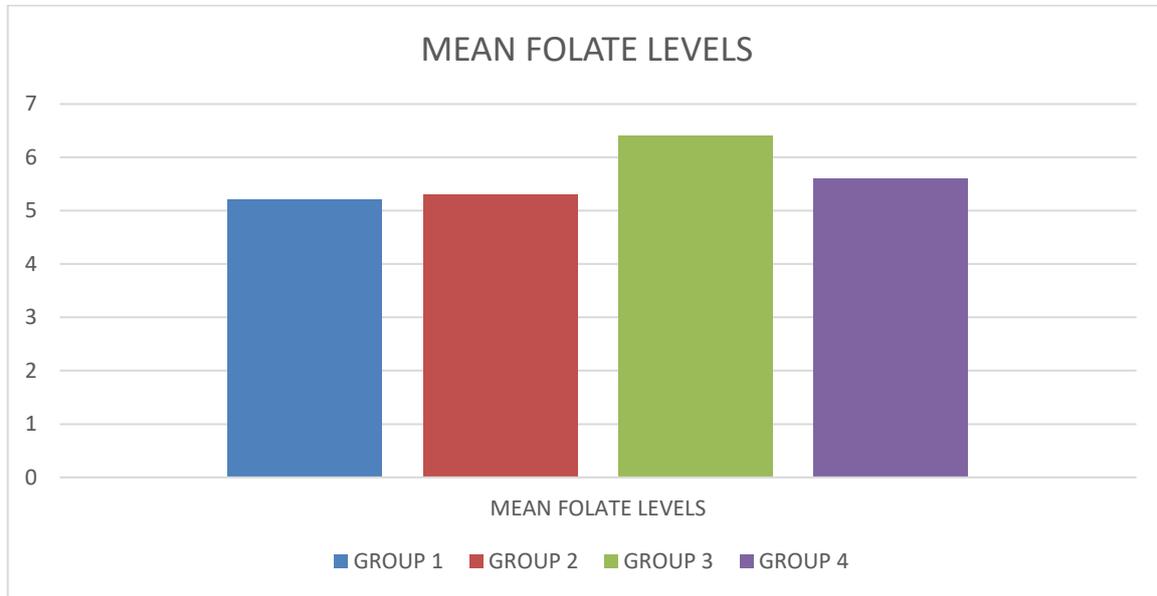
GROUP 3 – KOLKATA LEUKOPLAKIA PATIENTS

TABLE 5B: INTERGROUP COMPARISON of mean folate levels in patients with oral leukoplakia in Bangalore against kolkata
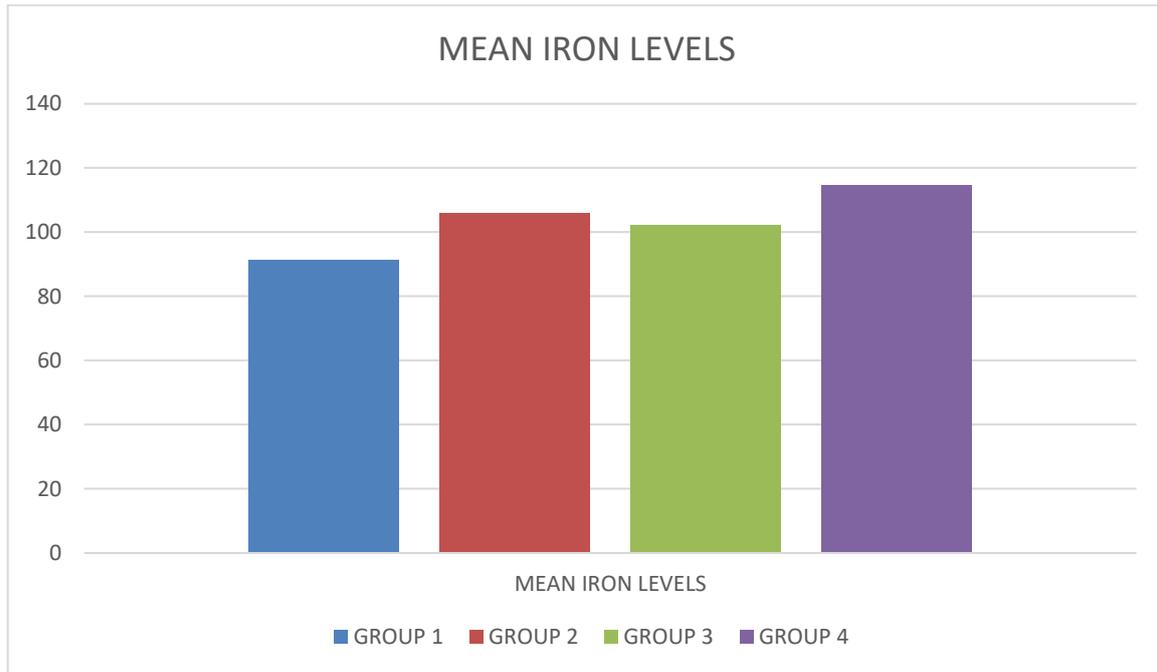
Mean Folate (ng/ml)	GROUP 1 (BOL)	GROUP 3 (KOL)
Mean	5.20	6.4
S.D	2.71	2.78
	P = 0.77551	

TABLE 5C: INTERGROUP COMPARISON of mean folate levels in patients without oral leukoplakia in Bangalore against kolkata

Mean Folate (ng/ml)	GROUP 2 (BWOL)	GROUP 4 (KWOL)
Mean	5.3	5.6
S.D	2.10	2.06
	P = 0.59817	

TABLE 6: Mean IRON levels across the groups

Mean IRON (µg/ml)	GROUP 1 (BOL)	GROUP 2 (BWOL)	GROUP 3 (KOL)	GROUP 4 (KWOL)
Mean	91.20	105.73	102.12	114.53
S.D	28.73	33.20	35.64	38.86
	P = 0.48789			

GROUP 4 – KOLKATA NON- LEUKOPLAKIA PATIENTS

TABLE 6B: INTERGROUP COMPARISON of mean iron levels in patients with oral leukoplakia in Bangalore against kolkata

Mean IRON (µg/ml)	GROUP 1 (BOL)	GROUP 3 (KOL)
Mean	91.20	102.12
S.D	28.73	35.64
	P = 0.169276	

TABLE 6C: INTERGROUP COMPARISON of mean iron levels in patients without oral leukoplakia in Bangalore against kolkata

Mean IRON (µg/ml)	GROUP 2 (BWOL)	GROUP 4 (KWOL)
Mean	105.73	114.53
S.D	33.20	38.86
	P = 0.3194	

TABLE 7A: Comparison of mean Folate (ng/ml) amongst Smokers across groups

Mean Folate (ng/ml) IN SMOKERS	GROUP 1 (19)	GROUP 2 (25)	GROUP 3 (22)	GROUP 4 (24)
<3	4.2(5)	4.9 (11)	0 (0)	5.4 (9)
3-6	6(4)	6.1 (9)	9 (6)	6.0 (11)
>6	6(10)	4 (5)	6.8 (16)	6.0 (4)

TABLE 7B: Comparison of mean Folate (ng/ml) amongst tobacco chewers across groups

Mean Folate (ng/ml) IN TOBACCO CHEWING	GROUP 1 (17)	GROUP 2 (10)	GROUP 3 (12)	GROUP 4 (11)
<3	4 (3)	4.4 (3)	0 (0)	2.6 (1)
3-6	5.4 (10)	5.8 (6)	4.9 (10)	5.5 (9)
>6	2.7 (4)	4.7 (1)	2.0 (2)	2.6 (1)

TABLE 8A: Comparison of mean IRON levels amongst Smokers across groups

Mean IRON (µg/ml) IN SMOKERS	GROUP 1 (19)	GROUP 2 (25)	GROUP 3 (22)	GROUP 4 (24)
<3	80(5)	97 (11)	0 (0)	118 (9)
3-6	90(4)	117 (9)	73 (6)	108 (11)
>6	92(10)	134 (5)	110 (16)	161 (4)

TABLE 8B: Comparison of mean IRON levels amongst tobacco chewers across groups

Mean IRON (µg/ml) IN TOBACCO CHEWING	GROUP 1 (17)	GROUP 2 (10)	GROUP 3 (12)	GROUP 4 (11)
<3	84 (3)	81 (3)	0 (0)	48 (1)
3-6	88 (10)	98 (6)	91 (10)	110 (9)
>6	107 (4)	51 (1)	189 (2)	48 (1)

(P is set O.5% CONFIDENCE INTERVAL
P<0.05 IS STATISTICALLY SIGNIFICANT

DISCUSSION

Cancer being a multi-phasic disease process, initially presenting as a precursor/pre-cancer lesion which progressively becomes a well-established disease process has been highly researched and investigated for the purpose of early intervention in order to prevent its progression and achieve a favorable prognosis.[7] However, it is the complexity of the disease process which has hindered the various attempts made by the physicians/researchers/scholars which has always kept its malignancy transformation rate high.

The conjecture that malignancy in a patient diagnosed with a potentially malignant lesion might be site-specific, however the same does not stand true for malignancy and can be non-specific with the capability to arise at any anatomical site.[7]

In our study, two elements i.e serum folic acid and iron levels were investigated owing to their indispensable role involving the metabolic activities within the body. Altercations in elements are reflective of underlying changes which can directly/indirectly be caused due to the disease process.

Conventionally, serum iron levels are assessed for nutritional assessment as they are as biochemical indicators. As cancer cells also express transferrin receptors to obtain iron, a drop in the iron levels may explain its depletion making hypoferremia an important prognostic indicator of cancer.[8,9] On the other hand iron overload is thought to aid carcinogenesis by provoking DNA damage due to oxidative stress (lipid peroxidation and DNA and protein damage).[8]

A multi-centric study design is highly advocated to reduce bias and have a more comprehensive data in terms of the biochemical alterations observed across the region. The diversity of the population in terms of their socio-economic status, educational level and the availability of data across both these cities, encouraged us to perform the study in these places as the data was more reliable and was recorded by the same researcher, eliminating the probability of observer bias.

We had an equilateral distributive evaluation of study subjects in Bangalore & Kolkata amongst patients with habits without leukoplakia and patients with habits & clinically diagnosed oral leukoplakia; we were able to analyze the changes in elements as well as the changes owing to the geographic location.

Maximum subjects were males irrespective of the group or their geographic location portraying the habit as a more gender specific factor. Further, majority of the subjects across all the groups in either states were found in the age group of 20-30 years, except for kolkata leukoplakic patients being higher in the age group of 31-40 years

This in agreement with Pooja et al., who assessed the role of serum iron, ferritin as well as total iron binding capacity (TIBC) in pathogenesis & treatment planning of OSMF & Leukoplakia, wherein 88% of oral leukoplakia and OSMF patients were males, accounting to 22 patients against only 3 female subjects (12%).[10]

Habits such as smoking & tobacco chewing has always been more commonly observed amongst males, therefore a higher incidence of male subjects is in agreement with the global epidemiology.

Khanna SS and Karjodkar FR, evaluated Circulating Immune Complexes & trace elements such as Copper, Iron and Selenium as markers in oral pre-cancer & cancer wherein there was a clear drop in serum iron levels in the pre-cancer group as well as in cancer patients.[9]

Mean folate levels in Bangalore & Kolkata was found to be 5.25 & 6.0 respectively, wherein it was found to be 5.20 & 5.3 in BOL & BWOL group, whereas in Kolkata group it was found to be 6.4 & 5.6 in KOL & KWOLM group. The folate levels were higher in Kolkata in comparison to the Bangalore group which can be associated with the geographic location of the patient. The mean folate levels in Bangalore patients with oral leukoplakia were found to be low in comparison to that in patients without oral leukoplakia; however the opposite was not true in Kolkata patients.

Moreover, mean folate levels BOL & KOL group was found to be 5.20 and 6.4 respectively, and in BWOL & KWOL group was found to be 5.3 and 5.6 respectively, which was statistically insignificant.

Organic nitrites, cyanates, and isocyanates are primary carcinogens in tobacco smoke which interact with folate and vitamin B12 coenzymes, transforming them into biologically inactive compounds, which is commonly seen amongst smokers and the buccal mucosal cells of tobacco smokers with decreased folate concentration.[11]

Highest mean folate levels in BOL was recorded to be 6 in 10 patients (>6 SMOKES/DAY), whereas it was higher i.e 6.8 in KOL group (16 patients) (>6 SMOKES/DAY), however it was as high as 9 in patients smoking (3-6 smokes/day). Similar analysis amongst tobacco chewers showed the highest mean folate levels in BWOL group to be 6.1 in 9 patients (3-6 /DAY), whereas it was higher i.e 6.8 in KOL group.

These results are inconsistent as the mean folate levels appear to be affected by the geographic distribution of patients wherein the serum folate levels are consistently higher in Kolkata than that observed in Bangalore.

We noted that the mean folate levels had depleted significantly in patients who chewed tobacco >6 times a day, wherein it was found to be decreased more in the Kolkata group than in Bangalore group. However the mean folate levels were comparatively higher in the BWOL (near normal) than in comparison with the other groups)

Raval N et al., in 2002 assessed Vitamin B12 and Folate Status in Head and Neck Cancer and found positive correlation between vitamin B12 and folate levels in the subjects consuming tobacco which was highly significant, especially in oropharyngeal cancer patients.[12] Further, they reported a decrease in the plasma vitamin B12 and folate levels with respect to tobacco habits.

Heimburger et al., 1988 and Ramaswamy et al., 1996 reported the mean plasma levels of vitamin B12 and folate were significantly lower in cancer patients compared to healthy individuals.[12]

Jaber MA et al., reported decreased plasma folate levels in patients consuming tobacco in comparison to the nonsmokers.[11] Almadori et al. also reported low serum folate levels in patients with head and neck carcinoma as well as in laryngeal leukoplakia.[8]

There was no disagreement by Ramaswamy et al. as they also reported low levels of vitamin B12 and folate in a group of Indian oral leukoplakia patients.[7]

It is hypothesized that folate inadequacy augments the development & progression of pre-neoplastic and neoplastic lesions, however the exact pathogenesis is not clear & thought to be a combination of genetic and environmental factors. Tobacco consists of carcinogens which increase the progression of tumor as they increase the susceptibility to mutagens.[13]

Similar to folate levels, the iron levels appear to be more in the Kolkata population than in comparison to that of the Bangalore population. An inter-group comparative analysis showed the mean iron levels in BOL and KOL to be 91.20 and 102.12 respectively, whereas it was found to be 105.73 and 114.53 respectively in BWOL & KWOL, which also found to be statistically insignificant

Irrespective of the geographic distribution, there was a definite drop in the mean iron levels in the patients who were clinically diagnosed with oral leukoplakia in comparison to that observed in patients with habits alone without oral leukoplakia.

A detailed correlation of the habit i.e smoking & tobacco chewers was also carried out wherein we found the mean iron levels amongst smokers in group 1, group 2, group 3 and group 4 was found to be 88.47, 111.88, 99.5 and 120.46 respectively. There was a definite drop in leukoplakia patients in comparison to non-leukoplakia patients.

The mean iron levels were found to be significantly increased amongst smokers wherein there was an indiscriminate proportional increase in the mean iron levels with the increased no of smokes with the highest being noted in patients consuming >6 smokes/day.

Iron levels were found to increase significantly between 3-6 smokes/day to those consuming >6 smokes/day in the Kolkata population than that observed in the Bangalore population. Nevertheless, the increase in the mean iron levels in KOL group was very high than in the BOL group.

The mean iron levels amongst tobacco chewers in group 1, group 2, group 3 and group 4 was found to be 91.94, 88.2, 106.92 and 98.82 respectively. Tobacco chewers with leukoplakia across both the states showed increased mean iron levels in comparison to that of non-oral leukoplakia patients.

There was some inconsistency in the mean iron levels in the tobacco chewers group as we found that the elevated mean iron levels in the KOL group was almost double than that in the BOL group amongst patients chewing tobacco >6 times a day . However, the no of subjects were feeble and increase the risk of bias comparatively. Therefore when we consider the mean iron levels in patients chewing tobacco 3-6 times/day the mean iron levels were not as significantly different amongst OL groups of either states, but was found to be higher in the non-OL groups with. The mean iron levels in either group in Kolkata population recorded higher mean iron levels in comparison to that of Bangalore population.

Tiwari R et al., assessed serum copper, iron and immune complexes in potentially malignant disorders and oral cancer wherein serum iron levels showed a significant decline in the PMD (110.9 ± 10.54 μg/100ml) & oral cancer (114.29 ± 25.83 μg/100ml) group in comparison with the control group (136.85 ± 14.48 μg/100ml).[8] Guruprasad R et al., assessed serum vitamin C & iron levels in 35 OSMF patients reported significantly dropped iron levels in OSMF patients than in controls.[14] Jayadeep A et al., study also found significantly drop in the iron levels amongst carcinoma patients, whereas there was marginal decline in oral leukoplakia patients than in controls.[15]

A poor correlation between iron indices, tumor parameters, serum iron and hemoglobin has been hypothesized to be caused by poor utilization of iron by bone marrow and tumor, wherein reduced iron levels appears to be the effect of the disease process rather than its cause.[9]

Apeksha et al., reported decreased serum iron levels in patient with OSMF, oral leukoplakia and oral cancer compared to control group, attributing it more commonly to compromised diet.[3,13]

Keerthika et al., put forward the idea that that utilization of iron in collagen synthesis by the hydroxylation of proline and lysine is the cause of decreased serum iron levels in patients with oral cancer.[16]

Our study was carried out across only two centers with a single observer in a limited time frame across different diagnostic centers which increase the chances of altered values. Nevertheless, the association between serum iron content and oral carcinogenesis is undeniable, therefore a comprehensive multi-institutional planned study is advocated for future studies to overcome the shortcomings of our study.

CONCLUSION

The mean serum folate & iron levels were found to be higher amongst the people of Kolkata population in comparison to that of the Bangalore population which can be attributed to various factors. Further, we found a clear decline in the serum iron & folate levels in patients with clinically diagnosed leukoplakia amongst smokers as well as in tobacco chewers, however the folate levels were found to increase amongst smokers. A cause-effect relationship is to be established between these elements and the etiological agents in order to use these elements in diagnosis as well as preventive/interventional treatment in the future.

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