ORIGINAL RESEARCH

Quantitative Analysis of Serum Sialic Acid as a Biochemical Marker in Oral Potentially Malignant Disorders and Oral Squamous Cell Carcinoma

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Abstract

Introduction: Oral Squamous Cell Carcinoma (OSCC) is the most common malignancy of the oral cavity and is usually preceded by Oral Potentially Malignant Disorders (OPMDs). Studies show that altered glycosylation of cell surface proteins leads to increased synthesis of Sialic Acid (SA) which is thought to be associated with the development and progression of malignancy.

Aim and Objectives: To estimate and compare the serum sialic acid levels in controls, in patients with OPMDs and different grades of OSCC. To assess the role of serum SA levels as a potential biomarker in predicting malignant transformation of OPMDs and progression of OSCC.

Materials and Methods: A total of 60 serum samples, 12 each of, controls, individuals with Oral Lichen Planus (OLP), Oral Leukoplakia (OL), Oral Submucous Fibrosis (OSMF) and Oral Squamous Cell Carcinoma (OSCC) were subjected to Enzyme-Linked Immunosorbent Assay (ELISA) to estimate the serum SA levels.

Results: Serum SA levels showed a statistically significant increase from controls to OSCC groups with a statistically significant increase in serum SA levels in Poorly Differentiated OSCC (PDSCC) when compared with Well Differentiated OSCC (WDSCC) and Moderately Differentiated OSCC (MDSCC).

Conclusion: Increased serum SA levels have a role in the malignant transformation of OPMDs.

Key Words: Sialic acid, ELISA, Oral Potentially Malignant Disorders, Oral Squamous Cell Carcinoma.

Introduction

Globally, cancer is the largest cause of mortality. The word cancer is derived from the Greek word 'Karkinos' meaning crab, denoting how carcinoma extends its claws like a crab into the adjacent tissues.[1] It affects approximately 10 million people annually worldwide, and more than six million die of the illness every year.[2] Both the incidence and death rate of cancer have shown a sharp escalation in the last two decades.[3] The most common cancer affecting men in India is oral cancer. Oral potentially malignant disorders (OPMDs), including oral leukoplakia (OL), oral submucous fibrosis (OSMF), oral lichen planus (OLP) and others, typically occur before oral cancer. OPMDs have an increased risk of developing cancer with malignant transformation rates that vary from 0.6% to 36%.[4]

Tumor indicators, often referred to as biochemical serum markers, are proteins that exhibit quantitative changes in the serum during the growth of cancer. These changes can aid in the early diagnosis and assessment of the prognosis of the disease.[5] Studies on malignant cells has revealed alterations in cell membranes and cell surfaces.[6] The two main components of cells are glycoproteins (GPs) and glycolipids (GLs), which are cell surface glycoconjugates that play crucial roles in cancer.[7] Any modification to the intracellular microenvironment may result in changes to the components of the surface membrane, releasing specific chemicals into the blood in malignancies.[8]

Sialic acid (SA) is the most common type of acetylated derivative of neuraminic acid (NANA) in humans.[9] It is a nine-carbon monosaccharide with a negative charge that is typically linked to the nonreducing or terminal end of the carbohydrate chains of GPs and GLs through a glycosidic bond.[6] The enlargement of oligosaccharides, which creates branching sites for the integration of SA, is

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How to cite the article: Purohit MR, Shyam N.D.V.N, Kumar GK, Narayen V, Konda P, Fatima F. Quantitative analysis of serum sialic acid as a biochemical marker in oral potentially malignant disorders and oral squamous cell carcinoma. Oral Maxillofac Pathol J 2025; 16(1); 29-33.

Source of Support: Nil

Conflict of Interest: None

Acknowledgements: I express my gratitude to my professors and family for their support and advice.

one of the most frequent modifications to glycoconjugates during malignant transformation.[5] Tumor cells release the increased glycoconjugates, which are then discharged into the bloodstream. Serum SA is a useful biomarker for several cancers, including oral cancer, and is positively linked with the growth of tumors.[10]

Despite frequent examinations of the oral cavity, 60% of carcinomas are detected at an advanced stage. Relentless challenges associated with oral cancer include delayed diagnosis and a dearth of trustworthy biomarkers for early detection.[5] In individuals with OPMDs and OSCC, altered serum SA levels may be used as a marker of early biochemical alterations that take place before clinically noticeable abnormalities appear.[5] The present study has been performed to quantitatively investigate serum SA as a biochemical marker in OPMDs and OSCC.

Aim and Objectives

To estimate and compare the serum SA levels in controls, in patients with OPMDs and different grades of OSCC. To assess the role of serum SA level as a potential biomarker in predicting malignant transformation of OPMDs and progression of OSCC.

Material and Methods

Twelve individuals from each of the study groups for OLP, OL, OSMF, and OSCC which had been clinically and histopathologically verified were included in the study and twelve healthy individuals served as the control group. Sample calculation was done by using G* Power Software. The institutional ethical committee of our institution affiliated to the Ethical Committee of Osmania Medical College, Koti, Hyderabad, with Regd. No. ECR/300/Inst/AP/2013/RR-16(GDCH-IEC/PG/20-21/07) examined and approved the research protocol. Before any patient could be included in the study, their informed consent was obtained, and all subjects were made aware of their purpose.

a. Inclusion criteria:

Patients diagnosed with OLP, OL, OSMF, and OSCC.

b. Method:

Two ml of blood was drawn under aseptic conditions from the patients and centrifuged at 3000 rpm for 10 minutes and serum was collected. Prior to the Sandwich ELISA procedure, serum samples and ELISA kit solutions were allowed to come to room temperature. A 96 well microtiter plate was used for incubation of the samples. 50 µL of the standard solution of SA was added to the standard wells. 40 µL of the serum sample was added to sample wells followed by 10µL of biotin labelled primary antibody. Next 50µL of HRP (Horseradish Peroxidase) conjugated secondary antibodywas added to both sample and standard wells, and the microtiter plate was sealed and incubated at 37°C for 60 minutes. After that, the seal was taken off, the microtiter plate was washed five times using a wash buffer (phosphate buffered saline), and then blotted onto absorbent paper. 50µL of substrate A (H_2O_2 solution) followed by 50µL of substrate B (3,3,5,5 - tetramethylbenzidine TMB solution) was added to each well. The microtiter plate was incubated for 10 minutes at 37°C in the dark which changes the color of the solution in the wells to blue. 50µL stop solution (Sulphuric acid) was then added to each well and then the blue color changed into yellow immediately. The Mean Absorbance (MA) value of solution in each well was determined within 10-15 minutes of adding the stop solution using the microplate reader set to 450 nm.

Human SA concentrations were determined by plotting the test samples MA value on the Y-axis and a horizontal line was drawn to the standard curve. At the point of intersection, a vertical line was drawn to the X-axis, and the serum SA concentration of each sample was read. The data was analyzed with the Statistical Package for Social Sciences (SPSS) for Windows 20.0 (SPSS, Inc. Chicago, Illinois). The observed data was analyzed using one-way ANOVA test and Tukey's post-hoc tests. Confidence intervals were set at 95% and values of 'p' < 0.05 were interpreted as statistically significant.

Results

Out of the 60 total participants in the study, 12 individuals in each group who were clinically and histopathologically diagnosed with OLP, OL, OSMF and OSCC, as well as 12 healthy persons serving as controls, yielded the following results. The one-way ANOVA test was used to analyze the mean serum SA levels. The mean serum SA values in control, OLP, OL, OSMF and OSCC groups were 0.86 pmol/ml, 1.36 pmol/ml, 1.64 pmol/

Table 1: Comparison of serum sialic acid levels between control and OPMDs (OLP, OL and OSMF), OSCC groups.

Multiple comparisons					
Dependent variable: Serum sialic acid levels					
Tukey's post-hoc test					
(I) Group	(J) Group	Mean Difference (I-J)	'p' value	95% Confidence Interval	
				Lower Bound	Upper Bound
Control	OLP	-0.49233	0.272	-1.1811	0.1965
	OL	-0.77567*	0.020	-1.4645	-0.0869
	OSMF	-0.98558*	0.002	-1.6744	-0.2968
	OSCC	-1.99333*	0.000	-2.6821	-1.3045

Table 2: Comparison of serum sialic acid levels between OPMDs (OLP, OL and OSMF) and OSCC groups.

Multiple comparisons					
Dependent variable: Serum sialic acid levels					
Tukey's post-hoc test					
(I) Group	(J) Group	Mean Difference (I-J)	'p' value	95% Confidence Interval	
				Lower Bound	Upper Bound
OSCC	OSMF	1.00775*	0.001	0.3190	1.6965
	OL	1.21767*	0.000	0.5289	1.9065
	OLP	1.50100*	0.000	0.8122	2.1898

ml, 1.85 pmol/ml, and 2.86 pmol/ml respectively. There was a statistically significant difference in the levels of serum SA among the different groups, with a 'p' value of 0.001. Serum SA levels were notably highest in OSCC, followed by OSMF, OL, OLP and least in controls (Figure 5).

Using Tukey's multiple post hoc tests, the serum SA levels of the control group, OPMDs, and OSCC were compared. The 'p' values obtained on comparison of SA levels in controls with the levels in OLP, OL, OSMF, and OSCC were 0.272, 0.020, 0.002 and 0.000 respectively. There was no discernible difference in the levels of serum SA between the OLP group and the control group. Whereas OSCC and OSMF showed significantly higher SA levels compared to controls (Table 1).

Using Tukey's multiple post hoc tests, the serum SA levels of the OPMDs and OSCC groups were compared, the 'p' value on comparison between OSCC and both OLP and OL groups was 0.000, and between OSCC and OSMF was 0.001. The OSCC group's serum SA levels were noticeably greater than those of any other group (Table 2).

A comparison of serum SA levels between different OPMDs groups was also done, and no significant difference in SA levels between these groups was found (Table 3). Through one-way ANOVA test serum SA levels among the various histological grades of OSCC was analyzed. The mean serum SA levels in WDSCC, MDSCC and PDSCC were 2.11 pm/ml, 2.54 pm/ml and 5.48 pm/ml respectively. The 'p' value obtained was 0.0001. Serum SA levels were significantly higher in PDSCC as compared to other grades of OSCC (Figure 6). Multiple comparisons were made between different histopathological grades of OSCC groups and there was a statistically significant increase in levels of serum SA in PDSCC when compared with WDSCC and MDSCC (Table 4).

Discussion

One of the commonest forms of cancer is head and neck cancer.[11] Its incidence varies across the globe, and in less developed nations like India, it is the most common cancer to be diagnosed in male patients.[12] In the head and neck region, OSCC accounts for more than 90% of cancer cases.[13]

Chewing betel nut, drinking alcohol, smoking tobacco and having inadequate nutrition are some of the etiological factors for OSCC to occur in the oropharynx and oral cavity.[14] An invasive carcinoma develops from a premalignant process largely due to local irritants.[15] Premalignant alterations in the mucous membrane and subsequent progression to OSCC may result from damage to the epithelium, which is followed by the basement membrane and submucosa as a result of chemical and mechanical injury. Carcinogens repress tumor suppressor genes (TP53, pRb, and p16) or activate proto-oncogenes (ras, myc, and EGFR), which can lead to the development of OSCC.[16]

OSCC shows very aggressive behaviour, lymph node metastasis and poor prognosis.[17] Timely intervention can help in eradication of the cancer as well as prevent more mutilating surgery.[18] According to reports, between 16% and 62% of epithelial dysplasia underwent malignant transformation and eventually developed into OSCC.[19] The prevention of OSCC greatly depends on the proper surveillance and treatment of OPMDs.[20]

OPMDs are defined as a group of oral mucosal lesions with an increased risk of malignant transformation and include a mixture of diseases with different risk factors, clinical appearance, and histological subtypes and comprise various entities, such as Oral leukoplakia, Erythroplakia, Erythroleukoplakia, Oral lichen planus and Oral submucous fibrosis.[21]

Changes in cell surface components are linked to neoplastic transformation and identifying these modifications may provide the basis for utilizing carbohydrate antigens as tumor markers. Assessing these entities could prove beneficial in terms of diagnosis, disease staging, metastatic detection, high-risk patient identification and therapy response.[22] One location where genetic alterations can be expressed is the cell membrane, which also plays a role in regulating cell behaviour and proliferation. It is made up of GPs, GLs and phospholipids.[23] These glycoconjugates protrude from the membrane's outer layer to create the cell coat. SA is the main component of the cell coat and is linked to glycoconjugates by glycosidic bonding.[24]

Salivary mucin is the primary source of SA, which is also present in serum. It has been observed to rise in people with several cancers as well as diseases like rheumatoid arthritis, acute inflammation and high fever.[24] SA by its negative charge

Table 3: Comparison of serum sialic acid levels between different OPMDs (OLP, OL, OSMF) groups.

Multiple comparisons			
Dependent variable: Serum sialic acid levels			
Tukey's post-hoc test			
(I) Group	(J) Group	Mean Difference (I-J)	'p' value
OSMF	OL	0.20992	0.910
	OLP	0.49325	0.270
OL	OSMF	-0.20992	0.910
	OLP	0.28333	0.774
OLP	OSMF	-0.49325	0.270
	OL	-0.28333	0.774

Table 4: Comparison of serum sialic acid levels between different histopathological grades of OSCC

Multiple comparisons			
Dependent variable: Serum sialic acid levels			
Tukey's post-hoc test			
(I) Group	(J) Group	Mean Difference (I-J)	'p' value
WDSCC	MDSCC	-0.42960	0.145
	PDSCC	-3.36970	0.000
MDSCC	WDSCC	0.42960	0.145
	PDSCC	-2.94010	0.000
PDSCC	WDSCC	3.36970	0.000
	MDSCC	2.94010	0.000

and hydrophilicity, has many structural and modulatory roles and it also serves as a component of binding sites for various pathogens and toxins.[25] Numerous phenomena, including the spread of metastatic disease, cell-cell contact, cell recognition, antigenicity of tumors, transport processes and viral receptors, have been linked to SA.[26] Increased negative charge imparted by SA in surface GPs creates a repulsive force between cells and causes the spread of cancer cells due to lack of adhesion with neighbouring cells.[27]

The current study revealed that OSCC had the greatest serum SA levels, followed by OPMDs (OSMF, OL and OLP), while controls had the lowest values (Figure 5). The findings of the research by Arthisri AS et al (2020), Chittemsetti S et al (2019), Dadich M et al (2014), Bose KS et al (2013) and Sawhney H et al (2012), showed that mean SA levels increased from the control group to OPMDs and OSCC groups, which is in accordance with our results.[28,5,4,22,7] This is most likely because different membrane-bound glycosyltransferases catalyse a sequence of events during the glycosylation of proteins. These glycosyltransferases are mutated in cancer, which results in the production of aberrant glycoconjugates with larger oligosaccharide chains. As a result, more branching sites for the inclusion of SA are produced.[4]

According to our study's assessment of SA levels between the control, OPMDs (OLP, OL, OSMF), and OSCC groups, there was no discernible difference in the serum SA levels between the control group and OLP alone. On the other hand, SA levels significantly increased in the OSMF and OSCC groups compared to the controls (Table 1). This was consistent with the research ofAchalli et al (2017), who discovered that, in comparison to healthy controls, individuals with OPMDs and OSCC had significantly higher serum SA levels.[29] The outcome of our investigation aligned with the findings of Krishnan K et al (2017), who found a significant rise in serum levels of both total SA and lipid-bound SA in OL individuals relative to healthy controls. According to a study by Chinnannavar SN et al (2015), OSCC patients had considerably higher estimated serum levels of fucose, SA, and fucose SA ratio than normal healthy controls.[2,30] The probable reason for this might be that from the control group to OSCC groups there would be an increase in sialylated glycoproteins such as alpha-1-acid glycoprotein which would lead to increased serum SA concentrations.[3]

In PDSCC, serum SA levels were noticeably greater than in other OSCC grades (Figure 6). This was consistent with the research of Poudel P et al (2019), who discovered that, in comparison to WDSCC, mean serum SA levels increased considerably in MDSCC and PDSCC.[8] The outcomes of our investigation aligned with the research carried out by Chittemsetti S et al (2019), who examined serum SA levels in patients with OSCC cases of different clinical staging and histological grading and found that the levels increased significantly as the stage moved from I to III.[5] Similarly, Rajaram et al (2017), Taqi SA (2012), Dhakar N et al (2013) and Sawhney H et al (2012) also discovered that SA levels increased

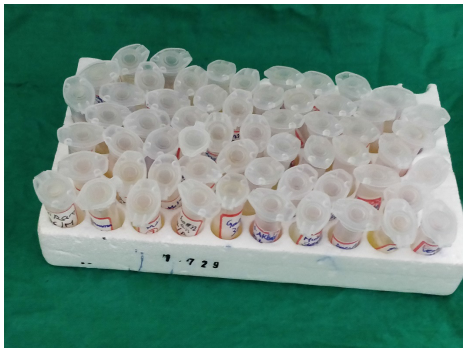

Fig. 1: Serum samples obtained after centrifugation of blood samples.

Fig. 2: Contents of sialic acid ELISA kit.

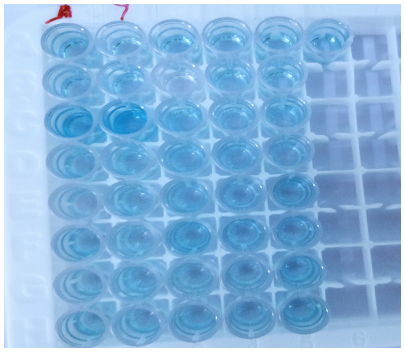

Fig. 3: Addition of TMB substrate and then incubation changes the color to blue.

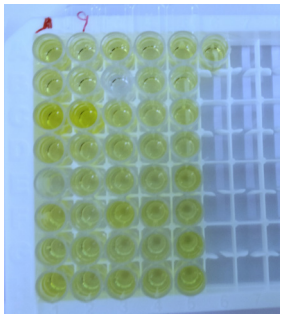

Fig. 4: Addition of a stop solution changes the color to yellow.

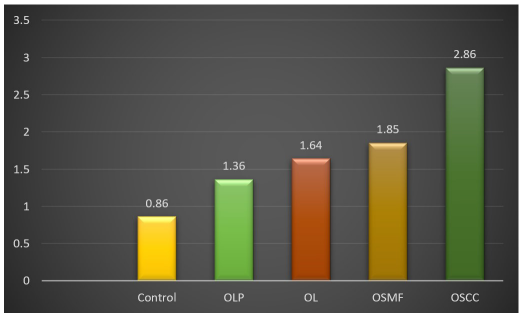

Fig. 5: Mean serum sialic acid levels in control, OPMDs and OSCC groups.

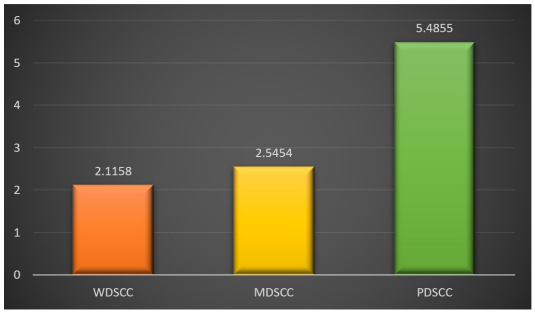

Fig. 6: Mean serum sialic acid levels in different histological grades of OSCC.

noticeably with increasing histopathological grade.[23,31,32,7]

Since SA has been shown to rise near the surface of tumor cells, an increase in its serum levels could be attributed to an increase in turnover, secretion, and shedding of these cells. This could be brought on by the tumor's differentiation and increased metastasis-related shedding of cancerous cells into the bloodstream. Our study's findings were at odds with those of Joshi M et al (2010), who discovered that the mean total SA level in WDSCC were higher than that of MDSCC and Rajpura KB et al (2005), who discovered that neither total SA nor lipid-bound SA exhibited a significant correlation with the disease's histological grade.[9,3]

Conclusion

Serum SA plays a key role in pathogenesis of OSCC and OPMDs. Serum SA concentrations increased when lesions progressed from OPMDs to OSCC. The increased concentration of serum SA levels may be associated with the malignant transition of OPMDs to OSCC and with tumour progression from WDSCC to PDSCC. Because the current study uses a simple method to estimate serum SA levels, it can be used as a screening marker to identify people who may have OPMDs like OLP, OL and OSMF and to evaluate any early malignant alterations.

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