



SERUM LEVELS OF IRON AND TOTAL IRON BINDING CAPACITY IN PREMALIGNANT LESION AND CONDITION

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ABSTRACT

Potentially malignant diseases are diseases which have a morphologically altered tissue that has a greater malignant potential. These are triggered by oral habits, nutritional deficiencies, immunological process, and genetic predisposition. Early detection of these diseases helps in better prognosis. Iron is an essential nutrient for the body, it has a central role in metabolism and it is also an essential component of DNA synthesis. There are studies done to estimate the iron indices in oral precancer versus cancer diseases, which shows the influence of iron in cell metabolism in these diseases.

Aim: To estimate the serum iron concentration and total iron binding capacity in subjects with premalignant lesions and conditions and to compare the result with normal subjects

Method: The present study comprised of 64 subjects in the age group of 30 to 70 years diagnosed with PML or PMC and both clinically and histopathologically confirmed. Control group consisted of 63 healthy subjects. Blood samples were assessed for serum iron and total iron binding capacity through a Biochemical method using an Autoanalyser.

Result: A statistical significance was noted in serum iron concentration between premalignant lesion and conditions ($p=0.000$) but not with total iron binding capacity. Similarly significance was noted between age of different patients ($p=0.006$), but not gender when serum iron was considered and not in total binding capacity.

Conclusion: Estimating the serum indices in potentially malignant disorder patients, serves as prognostic and diagnostic marker in high risk groups.

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INTRODUCTION

Oral diseases have broad impacts on health of a person. World Health Organization (WHO) in 2003 emphasised that, despite great improvements in the oral health status of populations across the world the impact of these diseases are still high. The use of tobacco for long duration lead to various lesions or conditions further leading to Oral Squamous cell Carcinoma(OSC). Premalignant Lesions are morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart e.g. Leukoplakia. Whereas Premalignant Condition is a generalized state associated with a significantly increased risk of cancer e.g.OSMFWHO in 2005 recommend the term Potentially Malignant Disorders (PMD) against the above terms as they have an increased potential for malignant transformation.¹ The malignant transformation rates of PMDs show a great variation. The etiologic factors are tobacco and areca quid. Histopathology is the gold standard in the diagnosis of dysplastic features in these diseases but it suffers from inter and intra observer

variation. Hence there is a need for an objective tool which can detect early dysplastic changes in a standardised and universal way². Use of biomarker is a booming strategy now eventhough inadequate sensitivity and specificity are limitation³. The role of essential trace elements and vitamins in health and in prevention of disease is well documented. These act as cofactor in metabolism and have antioxidant properties⁴. Among these iron is an important trace element which acts as a cofactorfor fundamental biochemical activities, such as oxygen transport, energy metabolism and DNA synthesis.⁵

Iron has an effect upon the oral epithelium and its deficiency shows increased susceptibility to the development of intra-oral squamous cell carcinomas in susceptible individuals. Hence it is reasonable to assume variations of iron in serum level are often used as an index. The importance of these elements in cancer was reported by Schwartz.Reduction in the serum iron level may be due to malnutrition caused by the tumour burden in cancer patients.⁶ Iron deficiency may cause oral cancer via the induction of oxidative stress which produces free radicals causing cellular injury. Oxidative stressis the disturbance of equilibrium leading to direct

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damage of cellular molecules such as DNA. Hence it has also been linked to the development of oral cancer.⁷ Oral habits, nutritional deficiencies, and genetic predisposition all lead to oxidative stress formation. Hence early detection of these diseases helps in better prognosis.

MATERIALS AND METHOD

This study was conducted on outpatients visiting the Department of Oral Medicine and Radiology, Coorg Institute of Dental Sciences, Virajpet. Patients of age group 30-70 years males and females who gave their consent to participate in the study were only considered. Case group had 64 patients out of which 48 were males and 16 were females. Control group had 63 subjects out of which 43 were males and 20 were females. The ethical committee approval was obtained.

Inclusion criteria: Patient in the age 30 to 70 years with premalignant lesions and conditions and had who no contraindication for biopsy.

Exclusion criteria: Patient with anaemia, liver diseases, thyroid diseases, and physically and mentally disabled. All the patients were informed about the study protocol and all the demographic details and clinical findings were recorded. Chair side examination of the lesion was done and the lesion was provisionally diagnosed. The routine haematological examination was done and confirmed that the results were within normal limits. 5-6 ml of venous blood was withdrawn into a vacuum tube. And it was sent for biochemical analysis of serum iron and TIBC using Autoanalyser (COBASU 411-ROCH).

The results were tabulated and assessed using chi-square test.

RESULT

The present study comprised of 64 subjects diagnosed with PML or PMC. The patients were divided into three groups based on age. Age less than 40, between 40-60 and greater than 60-70 for age correlation with PML and PMC. Serum Iron group was further divided into two as serum iron less than 80 gm/dl and serum iron 80-140 gm/dl. While for TIBC, it was TIBC less than 250 gm/dl and TIBC 250-400 gm/dl. The serum iron and TIBC were correlated between PML versus PMC.

Table 1 PML/PMC with Serum Iron

PML/PMC	Serum Iron Less than 80gm/dl	Serum Iron 80-140 gm/dl	P value
Pre Malignant lesion	11	16	0.000
Pre Malignant Condition	8	29	Highly Significant

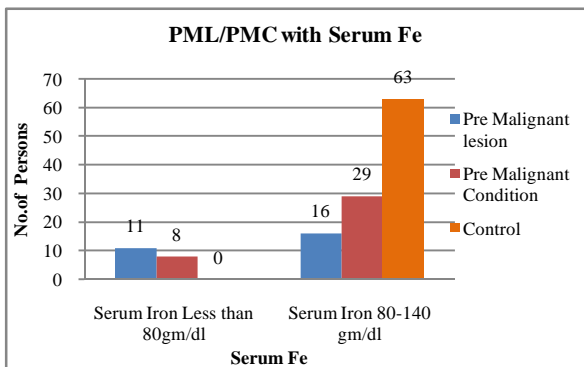


Figure 1 PML/PMC with Serum Fe

There were 11 patients in PML but only 8 patients in PMC belonging to the group less than 80gm/dl, however 16 patients in PML and 29 patients in PMC in the group 80-140 gm/dl with respect to serum iron levels (p=0.000) which shows a high significance (table 1, figure 1).

But in TIBC only 1 patient had less than 250gm /dl in that group whereas majority had the value between 250-400gm/dl in PML. Similarly in PMC also only one patient had less than 250 gm/dl in that group, and 35 patients had the value between 250-400 gm/dl in that group (p = 0.563, not significant).

Serum iron in leukoplakia was as follows: there were only 10 patients in less than 80gm/dl group whereas in the group 80-140gm /dl there were 13 patients when compared with the 34 controls (p=0.000, highly significant). Only one patient with leukoplakia had TIBC less than 250gm/dl, whereas 22 patients had the value in between 250-400gm/dl (p= 0.777). In erythroplakia only 1 patient had serum iron less than 80gm/dl but 3 were under the group of 80-140gm/dl against the control group 0 and 4 respectively for serum iron (0.285, not statistically significant) (table 2, figure 2).

Table 2 Premalignant lesions with Serum Iron and total iron binding capacity

Pre Malignant Lesion	Serum Iron Less than 80gm/dl	Serum Iron 80-140 gm/dl	P value	TIBC Less than 250 gm/dl	TIBC 250-400 gm/dl	P value	
Leukoplakia	case	10	13	0.00000	1	22	1.00000
	control	0	23	Highly Significant	1	22	Not Significant
Erythroplakia	case	1	3	0.285 Not Significant	Erythroplakia and TIBC- cannot be done b/c it is a constant which means there are no cases or controls in the group tbc <250gm/dl to do statistical analysis		
	control	0	4				

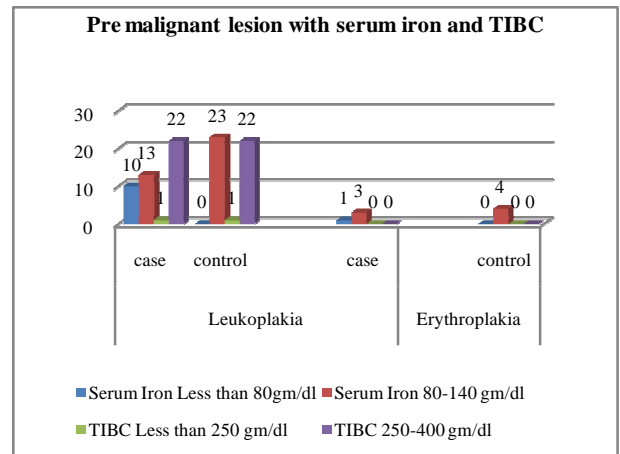


Figure 2 Pre malignant lesion with serum iron and TIBC

With respect to TIBC in Erythroplakia, the analysis could not be done because there are no subjects falling either in case or control group in both the sub groups. Six patients with OSMF had serum iron less than 80gm/dl but no subjects in control had less than 80 gm/dl; however 19 patients had between 80-140gm/dl whereas there were 25 subjects in control group (p = 0.009) and is statistically highly significant. Only one patient with OSMF and control had TIBC less than 250gm/dl but 24

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were there both in control and patient group, under the category of 250-400gm/dl ($p= 1.000$) and is not significant. Likewise in OLP there were only 2 patients who had less than 80gm/dl, but 10 patients were under 80-140gm/dl ($p = 0.140$). Only 1 patient with OLP had TIBC less than 250gm/dl whereas 11 patients had values between 250-400gm/dl ($p= 0.307$) and it is not statistically significant (table 3, figure 3).

Table 3 Pre Malignant Condition with Serum Iron and Total Iron Binding Capacity

Pre Malignant Condition	Case/Control	Serum Iron Less than 80gm/dl	Serum Iron 80-140 gm/dl	P value	TIBC	TIBC	P value
					Less than 250 gm/dl	250-400 gm/dl	
OSMF	case	6	19	0.009	1	24	1.000
	control	0	25	Highly Significant	1	24	Not Significant
Lichen Planus	case	2	10	0.140	1	11	0.307
	control	0	12	Not Significant	0	12	Not Significant

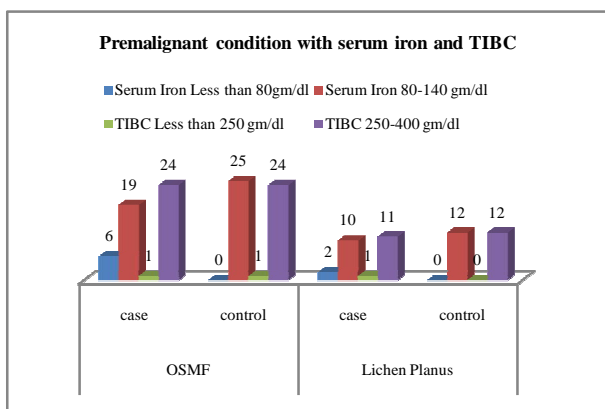


Figure 3 Premalignant condition with serum iron and TIBC

The correlation between the gender in PML versus PMC was also done where a p value of 0.213 was obtained. This also shows no significance. There were 23 and 25 males versus 4 and 12 females in lesions and conditions respectively against the control subjects of 43 males and 20 females (table 4).

Table 4 PML Versus PMC with Gender

PML/PMC	Gender		P value
	Male	Female	
Lesions	23	4	0.213
Conditions	25	12	Not Significant
Control	43	20	Significant

However when analysis was done with respect to age in PML versus PMC had a p value of 0.006 which gives a high statistical significance. Subjects were divided in to three groups based on age, as age less than 40years, 40-60years and 60-70years. There were only 4 patients with lesion, 3 with condition and 3 in control group under the first age group. But there were 21 patients with lesion, 34 patients with conditions and 45 in control group under the second age group. However there were only 2 patients with lesion, and no patients with conditions against 15 in control group in the third category (table 5, figure 4).

Table 5 PML/PMC with Age

PML/PMC	Age			P value
	Less than 40 yrs	40-60 yrs	Greater than 60 yrs	
Lesions	4	21	2	0.006
Conditions	3	34	0	Highly Significant

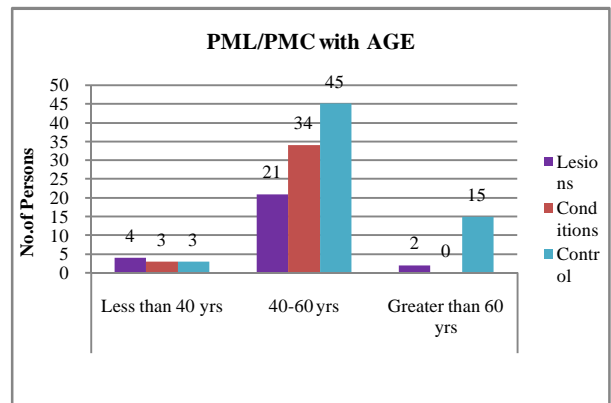


Figure 4 PML/PMC with AGE

Table 6 Table showing Comparison between mean Serum Iron and TIBC in Study and Control Group

Sex	Total	Premalignant Lesion	Premalignant Condition	
			Oral Leukoplakia	Oral Erythroplakia
Serum iron	84.0	81.0	84.4	80.0
Males	84.0	87.0	86.5	86.0
Females	85.0	76.0	77.7	80.0
TIBC	309.0	325.0	300.4	310.0
Males	309.0	325.0	285.1	304.0
Females	305.0	328.0	296.2	270.0

DISCUSSION

Health is “a state of complete physical, mental, and social well-being and not merely the absence of disease. Nutrients play an important role in preserving health of the human body. Micronutrients and antioxidants are a major constituent of daily diet which play an essential role for coping with oxidative stress. Trace elements like iron, copper, manganese are essential components of biological enzyme systems.

Iron is an important constituent of succinate dehydrogenase and important for cell viability. In Iron depletion the levels remain normal as there is still enough iron for normal erythropoiesis.^{29,31,45/8} During negative iron balance a wide range of non-erythroid changes include angular cheilitis, and atrophic glossitis.

The oral epithelial changes are seen in the middle cell layers of the epithelium and there is an alteration in the production of new epithelial cells. This also can be substantiated by the explanation given by Rennie J S et al The development of oral cancer from a precancerous lesion alters the regulation of iron metabolism which affects the serum levels of iron in patients with precancerous oral lesions, which can be substantiated in our study and supported by the finding mentioned by De Souza and Potazanik M as the iron status of the host can be a critical etiological influence on neoplastic growth, and the quantitative evaluation of iron has a prognostic value in precancer and cancer patients. This alteration can be due to the usage of iron in formation of fibrous bands as in oral submucous fibrosis cases as stated by Rajendran⁹. Frank M says the perturbations in cellular iron and ferritin are emerging as an important element in the pathogenesis of variety of premalignant conditions¹⁰.

WHO recommend the term Potentially Malignant Disorders (PMD) against lesions and conditions as they show an increased potential for malignant transformation. This

terminology is based on certain findings of the collaborating centre like the origin of a malignancy in the mouth of a patient known to have precancerous lesion would correspond with the site of precancer. But in precancerous conditions, cancer may arise in any anatomical site of the mouth or pharynx. The clinically appearing mucosa in a patient harbouring a precancerous lesion may have dysplasia on the contralateral anatomic site or molecular aberrations in other oral mucosa sites suggestive of a pathway to malignant transformation and that cancer could subsequently arise in apparently normal tissues.¹¹

The prevalence of oral precancerous lesions is a useful clinical marker for oral cancer. Oral cancer is an extremely deadly disease. It comprises approximately 2% of the total malignant tumours in Western Europe and North America, but in India, up to half of the cancers may be present in the mouth. Many oral cancers are preceded by clinically evident Oral Potentially Malignant Disorders (OPMDs). The malignant transformation rates of OPMDs show a great variation; Study done by Pei-Shan Ho observed that hyperkeratosis or epithelial hyperplasia, had a malignant transformation rate from 8% to 24%, and the annual rate is 3–8 per 100 person's year¹²

Researches across the globe worked to find out the possible relationship of trace elements like zinc, copper, iron with the risk of cancer in humans¹³. Several studies show the association of serum iron with oral cancers and precancerous diseases but no much work has been done exclusively in PMD's. Estimation of serum iron level in subjects with PMD can aid in determining the status of the disease, and prognosis of disease because iron metabolism gets altered in these subjects at cellular level.

An enzyme known as Cytochrome oxidase is an iron dependent enzyme which is required for the normal maturation of the epithelium. In iron deficiency state, the levels of cytochrome oxidase are low, consequently leading to epithelial atrophy. An atrophic epithelium makes the oral mucosa vulnerable to the soluble irritants.¹⁴ With the above background we designed a study to estimate the level of serum iron and total iron binding capacity in patients with premalignant lesion and condition through a biochemical assessment.

In the present study we had 27 PML cases out of which 24 were males and 3 were females and 37 PMC which included 27 males and 10 females. Serum iron concentration were found to be significantly lower in patients with PML and PMC ($p < 0.000$) which coincides with the results of other studies on these kind of patients like the study done by Rajeshwari G A¹⁵ *et al*, Karthik Hegde *et al*,¹⁶ Joythi T¹⁷, Teijan Wu *et al*¹⁸ and also as mentioned by Saba Khan *et al*¹⁹, Shishir S *et al*²⁰, Manasi A²¹ *et al*. The decrease in iron content leads to thinning of epithelial mucosa, decrease in epithelial vascularity and increased penetration of arecoline which leads to dysplastic changes in these subjects.

Serum iron concentration was less in subjects with leukoplakia (average being 84 μ gm /dl) when compared with erythroplakia (average being 81 μ gm /dl). This could be reasoned against the small number of sample size of erythroplakia group. The study of Challacombe SJ in 1986 in leukoplakia patients showed a significant decrease in serum iron similar to our study.²² When considering PML we had 11

subjects in group less than 80 gm/dl and 16 subjects in group 80 to 140 gm/dl. The p value is 0.000 and is highly significant for leukoplakia against erythroplakia which has p value of 1.000.

Serum iron concentration was less in subjects with oral submucous fibrosis (average being 84 gm /dl) when compared with lichenplanus (average being 80 gm /dl). When PMC are taken total we had 8 subjects in less than 80 gm/dl group and 29 subjects in group 80 to 140 gm/dl. The P value is 0.009 and is significant when compared to case with lichenplanus who had a P value of 0.140. This can be substantiated by a study done in OSMF patients by Paul RR²³. Study done by Tadakamadla J²⁴ *et al* also revealed a significant decrease in serum iron in OSMF patients just like our study. Utilization of iron in collagen synthesis by the hydroxylation of proline and lysine leads to decreased serum iron levels in OSMF patients. In most cases clinical anaemia may be a contributing factor but our patients had no features of anaemia. In the present study lichen planus did not show any significant change with serum iron. However the study done by Challacombe SJ²⁵ in 1986 in lichen planus patients showed a significant decrease in serum iron unlike our study.

Total iron-binding capacity (TIBC) is a test that measures the blood's capacity to bind iron with transferrin. Transferrin is the globulin component of the plasma protein to which iron binds (Schade and Caroline, 1946). Holmberg and Laurell (1945) concluded that the amount of iron in normal plasma by no means attains the limit of saturation of the specific iron binding protein. This saturation limit has been termed by Laurell (1947) as the iron-binding capacity of plasma (TIBC). Total iron binding capacity (TIBC) did not show any significant change in patients with PML and PMC ($p=0.563$) which can be substantiated by the study done by Vidhi D *et al*.²⁶ In that study done in 15 patients each, OSMF and leukoplakia had a value of 336 μ gm /dl and 301 μ gm /dl respectively against the control group value of 349 μ gm /dl which showed that TIBC is not altered in these diseases. The values in our study for TIBC also showed no significance. In the present study the average value of TIBC was 309 μ gm /dl in leukoplakia and 325 μ gm /dl in erythroplakia. However in OSMF and Lichenplanus it was 300 μ gm /dl and 310 μ gm /dl respectively. When PML are taken in total we had only 1 subject who was in group less than 250 μ gm /dl but had 26 in second group between 250 to 400 μ gm/dl. When PMC are considered we had 2 under group less than 250 μ gm /dl and 35 under second group between 250 to 400 μ gm/dl. The p value is 1.000 and 0.307 in PML and PMC respectively and is not significant.

There is no gender difference between PML and PMC noted in the present study, but there is a statistical significance of age between PML and PMC ($p < 0.006$) which indicates an increase in the occurrence of PML or PMC in older age groups. This may be because of the habit of tobacco chewing in the older age groups in the study population which can be substantiated with the study done by Punayya V²⁷, Gupta M.K²⁸ and Babu M²⁹ *et al*. Tobacco chewing, smoking, and use of pan etc play an important role in the development of oral cancer. According to Laletal, use of 'pan' (betel leaf) and 'supari' (betel nut), may be important. Pan is betel leaf on to which slaked lime is smeared and this is wrapped over a mixture of betel nut and other additives such as tobacco powder, cardoman seeds, aniseed, or gambier (acacia catechu

extract) It is clear from the literature that arecamay have significant effects upon the hard and soft tissues of the oral cavity.

The estimated level of malignant transformation for erythroplakia is 50 % and for leukoplakia it is 3.6 % to 17.5 % .³⁰ The incidence of malignant changes in patients with oral submucous fibrosis ranges from 3 to 19%.³¹. Several factors such as chillies consumption, areca nut chewing, and collagen disorders have suggested to be involved in the pathogenesis of this condition. Currently areca nut chewing is considered to be most important etiologic factor of oral submucous fibrosis . Serum Iron levels are considered as biochemical indicators for nutritional assessment. OLP is a chronic disease with diverse clinical manifestations and multiple site involvement is frequent. The risk of malignant transformation in OLP is controversial. In a study done by John I reports 2 % along with other studies done by Grispan who reported a 7 % , Warm reported 9.4 % in 53 patients, few authors reported as low while others as high as 5.3%.

Though we had few limitations in our study like the sample size, habithistory our study showed that the estimation of serum iron level in PMD's can be used as biomarker and can aid in early diagnosis. This requires the patients to seek a regular oral examination at frequent intervals so that, the disease can be diagnosed at an early stage.

CONCLUSION

The inference of this study is that, the estimation of iron indices in PMD's through a biochemical assessment serve both as a potential diagnostic and prognostic markers.

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