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Estimation of Retinoid Binding Protein (RBP-4) in Potentially Malignant Disorders: A Case–Control Study.

(Retinoid binding proteins in Oral Pre-Cancer)

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KEYWORDS-

Retinoid binding protein, leukoplakia, oral submucous fibrosis, oral lichen planus, potentially malignant disorders.

ABSTRACT:

Background: Potentially malignant disorders (PMD) such as leukoplakia, oral submucous fibrosis (OSMF), and oral lichen planus (OLP) precede a significant proportion of oral squamous cell carcinoma cases. Retinoids, derivatives of vitamin A, are known to influence cellular differentiation, proliferation, and apoptosis. Retinol-binding protein 4 (RBP-4) is the principal carrier of retinol and may serve as a biomarker in PMDs.

Aim: To estimate serum RBP-4 levels in patients with PMDs and compare them with healthy controls. Materials and Methods: This case–control study included 80 individuals (60 males, 20 females) attending the outpatient department of Oral Medicine and Radiology, Haldia Institute of Dental Sciences and Research, West Bengal. Participants were grouped as: Group 1: Healthy controls (n=20), Group 2: Leukoplakia (n=20), Group 3: OSMF (n=20), Group 4: OLP (n=20). Serum RBP-4 levels were estimated using a human RBP-4 ELISA kit. Data were analyzed for statistical significance. Results: Mean serum RBP-4 levels were highest in leukoplakia patients (statistically highly significant), moderately elevated in OSMF (statistically significant), and comparable to controls in OLP (not significant).

Conclusion: Serum RBP-4 shows potential as a diagnostic biomarker for leukoplakia and possibly OSMF, while its role in OLP remains uncertain. Larger, multicentric studies are needed to validate these findings.

Introduction

Oral squamous cell carcinoma (OSCC) is often preceded by a spectrum of mucosal changes collectively referred to as potentially malignant disorders (PMDs).[1] Common PMDs include leukoplakia, oral submucous fibrosis (OSMF), and oral lichen planus (OLP), each with variable malignant transformation rates.[2] Early detection of molecular changes in PMDs could help predict malignant potential and improve patient outcomes.[3]

Vitamin A and its derivatives, retinoids, are essential regulators of epithelial cell differentiation and proliferation. Retinol-binding protein 4 (RBP-4), the

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primary transporter of vitamin A in circulation, has been implicated in carcinogenesis and may serve as a biomarker in PMDs.[4] While previous studies have explored retinoids in cancer prevention and therapy, the role of RBP-4 in PMDs remains unclear.

The present study aimed to estimate serum RBP-4 levels in leukoplakia, OSMF, and OLP, and compare them with healthy controls.

Materials and Methods

Study design and setting: This was a case–control study conducted in the Department of Oral Medicine and Radiology, Haldia Institute of Dental Sciences and Research, Haldia, West Bengal.
Sample selection: A total of 80 participants were included: 20 healthy controls without deleterious habits (Group 1) and 60 patients with clinically diagnosed PMDs — leukoplakia (Group 2), OSMF (Group 3), and OLP (Group 4), with 20 subjects in each group.
Inclusion-criteria:
- Age- and sex-matched participants
- Clinically diagnosed cases of leukoplakia, OSMF, or OLP
- Healthy controls without tobacco, areca nut, or alcohol use

Exclusion criteria:

Patients undergoing treatment with steroids were excluded from the study. Patients with, any other intra oral potentially malignant disorder or cancer or any autoimmune diseases like systemic lupus erythematosus, multiple sclerosis etc. and taking any drugs (including immune suppressive, immune modulators, anti inflammatory) for the same were excluded. Patients with known major systemic illness or major surgery in recent past were excluded.

Clinical examination

Clinical examination was done in dental chair in a proper aseptic condition under halogen illumination using dental mouth mirror, dental probe, standard latex gloves and sterile gauze. Clinical diagnosis of leukoplakia, oral submucous fibrosis, oral lichen planus were made by clinical presentation.

The patients were instructed about the study and informed consent was obtained. They were sent for routine blood investigations.

Biopsy procedure

Incision biopsy was done under local anaesthesia using 2 % Lignocaine with no. 15 Bard Parker surgical blade with handle and standard black silk suture. Biopsy samples were sent for histopathological evaluation in a properly labelled plastic container with 10 % formalin solution.

Sample collection

After histopathological confirmation, the patients were asked to come for collection of blood. Blood samples were collected by venipuncture. 2ml of venous blood will be aspirated by venipuncture using 23G needle and 2 ml syringe, from antecubital fossa, and collected in a vial, labelled and stored in an ice box containing dry ice and were sent to the Department of Biochemistry, ICARE Institute of Medical Sciences & Research, Haldia.

Samples should be clear and transparent and be centrifuged to remove suspended solids. Allow samples to clot for 2 hours at room temperature or overnight at 4°C before centrifugation for 15 minutes at 1000×g.

Rbp-4 elisa kit Storage: All the reagents in the kit were stored according to the labels on vials. Unused wells were returned to the foil pouch with the desiccant pack and resealed along entire edge of zip-seal. Substrate Reagent shouldn't be kept at -20°C. Exposure of reagents to strong light was avoided in the process of incubation and storage. All the taps of reagents were tightened to prevent evaporation and microbial contamination.

Test principle

The ELISA kit uses Sandwich-ELISA as the method. The micro ELISA plate provided in the kit has been pre-coated with an antibody specific to RBP4. Standards or samples are added to the appropriate micro ELISA plate wells and combined with the specific antibody. Then a biotinylated detection antibody specific for RBP4 and Avidin-Horseradish Peroxidase (HRP) conjugate is added to each micro plate well successively and incubated. Free components are washed away. The substrate solution is added to each well. Only those wells that contain RBP4, biotinylated detection antibody and

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Avidin-HRP conjugate will appear blue in color. The enzyme-substrate reaction is terminated by the addition of a sulphuric acid solution and the color turns yellow. The optical density (OD) is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The OD value is proportional to the concentration of RBP4.

Now the obtained values will be compared with the values of the standard curve and results will be noted.

Statistical analysis: Data were analyzed using appropriate statistical tests (ANOVA and post hoc comparisons), with $p < 0.05$ considered statistically significant.

Results

Table 1: distribution of subjects by age

Age groups	Numbers	%
15-25	7	8.75
26-35	20	25
36-45	21	26.25
46-55	18	22.5
56-65	14	17.5
Total	80	100

Table 2: distribution of subjects according to age and habit

Age groups	Smoking	%	Chewing	%	Alcohol	%	Smoke+ Chew	%	Smoke+ Alcohol	%	Chew+ Alcohol	%	Smoke+ Chew+ alcohol	%
15-25	2	2.5	3	3.75			2	2.5						
26-35	9	11.25	11	13.75	5	6.25	4	5	1	1.25	1	1.25	2	2.5
36-45	7	8.75	7	8.75	4	5	3	3.75	2	2.5	1	1.25	1	1.25
46-55	8	10	5	6.25	2	2.5	3	3.75	1	1.25			1	1.25
56-65	6	7.5	5	6.25	3	3.75	2	2.5	1	1.25			2	2.5
total	32	40	31	38.75	14	17.5	14	17.5	5	6.25	2	2.5	6	7.5

Table 3: distribution of subjects according to disease groups

Age groups	Group 1 (control)	%	Group 2 (leukoplakia)	%	Group 3 (oral submucous fibrosis)	%	Group 4 (oral lchen planus)	%
15-25 (years)	1	1.25			4	5	2	2.5
26-35	1	1.25	5	6.25	8	10	6	7.5

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36-45	7	8.75	5	6.25	4	5	5	6.25
46-55	7	8.75	4	5	3	3.75	4	5
56-65	4	5	6	7.5	1	1.25	3	3.75
Total	20	25	20	25	20	25	20	25

Table 4: distribution of subjects according to disease groups

Habit	leukoplakia	%	Oral submucous fibrosis	%	Oral lichen planus	%
Chewing	9	11.25	20	25	2	2.5
Smoking	18	22.5	12	15	2	2.5
Alcohol	8	10	5	6.25	1	1.25
Chew + smoke	4	5	9	11.25	1	1.25
Chew + alcohol			1	1.25	1	1.25
Smoke + alcohol	5	6.25				
Smoke + chew + alcohol	3	3.75	3	3.75		

Table 5: distribution of subjects according to habit and site of lesion

Habit	Buccal mucosa	%	Alveolar mucosa	%	Labial mucosa	%	Tongue	%	Total	%
Chewing	26	32.5	5	6.25					31	38.75
Smoking	27	33.75	5	6.25					32	40
Alcohol	11	13.75	3	3.75					14	17.5
Chew + smoke	12	15	2	2.5					14	17.5
Chew + alcohol	2	2.5							2	2.5
Smoke + alcohol	4	5	1	1.25					5	6.25

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Smoke + chew + alcohol	4	5	2	2.5					6	7.5

Table 6: distribution of subjects according to type and site of lesion

type	Buccal mucosa	%	Alveolar mucosa	%	Labial mucosa	%	Tongue	%	Total	%
Leukoplakia	15	18.75	5	6.25					20	25
OSMF	18	22.5	2	2.5					20	25
OLP	14	17.5			4	5	2	2.5	20	25
total	47	58.75	7	8.75	4	5	2	2.5	60	75

Table 7: distribution of RBP-4 level in PMD

RBP (ng/ml)	Leukoplakia	%	OSMF	%	OLP	%
0-20					17	21.25
21-40			6	7.5	3	3.75
41-60			9	11.25		
61-80			5	6.25		
81-100	7	8.75				
101-	13	16.25				
TOTAL	20	25	20	25	20	25

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Table 8: distribution of subjects according to RBP-4 level and habit

rbp-4	chew	%	smoke	%	Alcohol	%	Chew + Alcohol	%	Smoke + Chew	%	Smoke + Alcohol	%	Smoke + Chew+ alcohol	%
0-20	3	3.75	2	2.5			1	1.25						
21-40	11	13.75	9	11.25	5	6.25	1	1.25	4	5				
41-60	7	8.75	7	8.75	3	3.75			3	3.75				
61-80	5	6.25	8	10	1	1.25			2	2.5			1	1.25
81-100	5	6.25	5	6.25	2	2.5			2	2.5			2	2.5
101-			1	1.25	3	3.75			3	3.75	5	6.25	3	3.75
Total	31	38.75	32	40	14	17.5	2	2.5	14	17.5	5	6.25	6	7.5

Table 1 shows distribution of subjects by the following five age groups: 7 subjects are in age group 15 – 25 years. 20 subjects are in age group 26 – 35 years. 21 subjects are in age group 36 – 45 years. 18 subjects are in age group 46 – 55 years. 14 subjects are in age group 56 – 65 years.

Table 2 shows the distribution of subjects according to age and habit. 32 subjects had a habit of smoking. 31 subjects had a habit of chewing. 14 subjects had a habit of drinking alcohol. 14 subjects had a habit of smoking and chewing. 5 subjects had a habit of smoking and alcohol. 2 subjects had a habit of chewing and alcohol. 6 subjects had a habit of smoking, chewing and alcohol. 7 subjects with habits were within 15-25 years. 33 subjects with habits were within 26-35 years. 25 subjects with habits were within 36-45 years. 20 subjects with habits were within 46-55 years. 19 subjects with habits were within 56-65 years.

Table 3 shows age wise distribution of subjects according to disease groups and control. 1 subject in the control group was aged between 15-25 years. 4 subjects in the OSMF group were aged between 15-25 years. 2 subjects in the OLP group were aged between 15-25 years. 1 subject in the control group was aged between 26-35 years. 5 subjects in the leukoplakia group were aged between 26-35 years. 8 subjects in the OSMF group were aged between 26-35 years. 6 subjects in the OLP group were aged between 26-35 years. 7 subjects in the control group were aged between 36-45 years. 5 subjects in the Leukoplakia group were aged between 36-45 years. 4 subjects in the OSMF group were aged between 36-45 years. 5 subjects in the OLP group were aged between 36-45 years. 7 subjects in the control group were aged between 46-55 years. 4 subjects in the leukoplakia group were aged between 46-55 years. 3 subjects in the OSMF group were aged between 46-55 years. 4 subjects in the OLP group were aged between 46-55 years. 4 subjects in the control group were aged between 56-65 years. 6 subjects in the leukoplakia group were aged between 56-65 years. 1 subject in the OSMF group was aged between 56-65 years. 3 subjects in the OLP group were aged between 56-65 years.

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Table 4 shows distribution of subjects according to habit and PMD. 9 subjects with chewing habit were patients of leukoplakia. 20 subjects with chewing habit were patients of OSMF. 2 subjects with chewing habit were patients of OLP. 18 subjects with smoking habit were patients of leukoplakia. 12 subjects with smoking habit were patients of OSMF. 2 subjects with smoking habit were patients of OLP. 8 subjects with alcohol habit were patients of leukoplakia. 5 subjects with alcohol habit were patients of OSMF. 1 subject with alcohol habit was patient of OLP. 4 subjects with smoking+chewing habit were patients of leukoplakia. 9 subjects with smoking+chewing habit were patients of OSMF. 1 subject with smoking+chewing habit was patient of OLP. 1 subject with alcohol+chewing habit was patients of OSMF. 1 subject with alcohol+chewing habit was patients of OLP. 5 subjects with smoking+alcohol habit were patients of leukoplakia. 3 subjects with smoking+chewing+alcohol habit were patients of leukoplakia. 3 subjects with smoking+chewing+alcohol habit were patients of OSMF.

Table 5 shows distribution of subjects according to site of lesion and habit. 26 patients with chewing habit had lesions in buccal mucosa. 5 patients with chewing habit had lesions in alveolar mucosa. 27 patients with smoking habit had lesions in buccal mucosa. 5 patients with smoking habit had lesions in alveolar mucosa. 11 patients with alcohol habit had lesions in buccal mucosa. 3 patients with alcohol habit had lesions in alveolar mucosa. 12 patients with smoking+chewing habit had lesions in buccal mucosa. 2 patients with smoking+chewing habit had lesions in alveolar mucosa. 2 patients with alcohol+chewing habit had lesions in buccal mucosa. 4 patients with smoking+alcohol habit had lesions in buccal mucosa. 1 patient with smoking+alcohol habit had lesions in alveolar mucosa. 4 patients with smoking+chewing+alcohol habit had lesions in buccal mucosa. 2 patients with smoking+chewing+alcohol habit had lesions in alveolar mucosa.

Table 6 shows distribution of subjects according to site of lesion and PMD. 15 patients with leukoplakia had lesions in buccal mucosa. 5 patients with leukoplakia had lesions in alveolar mucosa. 18 patients with OSMF had lesions in buccal mucosa. 2 patients with OSMF had lesions in alveolar mucosa. 14 patients with OLP had lesions in buccal mucosa. 4 patients with OLP had lesions in labial mucosa. 2 patients with OLP had lesions in tongue.

Table 7 shows distribution of subjects according to RBP-4 conc. and PMD. 17 patients of OLP had RBP-4 conc. Between 0-20 ng/ml. 6 patients of OSMF had RBP-4 conc. Between 21-40 ng/ml. 3 patients of OLP had RBP-4 conc. Between 21-40 ng/ml. 9 patients of OSMF had RBP-4 conc. Between 41-60 ng/ml. 5 patients of OSMF had RBP-4 conc. Between 61-80 ng/ml. 7 patients of Leukoplakia had RBP-4 conc. Between 81-100 ng/ml. 13 patients of Leukoplakia had RBP-4 conc. >100 ng/ml.

Table 8 shows distribution of subjects according to RBP-4 conc and habit. 3 subjects of chewing habit had a conc between 0-20 ng/ml. 2 subjects of smoking habit had a conc between 0-20 ng/ml. 1 subject of chewing+alcohol habit had a conc between 0-20 ng/ml. 11 subjects of chewing habit had a conc between 21-40 ng/ml. 9 subjects of smoking habit had a conc between 21-40 ng/ml. 5 subjects of alcohol habit had a conc between 21-40 ng/ml. 1 subject of chewing+alcohol habit had a conc between 21-40 ng/ml. 4 subjects of smoking+chewing had conc between 21-40 ng/ml. 7 subjects of chewing habit had a conc between 41-60 ng/ml. 7 subjects of smoking habit had a conc between 41-60 ng/ml. 3 subjects of alcohol habit had a conc between 41-60 ng/ml. 3 subjects of smoking+chewing had conc between 41-60 ng/ml. 5 subjects of chewing had conc between 61-80 ng/ml. 8 subjects of smoking had conc between 61-80 ng/ml. 1 subject of alcohol had conc between 61-80 ng/ml. 2 subjects of smoking+chewing had conc between 61-80 ng/ml. 1 subject of smoking+chewing+alcohol had conc between 61-80 ng/ml. 5 subjects of chewing had conc between 81-100 ng/ml. 5 subjects of smoking had conc between 81-100 ng/ml. 2 subjects of alcohol had conc between 81-100 ng/ml. 2 subjects of smoking+chewing had conc between 81-100 ng/ml. 5 subjects of smoking+alcohol had conc between 81-100 ng/ml. 2 subjects of smoking+chewing+alcohol had conc between 81-100 ng/ml. 1 subject of smoking had conc >100 ng/ml. 3 subjects of alcohol had conc >100 ng/ml. 3 subjects of smoking+chewing had conc >100 ng/ml. 5 subjects of smoking+alcohol had conc >100 ng/ml. 3 subjects of chewing+smoking+alcohol had conc >100 ng/ml.

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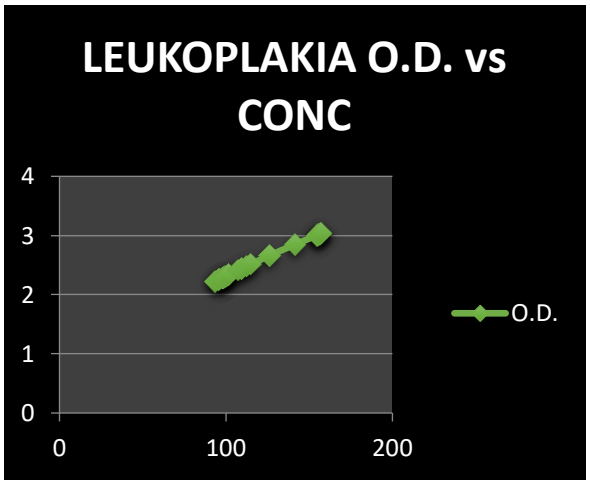
The data thus obtained were statistically analysed. Chi square tests and ANNOVA were calculated. The results were depicted in the following graphs.

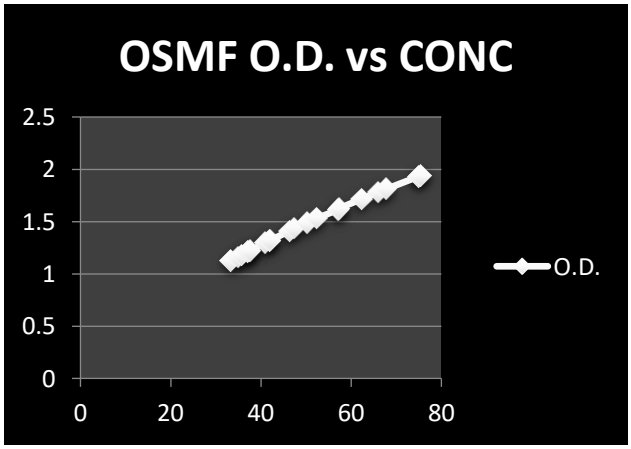
Graph 1 shows the optical densities of leukoplakia patients plotted against their RBP-4 conc. P value (<0.001) was found to be statistically highly significant when compared with the standard curve.

Graph 1: Optical Density of Leukoplakia cases vs concentration in ng/ml



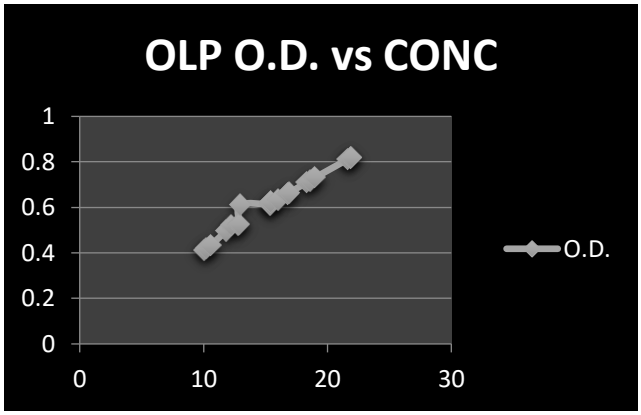
Graph 2 shows the optical densities of OSMF patients plotted against their RBP-4 conc. P value (<0.005) was found to be statistically significant when compared with the standard curve.

Graph 2: Optical Density of OSMF cases vs concentration in ng/ml



Graph 3 shows the optical densities of OLP patients plotted against their RBP-4 conc. P value (<0.08) was found to be statistically not significant when compared with the standard curve.

Graph 3: Optical Density of OLP cases vs concentration in ng/ml



Leukoplakia: Serum RBP-4 levels were significantly higher than controls ($p < 0.001$).

OSMF: Moderate but statistically significant increase in RBP-4 compared to controls ($p < 0.05$).

OLP: No significant difference compared to controls ($p > 0.05$).

The findings indicate that RBP-4 elevation is most pronounced in leukoplakia, less in OSMF, and minimal in OLP.

Discussion

Vitamins are essential compounds required for human metabolism. They are not bio-synthesised in the human body.[5] Thus they are required in the diet for maintaining good health. Vitamin A can be acquired from the diet either as pre formed vitamin A (primarily as retinyl ester, retinol, and in much smaller amount as retinoic acid) or provitamin A carotenoids.[6]

Dietary retinyl esters are converted to retinol within the lumen of the small intestine or the intestinal mucosa and then re-esterified to form retinyl ester (RE) within the enterocyte.[7] Provitamin A carotenoids, absorbed by the mucosal cells, are converted first to retinaldehyde and then to retinol.[8] After secretion of the nascent chylomicrons into the lymphatic system, the bulk of dietary vitamin A is taken up by hepatocytes and hydrolyzed again. Intracellular retinoid bioavailability is regulated by the presence of specific cytoplasmic retinol and retinoic acid binding proteins (CRBPs and

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CRABPs). [9, 10] The free retinol binds the epididymal retinoic acid binding protein (ERABP) and the retinol binding protein (RBP) and into plasma transthyretin.[11] Natural and synthetic retinoids have been demonstrated to inhibit the growth and the development of different types of tumours, including skin, breast, oral cavity, lung, hepatic, gastrointestinal, prostatic, and bladder cancers.[12] Natural retinoids act as chemotherapeutic agents for treatment of acute promyelocytic leukemia (APL). The combination treatment of histone deacetylase inhibitors with retinoic acids exerts a significant antitumor affect and is a promising therapeutic candidate to treat human lung cancer.[13, 14]

Recently tazarotene demonstrated a good efficacy in treating basal cell carcinoma. The ability of retinoids to inhibit the growth of Squamous Cell Carcinoma has been known for some time.[15] Recently, retinoids have been successfully used in vivo to prevent the progression of preneoplastic oral, bronchial and head and neck lesions to frank malignant tumors.[16] More specifically, treatment with isotretinoin has been shown to significantly reduce the appearance of head and neck squamous carcinomas in patients at high risk for development of second primary tumors.[17]

Vitamin A is carried in the blood by retinoid binding protein (RBP). One such carrier protein is designated as RBP-4.[18] The present study was conducted to estimate the level of RBP-4 in potentially malignant disorders of the oral cavity.

Multiple studies pertaining to lung cancer, breast cancer, colon cancer has shown increased level of RBP.[19] One study has been reported till date that countered the previous hypothesis and showed decreased RBP levels in ovarian cancer. So, this remains till date, a great debate as to the definite role of RBP in cancer.[20]

The role of retinoic acid in health and chemo prevention is beyond doubt. Aberrant regulation of RBP-4 might play a scrupulous role in development of malignancy.[21] Therefore in the current study we evaluated the role of RBP-4 as a minimally invasive & economical diagnostic as well as prognostic marker.

Estimation of RBP-4 level in PMD will give a vital insight as to the role of RBP-4 and in turn vitamin A in oral cancer and PMD, as there is no reported literature in this regard till date.

The present study showed that a strong correlation exists between level of RBP-4 in blood and PMD with maximum chances of cancer potential, like leukoplakia. OLP, on the other hand being a predominantly auto-immune disease had the least correlation when it comes to cancer potential. Relation of RBP-4 level with OSMF lies in between.

The study findings suggest that serum RBP-4 may serve as a useful biomarker for PMDs, particularly leukoplakia. The high RBP-4 levels in leukoplakia may reflect increased retinoid activity in early carcinogenesis, consistent with the established role of vitamin A derivatives in epithelial cell regulation. The moderate elevation in OSMF patients could be due to chronic inflammation and fibrosis, whereas the absence of significant change in OLP supports the ongoing debate regarding its malignant potential. Previous research has demonstrated that retinoids inhibit tumor cell proliferation and promote differentiation through retinoic acid receptor pathways. RBP-4, as the primary transporter of retinol, may be central to these mechanisms. However, the exact role of RBP-4 in PMDs is still unclear, and variations in levels may be influenced by lesion type, stage, and patient habits.[22-27]

Limitations:-
- Small sample size
- Single-center study
- No stratification by lesion severity or histopathological grading

Future directions:- Multi-centric studies with larger cohorts and inclusion of other PMDs could help establish RBP-4 as a reliable diagnostic or prognostic marker.

Conclusion

Serum RBP-4 levels are significantly elevated in leukoplakia and moderately increased in OSMF, while no significant difference is noted in OLP compared to healthy controls. RBP-4 may be a promising biomarker for certain PMDs, particularly leukoplakia.

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Figures-

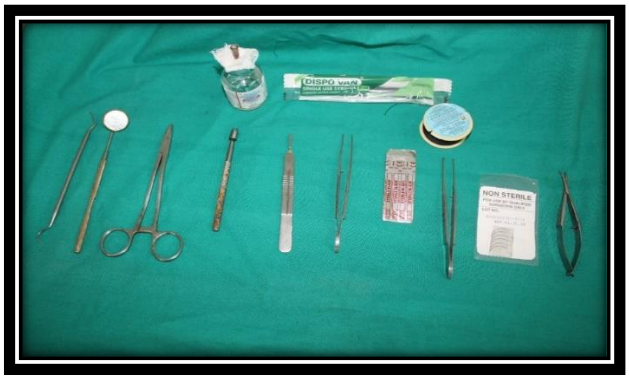

Figure 1 showing the armamentarium used for biopsy procedure, including Bard Parker surgical blade, handle, sutures, and other sterile instruments.

Figure 2 showing the clinical presentation of oral lichen planus involving the tongue, showing characteristic white striations.

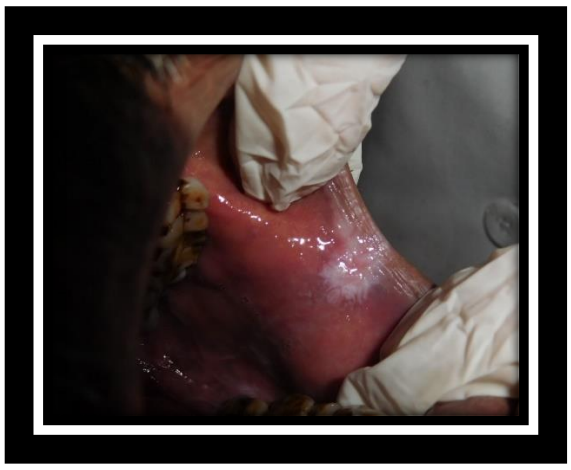

Figure 3 showing the clinical photograph of leukoplakia presenting as a well-demarcated white patch on the oral mucosa.

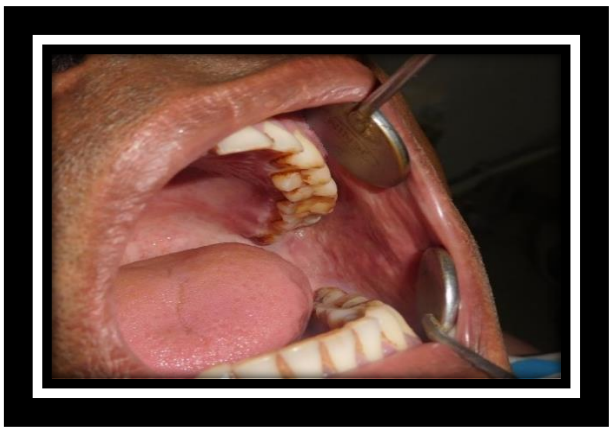

Figure 4 showing the clinical features of oral submucous fibrosis with blanching and fibrous bands in the oral mucosa.

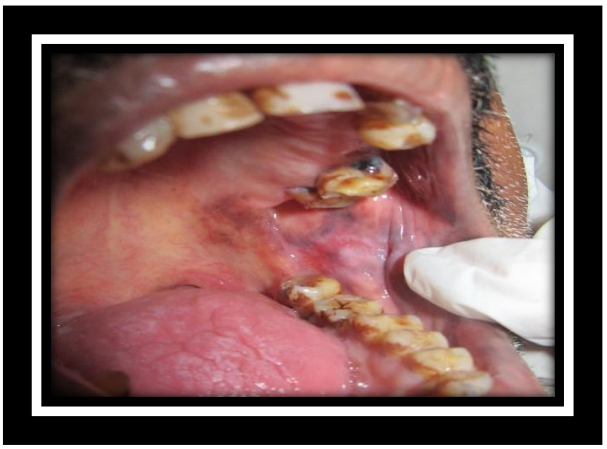

Figure 5 showing the erosive oral lichen planus on the buccal mucosa, characterized by erythematous and ulcerated areas.

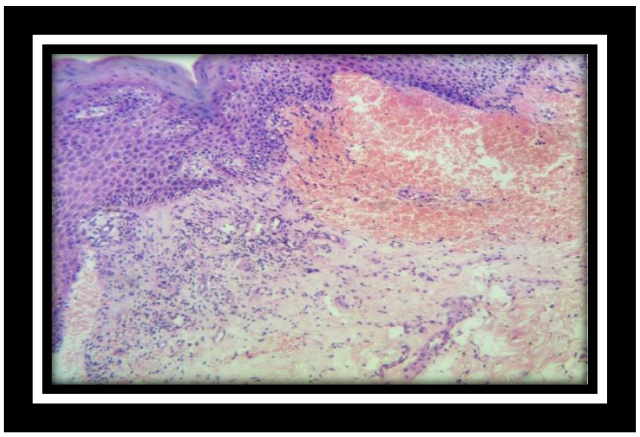

Figure 6 showing the photo-micrograph of the histo-pathological section of oral lichen planus (H&E stain,

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20×), showing band-like lymphocytic infiltrate in the sub-epithelial region.

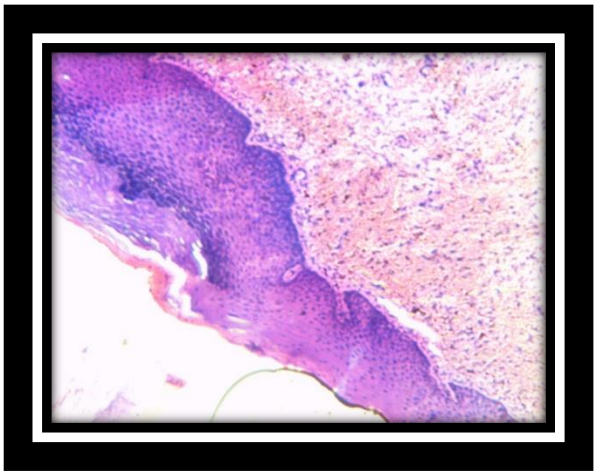

Figure 7 showing the photomicrograph of the histo-pathological section of leukoplakia (H&E stain, 20×), demonstrating epithelial hyperplasia with keratinization.

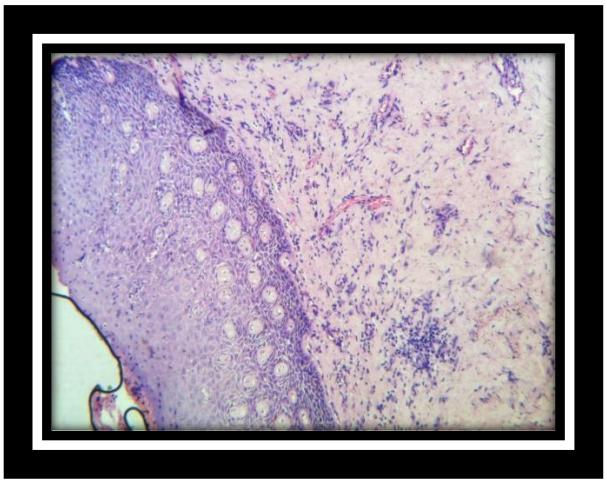

Figure 8 showing the photomicrograph of the histo-pathological section of oral submucous fibrosis (H&E stain, 20×), showing dense collagen deposition with juxtaepithelial hyalinization.