Original Article

# Serum fucose level in oral cancer, leukoplakia, and oral sub mucous fibrosis: A biochemical study

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## Abstract

**Aims:** To estimate the serum fucose levels in clinically and histopathologically diagnosed oral cancer, oral leukoplakia, and oral submucous fibrosis cases. To compare and correlate the severity of dysplasia or histopathological grading of the premalignant and malignant lesions with serum fucose levels. **Objective:** To determine the role of serum fucose as a reliable biomarker for early detection of malignant transformation of potentially malignant lesions and conditions and prediction of biologic behavior of the malignant lesions. **Material and Method:** The intended study shall include 100 participants divided into 4 groups. Groups I, II, and III will include 25 clinically and histological diagnosed cases of oral leukoplakia, oral submucous fibrosis, and oral cancer, and 25 normal control group. Fucose was measured according to the method of Dische and Shettles as adopted by Winzler. **Statistical Analysis:** Statistical analysis will be done using SPSS statistical software (Version 10), and the levels of significance will be analyzed using the paired and unpaired t-tests. **Result:** In subjects of 4 groups were age- and gender-matched and comparable thus these may also not influence the study outcome measure (fucose levels). ANOVA revealed significantly different fucose levels among the groups ($F = 17.00$, $P < 0.001$). Mean fucose level did not differ ($P > 0.05$) between oral leukoplakia, oral submucous fibrosis, and oral cancer (84.5%) groups. The increase in mean fucose levels with severity was the highest in the oral cancer group followed by oral submucous fibrosis and oral leukoplakia group. The mean fucose levels did not differ between mild and moderate grades ($P > 0.05$) in all the 3 groups. **Conclusion:** The evaluation of serum l-fucose would be of good help in assessing early malignant change in increasing the accuracy of clinical diagnosis and also in assessing the spread and invasiveness of oral cancer, oral submucous fibrosis, and leukoplakia.

**Keywords:** Fucose, oral cancer, oral leukoplakia, premalignant

## Introduction

Oral cancer (OC) is one of the leading causes of mortality and morbidity. It is a well-known fact that early detection of cancer is essential for best chances of cure. Use of biomarker measurements for early detection is a promising research innovation being applied to various human cancers.[1-6]

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It had been established that cancer cells synthesize certain glycoproteins that may be detected in body fluids.[7] Glycoproteins contain galactose, mannose, glucosamine, galactosamine, sialic acid, or fucose as the carbohydrate residue.[8] It has been reported that tumor cells modulate their surface by increasing fucosylation levels (addition of l-fucose at the terminal end of the oligosaccharide chain) to escape recognition, which contribute to several abnormal characteristics of tumor cells, such as decreased adhesion and uncontrolled tumor growth.[9] Hence, monitoring



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serum/tissue fucose levels could be a promising approach for the early detection, diagnosis, and prognosis of various cancer types.[8,9]

OC may be preceded by precancerous lesions or conditions such as leukoplakia, oral submucous fibrosis (OSMF), etc. Oral precancer represents an increased risk of malignant transformation.[10] Altered glycosylation of glycoconjugates, such as sialic acid, fucose, etc., are few important molecular changes that accompany malignant transformation. Alterations in serum fucose levels had been associated with certain precancerous lesions.[10-12] Early detection of malignant transformation improves the clinical outcome of patients. The search for a biomarker that could predict the changes in the premalignant lesions would immensely help in the recognition of high-risk lesions. Therefore, if patients with clinically suspicious lesions can be analyzed with biomarkers along with routine histopathological tests for the prediction of its malignant potential, the chance of minimizing the morbidity and mortality will be high.[10]

## Aims and Objectives

### Aims

1. To estimate the serum fucose levels in clinically and histopathologically diagnosed OC, oral leukoplakia, and OSMF cases.
2. To investigate the possible usefulness in the prediction of malignant potential of the premalignant lesions.
3. To compare and correlate the severity of dysplasia or histopathological grading of the premalignant and malignant lesions with serum fucose levels.

### Objective

To determine the role of serum fucose as a reliable biomarker for early detection of malignant transformation of potentially malignant lesions and conditions and prediction of biologic behavior of the malignant lesions.

## Materials and Method

### Source of data and sample size

The intended study included 100 subjects divided into 4 groups. Group I includes 25 age- and gender-matched healthy subjects, from patients attendants to serve as controls. Groups II, III, and IV include 25 each clinically and histological diagnosed cases of leukoplakia, OSMF, and OC patients each, respectively, between the age group 15 and 60 years, attending the Department of Oral Medicine and Radiology, Career Postgraduate Institute of Dental Sciences and Hospital. Informed consent was taken from the patients and the controls.

### Inclusion criteria

- Patients with clinically and histologically proven leukoplakia, OSMF, and OC.
- Patients between 15 and 60 years age group.
- Healthy subjects with no history of systemic or localized illness like allergies, renal problems, hypertension, and diabetes will be included as controls.

### Exclusion criteria

- Patients with known systemic conditions like diabetes, hypertension, pregnancy, allergies, infections, and liver disease will be excluded.
- Patients with >1 premalignant lesions coexisting in the oral cavity will be excluded.
- Healthy controls will be excluded on the basis of tobacco and alcohol consumption.

### Methodology

Fucose was measured according to the method of Dische and Shettles[13] as adopted by Winzler.[14]

## Material

- Ethyl alcohol (95% Ethanol)
- Sulphuric acid + $H_2O$ (6 Vol conc. $H_2SO_4$ + $H_2O$)
- Cysteine reagent (3%)
- Sodium hydroxide (0.2 N)
- Distilled water
- Working standard fucose solution (20 μg/mL).

### Statistical analysis

Data were summarized as mean ± SE. Groups were compared using one-way analysis of variance (ANOVA) and the significance of the mean difference between the groups was done by Tukey's *post hoc* test. All analyses were performed on SPSS software (PSAW, windows version 18).

## Results

### Fucose level in age

The age of normal, oral leukoplakia, OSMF, and OC groups ranged from 20 to 55, 20 to 56, 22 to 60, and 20 to 60 years, respectively with mean (±SE) 32.60 ± 2.34, 36.68 ± 2.06, 30.72 ± 1.84, and 33.80 ± 2.56 years, respectively, as shown in Table 1 [Figure 1]. The mean age of the oral leukoplakia

**Table 1: Age (Mean±SE, *n*=25) of four groups**

| Normal | Oral leukoplakia | Oral submucous fibrosis | Oral cancer | *F* | *P* |
|---|---|---|---|---|---|
| 32.60±2.34 (20-55) | 36.68±2.06 (20-56) | 30.72±1.84 (22-60) | 33.80±2.56 (20-60) | 1.27 | 0.289 |

**Table 2: Fucose levels (Mean±SE, *n*=25) of four groups**

| Normal | Oral leukoplakia | Oral submucous fibrosis | Oral cancer |
|---|---|---|---|
| 7.22±0.26 (2.7-8.9) | 35.28±4.25 (10.0-73.0) | 37.83±4.73 (12.9-80.0) | 46.63±5.29 (12.0-85.0) |

**Table 3: Comparison of fucose levels of four groups by one way ANOVA**

| Source of variations (SV) | Sum of squares (SS) | Degrees of freedom (DF) | Mean sum of squares (MS) | *F* | *P* |
|---|---|---|---|---|---|
| Groups | 21813.39 | 3 | 7271.13 | 17.00 | <0.001 |
| Error | 41064.61 | 96 | 427.76 | | |
| Total | 62878.00 | 99 | 7698.89 | | |

**Table 4: Comparison (*P*) of mean fucose levels between the groups by Tukey *post hoc* test**

| Comparisons | *P* |
|---|---|
| Normal vs. Oral leukoplakia | <0.001 |
| Normal vs. Oral submucous fibrosis | <0.001 |
| Normal vs. Oral cancer | <0.001 |
| Oral leukoplakia vs. Oral submucous fibrosis | 0.972 |
| Oral leukoplakia vs. Oral cancer | 0.218 |
| Oral submucous fibrosis vs. Oral cancer | 0.439 |

**Table 5: Fucose levels (Mean±SE) of three groups according to grades**

| Groups | Histopathological/clinical grades | | | | | |
|---|---|---|---|---|---|---|
| | *n* | Mild | *n* | Moderate | *n* | Severe |
| Oral leukoplakia | 6 | 14.82±2.43 | 9 | 23.92±0.72 | 10 | 57.78±4.56 |
| Oral submucous fibrosis | 6 | 15.43±0.86 | 10 | 27.88±4.75 | 9 | 63.82±4.25 |
| Oral cancer | 6 | 15.11±1.01 | 7 | 31.43±2.83 | 12 | 71.27±3.41 |

group was slightly higher than the other groups. Comparing the age of 4 groups, ANOVA revealed a similar age among the groups (F = 1.27, *P* = 0.289). In other words, subjects of 4 groups were age- and gender-matched and comparable, thus these may also not influence the study outcome measure (fucose levels).

## Fucose level between 4 groups

The fucose level of normal, oral leukoplakia, OSMF and OC groups ranged from 2.7 to 8.9, 10.0 to 73.0, 12.9 to 80.0, and 12.0 to 85.0 mg/dL, respectively with mean (±SE) 7.22 ± 0.26, 35.28 ± 4.25, 37.83 ± 4.73, and 46.63 ± 5.29 mg/dL, respectively, as shown in Table 2. The mean fucose level of the OC group was comparatively higher than other groups. Comparing the fucose level of 4 groups [Table 3], ANOVA revealed significantly different fucose levels among the groups (F = 17.00, *P* < 0.001).

Further comparing the mean fucose levels between the groups [Table 4], the Tukey test revealed significantly higher fucose levels in oral leukoplakia (79.5%), OSMF (80.9%), and OC (84.5%) groups as compared with the normal group [Figure 2]. However, the mean fucose level did not differ (*P* > 0.05) between oral leukoplakia, OSMF, and OC (84.5%) groups.

## According to histopathological/clinical grade

When the mean fucose levels were compared with the degree of dysplasia in case of potentially malignant disorders and degree of differentiation in OC, it was observed that the mean fucose levels in all 3 groups increased with severity (mild to moderate to severe), as shown in Table 5. The mean serum fucose was higher in OSMF cases with mild dysplasia than well-differentiated OC and mildly dysplastic oral leukoplakia. Mean fucose levels for moderately and severely dysplastic potentially malignant disorders/moderately and poorly differentiated OC were highest for OC, followed by OSMF and oral leukoplakia. The increase in mean fucose levels with severity was the highest in the OC group followed by OSMF and oral leukoplakia groups.

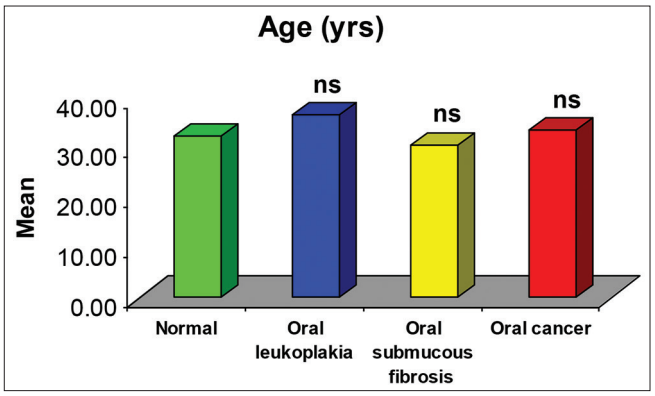


**Figure 1:** Mean age of four groups. ns: *P*>0.05- as compared Normal

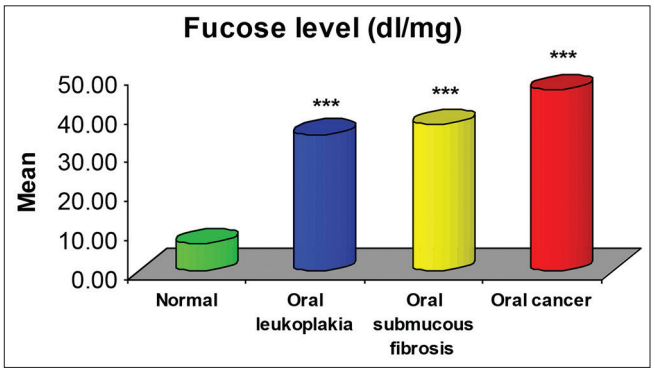


**Figure 2:** Mean fucose levels of four groups. ***P<0.001- as compared to Normal

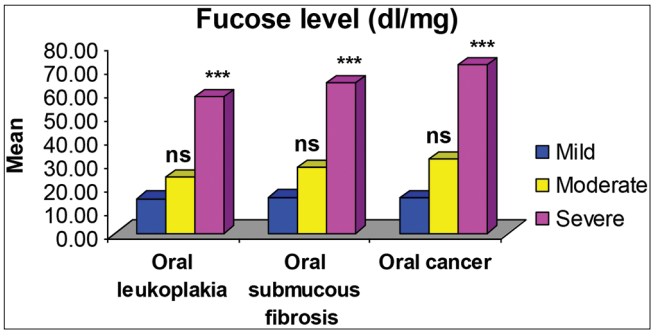


**Figure 3:** For each group, mean fucose levels between the grades (within groups). ns: *P*>0.05, ***P<0.001- as compared to Mild

**Table 6: Comparison of fucose levels of three groups and three grades together by two way ANOVA**

| Source of variations (SV) | Sum of squares (SS) | Degrees of freedom (DF) | Mean sum of squares (MS) | *F* | *P* |
|---|---|---|---|---|---|
| Groups | 587.50 | 2 | 293.75 | 2.64 | 0.079 |
| Grades | 32988.23 | 2 | 16494.12 | 148.14 | <0.001 |
| Groups x Grades | 347.98 | 4 | 87.00 | 0.78 | 0.541 |
| Error | 7348.39 | 66 | 111.34 | - | - |
| Total | 42798.43 | 74 | 16986.21 | - | |

**Table 7: For each group, comparison (*P*) of mean fucose levels between the grades (within groups) by Tukey *post hoc* test**

| Comparisons | Oral leukoplakia | Oral submucous fibrosis | Oral cancer |
|---|---|---|---|
| Mild vs. Moderate | 0.781 | 0.367 | 0.141 |
| Mild vs. Severe | <0.001 | <0.001 | <0.001 |
| Moderate vs. Severe | <0.001 | <0.001 | <0.001 |

**Table 8: For each grade, comparison (*P*) of mean fucose levels between the groups by Tukey *post hoc* test**

| Comparisons | Mild | Moderate | Severe |
|---|---|---|---|
| Oral leukoplakia vs. Oral submucous fibrosis | 1.000 | 0.996 | 0.943 |
| Oral leukoplakia vs. Oral cancer | 1.000 | 0.890 | 0.088 |
| Oral submucous fibrosis vs. Oral cancer | 1.000 | 0.999 | 0.801 |

Comparing the fucose levels of 3 groups and 3 grades together [Table 6], ANOVA revealed similar fucose levels among the groups ($F = 2.64$, $P = 0.079$) while significantly different among the grades ($F = 148.14$, $P < 0.001$). Further, the interaction effect of both (groups x grades) on fucose level was also found similar ($F = 0.78$, $P = 0.541$).

Further, for each group, comparing the mean fucose levels within the groups (i.e. between grades) [Table 7], Tukey test revealed significantly higher ($P < 0.001$) fucose levels in severe grade as compared with both mild and moderate grades in all 3 groups [Figure 3]. However, the mean fucose levels did not differ between mild and moderate grades ($P > 0.05$) in all the 3 groups.

When the mean fucose levels were compared for each grade between the groups, Tukey test revealed no significant difference ($P > 0.05$) in fucose levels among the groups in all grades, as shown in Table 8.

## Discussion

Oral cancer (OC) accounts for ~30%–40% of all cancers in India. During the malignant transformation of cells, there may be either an up-regulation or down-regulation of the biochemical substances.[15] With the development of new and sensitive techniques for measuring very minute quantities of biochemical substances, now it is possible to identify early malignant transformation of the cells. Such biochemical substances are known as tumor markers.[13-16]

Increased level of different glycoproteins has been associated with different types of malignancies, like higher serum fucose level found in cancer of the cervix, breast, oral cavity, and lymphoma. Glycoconjugate molecules expressed in the plasma membrane of mammalian cells have also been reported to be associated with cell-to-cell adhesion, tumor progression, and metastasis.[8]

Measurement of protein-bound carbohydrates of glycoproteins has been used as an index to glycoprotein levels now more recent trend need to be used to measure the amount of given monosaccharide as a measure of glycoproteins.[17-19]

One of the monosaccharides is l-fucose, a hexose, which is a terminal sugar in most of the plasma glycoproteins. L-Fucose is found in many glycolipids and glycoproteins, including several families of blood group antigens.[18,19] Changes have been detected in the fucosylation pattern of these molecules in the tissue of cancer patients because of fucosyltransferase activity, which is especially high in the serum of patients suffering from highly malignant or metastatic tumors.[9,17,19]

In this study, the normal fucose level in the control group is 7.22 ± 0.26 mg/dL with levels ranging between 2.7 and 8.9 mg/dL. In contrast, the established normal fucose level by Parwani and Parwani[8] was found to be 5.32 ± 0.67 mg/dL which ranges in between 4.25 and 7.1 mg. The level obtained in this study was much similar to that obtained by Wang *et al.*,[17] Sharma *et al.*,[20] and Arya *et al.*[21] Serum fucose level in this study was significantly found to be elevated among cancer patients (46.63 ± 5.29 mg/dL) when compared with leukoplakia (35.28 ± 4.25 mg/dL) and with OSMF (37.83 ± 4.73) and control group (7.22 ± 0.26 mg/dL).

Bhairavi *et al.* found serum l-fucosidase activity were significantly higher in OPC and OC patients compared to the controls.[22] The OC patient showed a mean serum fucose level of 46.63 ± 5.29 mg %. Similarly, the study shows higher serum fucose levels compared with those of the control have been observed by Solanki *et al.*,[16] Kaswan and Kaushik *et al.*[23] Agarwal *et al.*,[24] and Sen *et al.*[25]

In this study, we observed very high serum fucose in OSMF, leukoplakia, and OC when compared with controls ($P < 0.001$) as like that was observed by Parwani and Parwani *et al.*[8] in their study. According to Shah *et al.*,[2] high fucosylation is one of the characteristic features of malignancies mainly because of increased activity of fucosyltransferase activity in malignant

tissue. Bose *et al.* also showed significantly very high levels of fucose in OC, leukoplakia, and OSMF patients ($P < 0.001$) when compared with control groups.[26]

In this study, fucose level estimation is done on the basis of histopathological and clinical grade. In leukoplakia, in the mild ($n = 6$) histopathological condition, the fucose level is 14.82 ± 2.43, in moderate ($n = 9$), fucose level is 23.92 ± 0.72, and in severe ($n = 10$), fucose level is 57.78 ± 4.56.

In leukoplakia, in mild versus moderate condition, fucose level is not significant ($P = 0.781$), but in mild versus severe and moderate versus severe conditions fucose levels are significant ($P < 0.001$).

Estimation of fucose in oral submucosa fibrosis on the basis of histopathological/clinical grade is done in this study. In mild (grade 1, $n = 6$) condition, OSMF level of fucose is 15.43 ± 0.86, moderate (grade 2, $n = 10$) fucose level is 27.88 ± 4.75, and severe ($n = 9$, grade 3) fucose level is 63 ± 4.25 [Table 5].

In OSMF, comparison between mild (grade1) versus moderate (grade 2) is not significant ($P = 0.367$), but mild (grade 1) versus severe (grade 3) and moderate (grade 2) versus severe (grade 3) is highly significant ($P < 0.001$) [Table 7].

A similar study is also done in OC. In mild ($n = 6$) histopathological condition, fucose level is 15.11 ± 1.01, moderate ($n = 7$) fucose level is 31.43 ± 2.83 and in severe ($n = 12$) fucose level is 71.27 ± 3.41 [Table 5].

Histopathological comparison group between mild versus moderate is not significant ($P = 0.141$), but mild versus severe and moderate versus severe is significant ($P < 0.001$) [Table 7].

Bose *et al.* (2013) studied on patients with metastases had higher levels of the biomarkers than the patients with primary OC. However, elevations only in LSA levels were statistically significant and also a significant change present is severe in comparison with moderate.[27]

Similarly, the current study also shows the level of serum fucose is significant in severe in comparison of mild and severe to moderate.

Seibert *et al.* suggested that the elevation of serum fucose merely reflects the occurrence of tissue destruction and release of preformed fucose at the site.[28] However, Shetlar *et al.* suggested that tissue proliferation rather than repair is a more probable cause for the increase in serum fucose.[29-31] Estimation of such fucose conjugated proteins is suggestive to be good biomarkers in the diagnosis of OC cases as well as in assessing the prognosis of such cases. The estimation of serum fucose levels may be used as a biomarker in the diagnosis as well as prognosis of different histopathological grades of OC.[32]

Rai *et al.*[33] in 2015 discuss the high significance of serum fucose in oral squamous cell carcinoma and leukoplakia subjects compared with normal controls. There was a gradual increase in the values noted from control to leukoplakia and to squamous cell carcinoma that is the same in our study.

## Conclusion

This study is aimed at evaluation of serum fucose in oral submucosa fibrosis, leukoplakia, and OC and the results obtained showed the very high significance for serum fucose levels in oral submucosa fibrosis, leukoplakia, OC group as compared with healthy individuals. Analysis of the markers can be an additional tool for diagnosis, prognosis, and treatment monitoring of cancer patients.

Therefore, the evaluation of serum l-fucose would be of good help in assessing early malignant change in increasing the accuracy of clinical diagnosis and also in assessing the spread and invasiveness of OC, OSMF, and leukoplakia.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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