

## Comparison of serum and salivary enzyme creatine phosphokinase in patients with oral dysplasias

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### Abstract

Oral Epithelial Dysplasia (OED) appears as chronic, progressive, premalignant lesions of the oral mucosa, which are considered as the forerunner of Oral cancers, is a threat to the public accounting for increasing number of new cases and deaths worldwide, every year. Most of the oral cancers are detected at a late stage which is difficult to treat as well as has poor prognosis. The application of advanced molecular biological and biochemical methodologies to elucidate the biomarkers of these potentially malignant disorders may help in early detection of these lesions. A precise and more accurate marker which has the potential to predict the progression of a potentially malignant disorder to a malignant state, will enable early diagnosis as well as targeting of these lesions for the subsequent modification of treatment and follow up. One of the important molecular change which accompanies the transformation of a potentially malignant disorder involving the oral cavity to a malignant state is, elevation of serum levels of enzyme, Creatine Phosphokinase, which occurs on account of damage to the connective tissue cells and the deeper submucosal layers due to invasion by the malignant cells. The present study is undertaken to compare the levels of enzyme, Creatine phosphokinase in the serum and saliva of patients with oral dysplastic lesions and henceforth to assess the usefulness of these enzymes as a diagnostic marker of early transformation of these dysplastic lesions to a malignant state.

**Keywords:** CPK, OED, PMD.

### Introduction

Oral Epithelial Dysplasia (OED) is the diagnostic term used to describe the histo - pathologic changes seen in a chronic, progressive, premalignant lesions of the oral mucosa which usually presents in the form of leukoplakia, erythroplakia or erythroleukoplakia which are considered as the forerunner of oral cancers.<sup>2</sup> Majority of oral cancer develop from oral potentially malignant disorders which appears as visible changes in the mucosa, which when detected early can be effectively treated and transformation to carcinogenesis can be prevented. Nevertheless, most of the oral cancers are detected at a late stage which is difficult to treat as well as has poor prognosis.<sup>1</sup> Even though the field of molecular biology has shown a tremendous progress in the recent years, there is not even a single biological marker available which reliably predicts the transformation of a potentially malignant disorder of the oral mucosa to a malignant state (or) prevent the possible development of a oral squamous cell carcinoma.<sup>3</sup> Many tumour markers have been used to assist the diagnosis of certain malignancies which includes Carcinoembryonic antigen (CEA), Lactic Dehydrogenase (LDH), Phosphohexoisomerase (PHI) which are found to be elevated in certain malignancies. The enzyme Creatine Phosphokinase (CPK) has also been hypothesized as a serum marker for various cancers involving lungs, colon, breast etc.<sup>6</sup>

One of the important molecular change which accompanies the transformation of a potentially malignant disorder involving the oral cavity to a malignant state is, elevation of serum levels of enzyme, Creatine Phosphokinase, which occurs on account of damage to the connective tissue cells and the deeper submucosal layers due to invasion by the malignant cells.<sup>7</sup> Clinically, CPK is assayed as a marker for various diseases which includes,

Myocardial Infarction, Rhabdomyolysis, Muscular dystrophy and in Acute renal failure. CPK is also assayed from the saliva of patients in case of periodontal diseases.<sup>7</sup> Due to the anatomical proximity of saliva to the potentially malignant disorders affecting the oral cavity, saliva can be considered to be ideal to estimate the CPK enzyme levels in patients with oral dysplastic lesions.<sup>8</sup> With this background, the present study is undertaken to compare the levels of enzyme, CPK in the serum and saliva of patients with oral dysplastic lesions and henceforth to assess the usefulness of these enzymes as a diagnostic marker of early transformation of these dysplastic lesions to a malignant state.

### Materials and Methods

Blood and saliva samples were collected from the patients, who had visited the outpatient department in Mahatma Gandhi Postgraduate Institute of Dental Sciences, who were clinically diagnosed to have oral potentially malignant disorders and proven to have dysplastic changes on histopathological examination and also from the control individuals, after obtaining written consent. 30 patients with oral dysplastic lesions and 30 healthy individuals were included in the study.

### Study Group

Patients with oral dysplasias

1. 13 cases of mild dysplasia
2. 12 cases of moderate dysplasia
3. 5 cases of severe dysplasia

### Control Group

30 cases of healthy individuals with no history of systemic illness or drug therapy.

The blood samples and whole unstimulated saliva were collected and kept undisturbed at room temperature for a period of 1 hour followed by centrifugation at 1500 – 2000 rpm for about 5 minutes. The resultant supernatant was obtained and CPK enzyme analysis was carried out by the IFCC method in a spectrophotometric analyzer.

## Results

The data obtained was subjected to statistical analysis. Mean and Standard deviations (SD) were calculated for the individual group. These were compared using the following test of significance,

1. Descriptive analysis
2. One way ANCOVA F test
3. LSD post – hoc test

**Table 1:** Descriptive statistics of serum CPK level of the two groups

Group	Mean	Standard deviaton	Minimum	Maximum	T-test value *	P-value
Control	178.77	95.21	66.0	479.0	4.011	<0.001
Experimental	414.30	346.91	50.0	1497.0		

\* Since standard deviation has been large, T-test has been applied for the logarithmic values.

Table 1 shows that the significant p-value confirms that oral dysplasia patients has higher mean serum CPK values than the control subjects.

**Table 2:** Descriptive Statistics of Saliva CPK level of the two groups

Group	Mean	Standard deviaton	Minimum	Maximum	T-test value *	P-value
Control	6.60	5.45	1.0	18.0	6.819	<0.001
Experimental	30.60	42.26	5.0	219.0		

Table 2 shows that the significant p-value confirms that oral dysplasia patients higher CPK values in saliva compared to the healthy subjects.

**Table 3:** Comparison of serum CPK level between the control subjects and by severity of the oral dysplasia after controlling the covariates effects of age and sex

Group	Mean	Standard deviaton	ANCOVA test value*			LSD post-hoc test result		
			Source	F-value	P-value	Category(i)	Category(j)	P-value
Control	178.77	95.21	age	1.151	0.288			
Mild dysplasia	411.86	403.84	sex	15.161	<0.001			
Moderate dysplasia	488.33	340.44	Group	4.229	0.009	Control	Mild	0.016
Severe dysplasia	244.00	108.54					Moderate	0.002
							Severe	0.349
							Mild	0.376
							Severe	0.404
						Moderate	Severe	0.137

ANCOVA test has been applied for the logarithmic values

Table 3. ANCOVA test and LSD post hoc test has been applied to compare these four mean values after controlling the effects age and sex, for the logarithmic serum values.

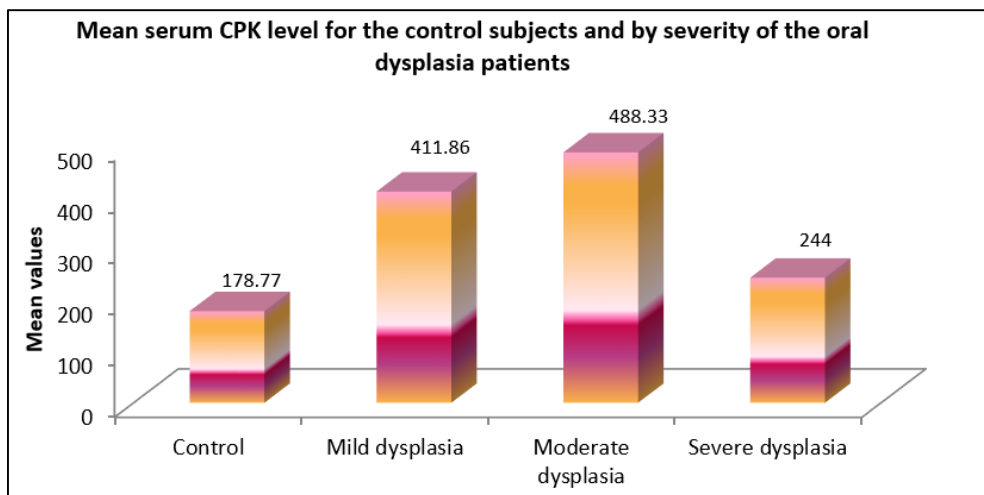


Fig. 1

Table 4: Comparison of saliva CPK level between the control subjects and by severity of the oral dysplasia after controlling the covariates effects of age and sex

Group	Mean	Standard deviaton	ANCOVA test value*			LSD post-hoc test result		
			Source	F-value	P-value	Category(i)	Category(j)	P-value
Control	6.60	5.45	age	0.037	0.848			
Mild dysplasia	40.31	57.36	sex	0.212	0.647			
Moderate dysplasia	17.17	9.41	Group	11.223	<0.001	Control	Mild	<0.001
Severe dysplasia	37.60	43.85					Moderate	0.001
						Severe	<0.001	
						Mild	Moderate	0.146
							Severe	0.909
						Moderate	Severe	0.223

ANCOVA test has been applied for the logarithmic values

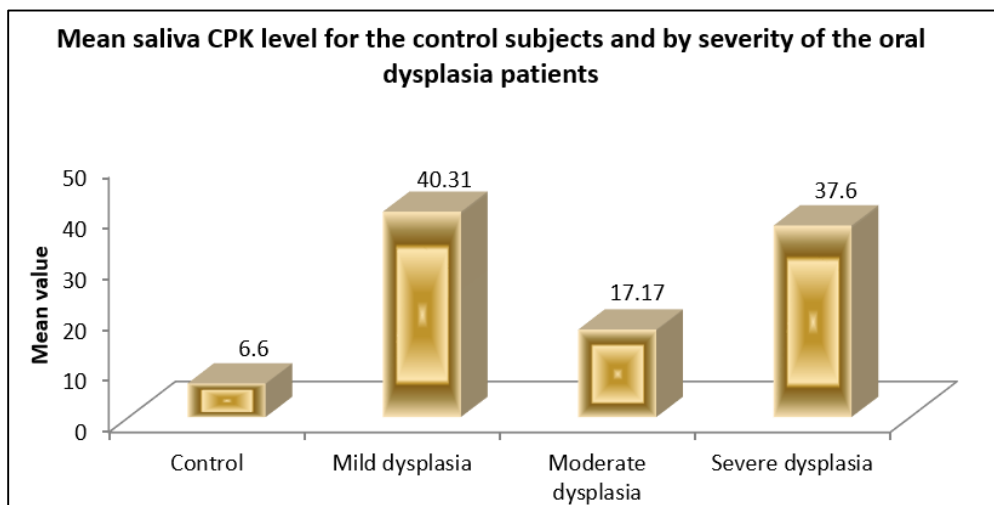
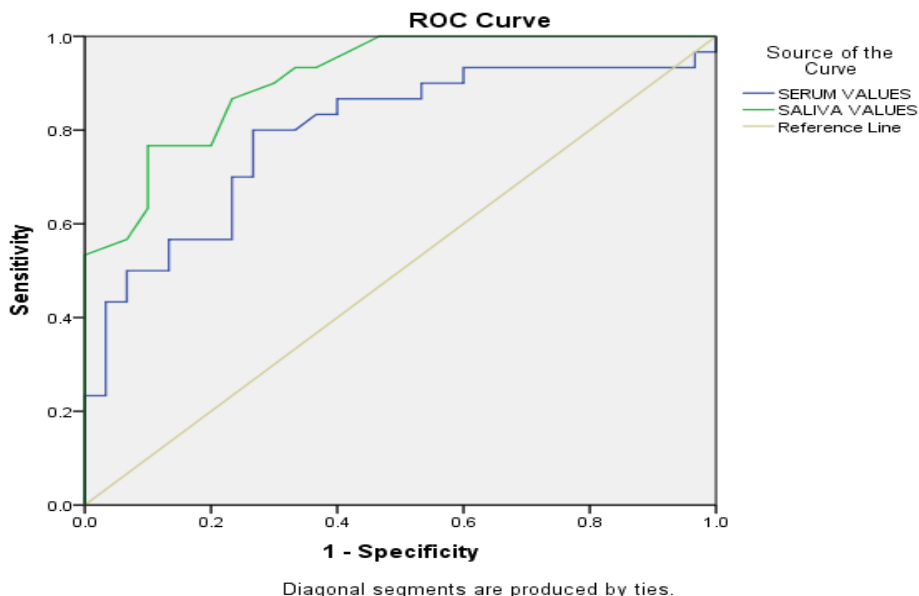


Fig. 2



**Fig. 3:** Receiver Operative Characteristic (ROC) curve for the serum and saliva CPK values

**Table 5:** Results of ROC Curve for serum and saliva CPK values

Variables	Area	Std. Error	P-value
Serum values	0.794	0.060	<0.001
Saliva values	0.911	0.035	<0.001

The area of ROC curve for saliva and serum CPK clearly infers that there is a relationship exists between the oral dysplasia and CPK levels. Using the ROC curve, the cut-off values 180 IU for serum CPK and 11 IU for saliva CPK has been obtained.

**Discussion**

Cancer is one of the most common causes of adult deaths worldwide.<sup>91</sup> More than 70 percent of all cancer deaths occur in the developing countries.<sup>92</sup> out of which, India alone represents about 8 percent of all estimated global cancers deaths and about 6 percent of all deaths occurring in India. Oral squamous cell carcinomas constitute majority of the cancers occurring in the head and neck region. Since its a well known fact that these cancers develop from premalignant lesions, intervention at an earlier stage would result in the reduction of mortality and the morbidity. Serum is one of the constituent in our body which may contain any specific enzyme which would act as a indicator for the neoplastic process. Enzyme CPK is one of the important enzyme which may act as a indicator of an underlying neoplastic process. Evaluation of BB isoenzyme of CPK in the serum might constitute as a specific indicator of the extent of the neoplastic process. The reason for this altered levels of CPK-BB may be attributed towards the cell damage which takes place during carcinogenesis as well the healing of tissues following the regression of the tumour process. During tumour process, there is increased keratinocyte stress, leading to increased levels of CPK in the skin and possibly increased circulating CPK levels in the serum.<sup>76</sup> Currently, the most accurate diagnostic tool available for the diagnosis of oral squamous cell carcinoma as well as the potentially malignant

disorders which precede the development of these oral cancers, is histopathological

examination. To prevent the malignant transformation of these potentially malignant disorders or dysplastic lesions, regular follow up and repeated biopsy procedures are required. To overcome all these invasive procedures, estimation of enzyme, Creatine Phosphokinase from the serum and saliva of the patients with oral dysplastic lesions is attempted to establish its role as a diagnostic marker in these oral dysplastic lesions.

In our study, we included a total of 30 patients with oral dysplasias and 30 healthy control subjects. Estimation of Creatine Phosphokinase enzyme level was done from serum and saliva of each individual participating in this study. In our study, the mean serum CPK enzyme levels in the control group was 178.8 and in the dysplasia group was 414.3. On comparing the mean serum CPK values between both the groups, it was observed that the oral dysplasia group has higher mean serum CPK values than the control group. This was in accordance with the previous studies of Spoorthi Banvar Ravi et al<sup>6</sup> where the mean serum CPK enzyme levels in patients with oral potentially malignant disorders were found to be higher when compared with the control group. The mean saliva CPK levels in the control group was found to be 6.6, whereas the mean values in the dysplasia group was

30.6, which proves that the oral dysplasia patients have a wide dispersion on saliva CPK levels. The statistical significance observed on comparing the mean between both the groups confirms that the oral dysplasia patients have higher CPK values in saliva when compared with the control subjects.

ROC curve was used for serum and saliva CPK values and a cut off value of 180 IU/L was obtained for serum CPK and 11 IU/L was obtained for saliva CPK. With the cut off values obtained for serum CPK, the sensitivity, specificity, and the positive predictive values were calculated and were found to be 80%, 73.3 % and 75% respectively. These values indicate that the serum CPK can be used as a supportive evidence, but not as a marker for the oral dysplasia. The sensitivity, specificity and the positive predictive values was calculated using the cut off value obtained from the ROC curve for saliva CPK and were found to be 87%, 77%, 79% respectively. These values again indicate that the saliva CPK can be used as a supportive evidence for oral dysplasia but not as a marker for oral dysplasia.

### Conclusion

From the present study, we have noticed that the reliability of the serum and saliva CPK based on the sensitivity, specificity and positive predictive values calculated using the cut off values obtained from the ROC curve, clearly indicates that both the serum and saliva CPK can be used as a supportive evidence for oral dysplasia but cannot be used as a marker. However in comparison between the reliability values of serum and saliva CPK, saliva seems to be more reliable as a supportive evidence for oral dysplasia than the serum CPK. Hence, we conclude that the Creatine phosphokinase enzyme cannot be used as a diagnostic marker for oral dysplastic lesions, but it can be considered as a supportive evidence for oral dysplasias. On comparison between serum and salivary Creatine Phosphokinase enzyme levels, saliva seems to be more reliable than the serum levels. However further studies with a larger sample size are required to evaluate the true potential of Creatine Phosphokinase as a marker for oral dysplastic lesions.

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### Conflict of interest

None.

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