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Original Research Article.

Serum Fucosylation Changes in Oral Cancer and Potentially Malignant Disorders

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ABSTRACT

Background: Cellular glycosylation changes are associated with different types of neoplastic transformation. Fucose is a deoxyhexose sugar that the body requires for optimal functions of cell to cell communications and which plays a role in several biological events. Fucose has been considered to play a significant role in cancer and its spread. Alpha L Fucosidase (ALF) is an exoglycosidase involved in the hydrolytic degradation of fucose containing components of glycoproteins, glycolipids and oligosaccharides. The significance of this enzyme in human catabolism is implied by genetic neurovisceral storage disease. Altered levels of ALF has been reported in the plasma/serum of patients with oral cancer.

Aims: To investigate the clinical usefulness of serum fucose and α-L-fucosidase in diagnosing oral pre-cancer and cancer and study the variations of the levels of both metabolites in normal, precancerous and cancerous conditions (Squamous cell carcinoma).

Methodology: The study group comprised of 87 samples of (age range: 20-70 years): control samples – healthy individuals without any systemic illness (n =20), clinically and histopathologically diagnosed cases of leukoplakia (n=16) and oral submucous fibrosis (n=16) and oral squamous cell carcinoma (n=35) respectively. 2ml blood was collected by venipuncture from every subject after informed consent, serum was separated and checked for fucose and fucosidase by spectrophotometric analysis.

Results: The Normal value range of fucose is 8.3 to 9.5 mg/ dl and that of fucosidase is 22.8 ± 7.1 U/L. There is an increase in the value range of fucose and fucosidase in the tissues of potentially malignant disorders and Squamous cell Carcinoma.

Key words: Oral Squamous Cell Carcinoma (OSCC), Potentially Malignant Disorders (PMDs), Serum Fucose, Serum Alpha- L- fucosidase.

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INTRODUCTION

The membrane, which defines the extent of the cell, is not only a physical boundary but also has many specific functions, among which is the capacity to react with other cells and the intracellular matrix.[1,2] Carbohydrates are structures found on the cell surface bound to either lipid or protein embedded in the membrane. Changes in the carbohydrate structure of these cell-surface glycolipids and glycoproteins have been demonstrated during development, during cell maturation in adult tissue and in relationship to malignant development.[3-9]

In tumors, changes in glycosylation are found in both glycolipids and glycoproteins[5, 8]. Many studies have shown that altered glycosylation plays a major role in most aspects of the malignant

phenotype, including signal transduction and apoptosis. These studies have recently been reviewed.[6,10]

Fucose is a deoxyhexose sugar and is the only sugar that is present in the L – form. Fucose behaves differently in the photoelectric field and can be easily estimated using colorimetric methods. Fucose has been considered to play a significant role in cancer and its spread.

ALF is an exoglycosidase involved in the hydrolytic degradation of fucose – containing components of glycoproteins, glycolipids and oligosaccharides. Alterations in levels of ALF have been reported in the plasma/serum of patients with oral squamous cell carcinoma.

Oral and pharyngeal cancer, grouped together is the sixth most common cancer in the world.[11,12] India has one third of the oral cancer cases in the world and oral cancer accounts for 30% of cancer cases in India. Age adjusted mortality rates from oral squamous cell carcinomas have been estimated at 3 to 4 per 100,000 men and 1.5 to 2.0 per 100,000 women. 5-year survival rates for most countries is around 50%.[12-14]

Oral squamous cell carcinoma is always preceded by early changes like hyperplasia, dysplasia and various PMDs like leukoplakia, oral submucous fibrosis (OSMF) etc. Among the PMDs, leukoplakia and OSMF are more prevalent in India. Prevalence of oral leukoplakia in India varies from 0.2%-5.2%.[15-19] The malignant transformation rates of oral potentially malignant disorders (PMDs) show a great variation; 10 to 20% of hyperkeratosis or epithelial hyperplasia, epithelial dysplasia may transform to cancer and the estimated annual rate is 1.4% to 7%.[13,20-23] Lesions diagnosed as moderate and severe dysplasia reportedly have malignant transformation potential of 4% to 11 % and 20% to 35%, respectively, with malignant transformation usually occurring within 3 years of the dysplasia diagnosis.[24,25] The prevalence of OSMF in India varies between 0.03% and 3.2%.[15-19,26] Malignant transformation rate was found to be in the range of 7 to13%. Overall, persons with OSMF are at least 19 times more likely to develop oral squamous cell carcinoma than persons without the disease.[24]

Earlier studies on serum fucose levels have shown it to be increased in case of cancer and precancer.[27-31] Here we try to prove this association to help in early diagnosis of cases and also evaluate another fucosylation change that is of serum ALF levels which hasn't been extensively studied in oral squamous cell carcinoma[27] and which might be a potential early diagnostic marker for PMDs and OSCC. Healthy individuals (controls) were enrolled in the study to obtain the baseline levels of markers, and serum levels in the OSCC and PMD groups were compared with levels in the control group.

MATERIALS AND METHODS

Source of Data

- The study mainly consisted of individuals in the age range of 20-70years who were divided into 3 groups, namely the control (20 healthy individuals with no history of any major illness in the recent past**),** Potentially malignant disorders group (32 patients with histopathologically proven oral potentially malignant disorders, out of which, 16 patients with diagnosed OSMF and 16 patients with diagnosed leukoplakia) and Oral squamous cell carcinoma group (35 patients with histopathologically proven, untreated OSCC).
- The study groups mainly comprised of patients who came to the outpatient/ inpatient departments of Krishnadevaraya College of Dental Sciences and Hospital, Bangalore. Informed/written consent is obtained from all the individuals who are participating in the study. Staging and grading for OSCC is done. Clinically TNM staging of malignant disease is determined according to TNM classification of malignant tumors, International Union against Cancer, Springer, Berlin, 1992[32]. Confirmation of the lesion with biopsy/review done. Blood samples were collected by venepuncture from all the participants and sera were separated and stored at -80 degree C until analyzed.

METHODS

Estimation of Serum Fucose

Fucose was estimated by the method described by Winzler.[33] In to the duplicate test tubes 50µl of serum and 2.5ml of 95%ethanol was added, and mixed. The mixture was centrifuged for 15 minutes, decanted, followed by suspending the precipitate in 2.5ml of 95% ethanol, which was then centrifuged and decanted. The precipitated proteins were dissolved in 0.5ml of 0.1N NaOH. In to this, 2.5ml of ice cold H_2SO_4 -H_2O was added and mixed well while maintaining the solutions cold in an ice bath. It was then heated for 3 minutes in a boiling water bath and cooled in tap water. 50µl of Cysteine reagent was added to this and mixed immediately. After 60 minutes at room temperature, optical density readings were taken in the spectrophotometer at 405nm with distilled water set at zero using the formula:

$$\frac{\text{O.D at 405nm} \times 0.1 \times 1000}{\text{O.D Standard}} = \text{mg/dl.}$$

O.D = optical density.

The Normal value range for fucose according to Winzler method is up to 8.3 to 9.5 mg/ dl[33]

Estimation of Serum Alpha-L-fucosidase[34]

To an eppendorf tube, 100 microlitre of serum sample, 100 microlitres of the substrate PNP alpha L fucopyranoside and 100 microlitres of CH_3COONa buffer were added and the eppendorf tube was incubated at 37 degrees centigrade for 30 minutes. In to this, 500 microlitres of 0.1MNa_2CO_3 was added and mixed well. The sample turned yellow if the enzyme was active. The absorbance was measured at 405 nm using the formula:

$$\frac{A\ (405nm) \times 0.1ml \times 18.5}{30} = \text{units/ml of enzyme activity}$$

Where A= absorbance

Serum ALF levels for healthy adults was estimated at 22.8±7.1 U/L according to Jun Jun Huang. [35]

Statistical Analysis

In our study, serum fucose and serum ALF levels were estimated using a digital spectrophotometer. Statistical analysis was carried out on the results obtained for serum fucose and serum ALF levels in control, PMDs (leukoplakia and OSMF) and OSCC groups, using ANOVA and Bonferroni method for serum fucose levels and ANOVA for serum ALF levels respectively with α=0.05 which was statistically significant.

RESULTS

The serum fucose levels for control group ranged from 0.2 to 9.3mg/dl with a mean of 5.36 mg/dl. The range of serum fucose in PMD group, which was subdivided into leukoplakia and OSMF wherein the values of leukoplakia cases were in the range between 0.19 and 29.31mg/dl with a mean of 11.65mg/dl and that of OSMF cases were in the range from 4.92 to 33.92mg/dl with a mean of 14.64mg/dl. The serum fucose levels in oral squamous cell carcinoma group were between 4.68 and 67.64 mg/dl with a mean of 20.19mg/dl. Higher mean fucose was recorded in OSCC group followed by OSMF, leukoplakia and control group respectively. The difference between them was found to be statistically significant ('p'<0.001).

The serum ALF levels in control group ranged between 9 and 39 U/L with a mean of 24.71U/L. The serum ALF levels in PMD group which was subdivided into Leukoplakia and OSMF, the serum levels of leukoplakia cases ranged between 13 and 83 U/L with a mean of 32.54 U/L and the serum levels were between 18 and 62 U/L in OSMF cases with a mean of 30.03 U/L.

The serum levels of ALF in oral squamous cell carcinoma ranged between 7 and 80 U/L with a mean of 35.44 U/L. Higher mean serum alpha – L- fucosidase levels were found in OSCC group followed by leukoplakia, OSMF and control group respectively. The difference between them was not statistically significant ('p'>0.05).

Table 1: Mean serum fucose levels in all the study groups (mg/dl)

Group	n	Mean	SD	SE of Mean	95% CI for Mean		Min	Max
					Lower Bound	Upper Bound		
Control	20	5.36	2.30	0.51	4.29	6.44	0.20	9.33
Leukoplakia	16	11.65	7.22	1.81	7.81	15.50	0.19	29.31
Oral Submucous Fibrosis	16	14.64	8.21	2.05	10.26	19.02	4.92	33.92
Oral Squamous Cell Carcinoma	35	20.19	17.13	2.89	14.30	26.07	4.68	67.64

n= number of cases; SD = Standard Deviation; SE= Standard Error;
CI= Confidence Interval; Lower bound = lower limit of mean; Upper bound= upper limit of mean

Table 2: Mean serum ALF values in all the study groups (U/L)

Group	n	Mean	SD	SE of Mean	95% CI for Mean		Min	Max
					Lower Bound	Upper Bound		
Control	20	24.71	8.29	1.85	20.83	28.59	9.25	39.03
Leukoplakia	16	32.54	17.96	4.49	22.97	42.11	13.80	83.80
Oral Submucous Fibrosis	16	30.03	11.46	2.87	23.93	36.14	15.35	62.71
Oral Squamous Cell Carcinoma	35	35.44	22.49	3.80	27.72	43.17	7.20	80.66

Figure 1: Mean serum fucose in all the study groups

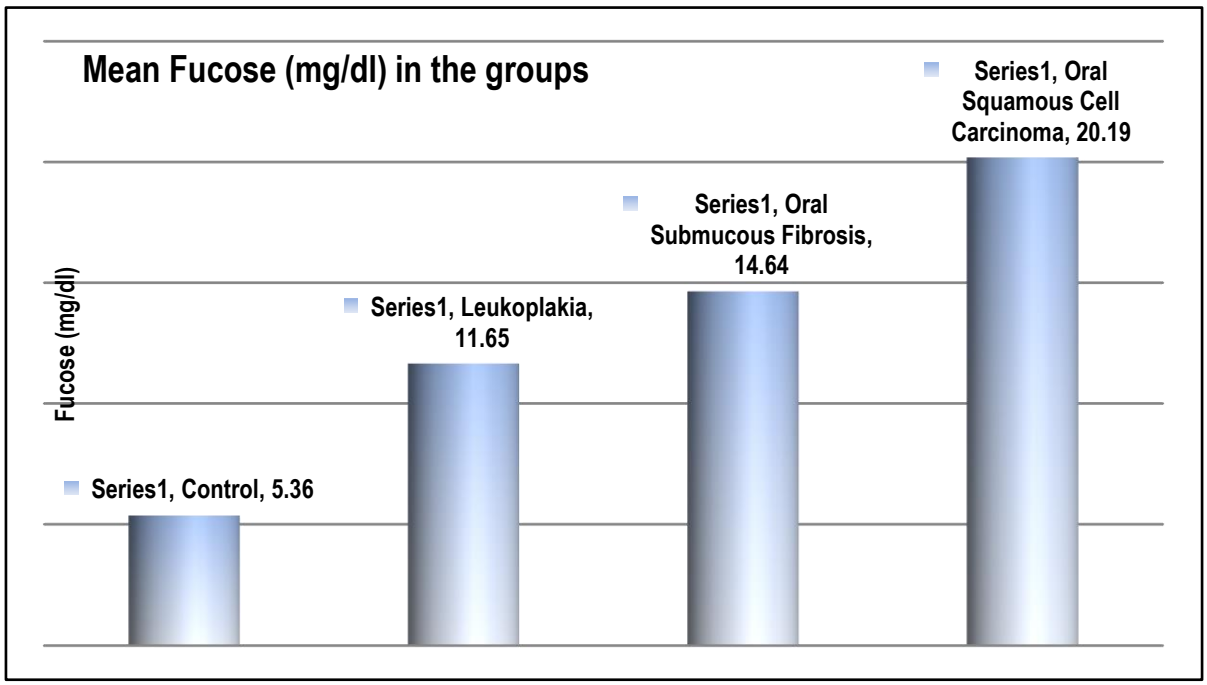
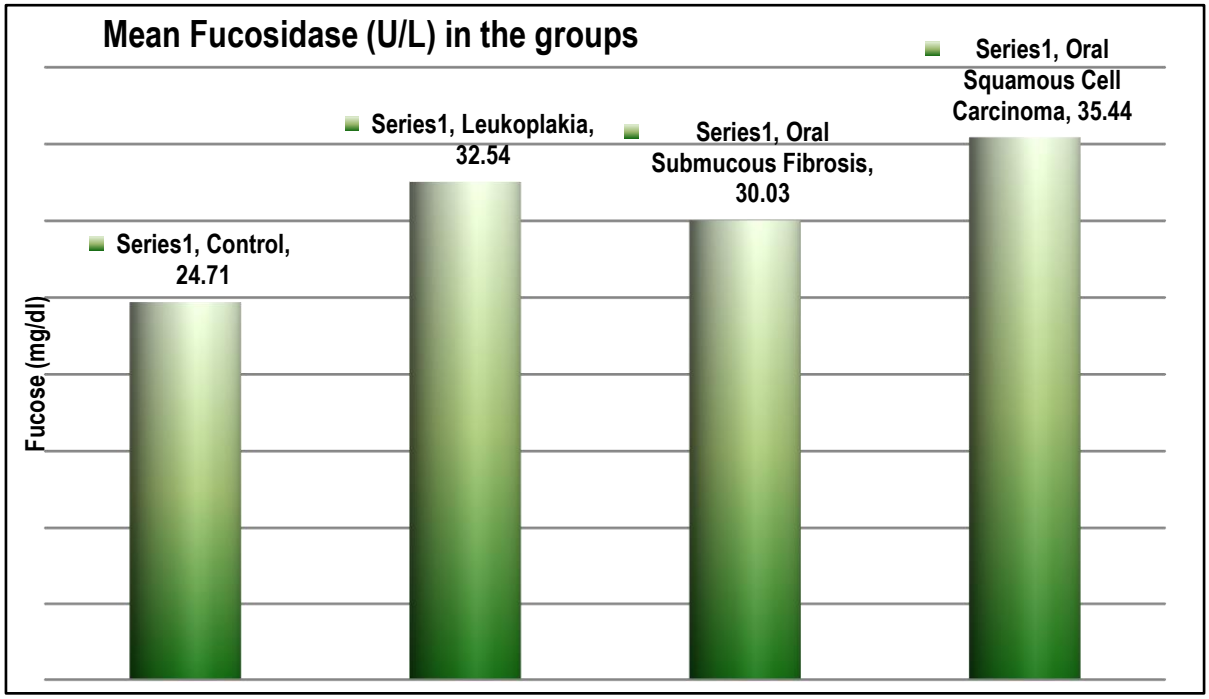


Figure 2: Mean serum ALF levels in all the study groups



DISCUSSION

Glycoproteins including fucose is an integral part of the structure of cell membrane and thus plays a very important role in cell to cell communication, adhesion, motility, transmembrane signaling of cells. By evaluating the changes in fucose and its corresponding hydrolytic enzyme ALF levels in blood or tissue we can determine the kind of alterations that is happening at a cellular level.

Fucose is a protein bound carbohydrate present as a carbon methyl pentose. In our study serum fucose level was determined using spectrophotometry according to the method described by Winzler[33] using cystein hydrochloride. The Normal value range for fucose according to Winzler is up to 8.3 to 9.5 mg/ dl.[33] In our study, the serum fucose levels for control samples ranged from 0.2 to 9.3mg/dl with a mean of 5.36 mg/dl which is well within the normal range according to the previous study.

Serum fucose levels are increased significantly in oral PMDs compared to the control subjects according to Manisha Shah, Prabhudas patel.[27] In 1998, Rao et al reported higher levels of serum fucose in OSCC and potentially malignant disorders in a small number of patients.[27]

In our study of 16 subjects each of leukoplakia and OSMF, we found serum fucose level in oral leukoplakia to be in the range between 0.19 and 29.31mg/dl with a mean of 11.65mg/dl and in OSMF to be in the range between 4.92 and 33.92mg/dl with a mean of 14.64mg/dl which are well above the normal limit and according to previous study results.

Also, in our study, the levels of serum fucose in OSMF was comparatively higher than in leukoplakia which suggests that OSMF might be more closely related to OSCC than leukoplakia. The malignant transformation rate for OSMF is found to be 7-13% and that for mild and moderate dysplasia (the histological grade of most of our leukoplakia patients belonged to this category) is 1.4 – 7% and 4-11% respectively which is comparatively lower than that of OSMF.[24] Serum fucose levels are significantly increased in OSCC compared to control and potentially malignant disorders.[27]

Serum fucose level in cancer in 1955 according to Winzler was reported to be 14.2+/-2.1mg%. In our study of 35 subjects, the range of serum fucose level in oral squamous cell carcinoma is between 4.68 and 67.64 mg/dl with a mean of 20.19mg/dl. There was a significant difference between normal and OSCC values obtained in our study with ('p'<0.001).

The other common methods used to determine serum fucose level is the method of Dische and Shettles using the modifications in Winzlers method.[36]

Alpha-L- fucosidase is an exoglycosidase involved in the hydrolytic degradation of fucose-containing components of glycoproteins, glycolipids and oligosaccharides. In our study, the serum ALF activity was determined according to the method described by Merino Visa and Siva Kumar Nadimpalli.[34] Serum ALF value for healthy adults was estimated at 22.8±7.1 U/L according to Jun Jun Huang[35] who carried out a study on ALF on 518 healthy adults and 366 patients with hepatocellular carcinoma.[35]

In our study, the normal ALF levels ranged between 9 and 39 U/L with a mean of 24.71U/L which is well within the normal limits. According to Manisha Shah and Prabhudas Patel, who conducted a study on 130 patients with untreated OSCC, from 75 patients with PMD and from 100 healthy controls, the mean serum ALF levels were found to be elevated significantly in patients who had untreated OSCC and in patients who had PMD compared with controls ('p'<0.001 and 'p'<0.001, respectively), whereas the levels were comparable between patients with OSCC and patients with PMD.[27]

In our study, the levels of serum ALF in oral PMDs ranged between 13 and 83 U/L in leukoplakia samples with a mean of 32.54 U/L and between 18 and 62 U/L in OSMF with a mean of 30.03 U/L both of which are higher than the normal range and according to the previous study. The levels of serum ALF in oral squamous cell carcinoma in our study ranged between 7 and 80 U/L with a mean of 35.44 U/L which is higher than the normal

range and higher than values of leukoplakia and OSMF and again is in accordance with previous study. The values are significantly increased between normal and OSCC ('p'<0.001) and there is no significant difference in values between normal and leukoplakia, normal and OSMF. There is no significant difference between leukoplakia and OSMF with OSCC. This finding is in accordance with the previous study.

Studies suggest that the increase in serum fucose levels in OSCC can be because of increased turnover of cells, secretion, shedding from malignant cells. It is suggested that ALF activity increases during early neoplastic changes to compensate for hyperfucosylation of cell surface glycoproteins.

However, the incorporation of fucose during malignant transformation may be several folds higher than the hydrolytic cleavage of this residue.[27]

But the rise in serum fucose levels is not specific for cancer. It is also increased in pathological states like rickets, osteomalacia, liver cirrhosis, tuberculosis, meningitis, cardiovascular diseases, various depressive disorders, various other malignancies like breast cancers, ovarian cancers, leukemias, brain tumors, colorectal adenocarcinomas.[30] Similarly serum ALF levels are also increased in cirrhosis, increased in hepatocellular, pancreatic and endometrial cancer to name a few. Therefore it becomes imperative to exclude other degenerative and proliferative disorders before evaluating serum fucose and ALF levels for oral potentially malignant disorders and OSCC.

Some other common methods used for estimation of serum ALF levels are those described by Wiederschain et al[27], and a modification of the method of Zielke et al. Apart from this a rapid developing kinetic rate assay kit for serum ALF levels by using a novel substrate 2-chloro-4-nitrophenyl-α-l-fucopyranoside (CNPF) and having clinical implication in the diagnosis of hepatocellular carcinoma was described by Ju-Jun Wang, En-Hua Cao in 2004.[35]

The screening of patients with minimally invasive serum tests are appealing because of the accessibility to repeated sampling for diagnosis, recall, prognosis and the sample can be coupled with other tests also. It is most valuable in cases of recall or to determine the prognosis of the patient where in repeated biopsy is not feasible. Though biopsy followed by histopathological examination is the gold standard for definitive diagnosis of potentially malignant disorders and oral squamous cell carcinoma, an increased serum fucose or ALF levels in an otherwise healthy individual can give us a clue of an underlying pathology so that we consider taking a biopsy. Also, the increase or decrease in marker levels shows whether the tumor is progressing or regressing.[27]

The inclusion of oral PMDs in the current study also established a link in the spectrum between normal and malignant conditions apart from it being used as a diagnostic and prognostic marker. Studies suggest an association of serum fucose and ALF levels with tumor differentiation, which suggests that the levels increased as the degree of differentiation decreased from well differentiated to poorly differentiated tumors.[27]

CONCLUSION

The current findings in our study provide a clear evidence of increased fucosylation of serum glycoproteins and its association with OSCC development. Serum fucose and ALF can be used as early diagnostic markers. Thus, monitoring of serum fucosylation changes may be promising as a tool for patients with OSCC.[27]

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