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Evaluation of Salivary and Serum Total Carbohydrate Levels in Oral Precancerous Disorders and Oral Cancer: A Novel Approach

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ABSTRACT

Background & Objective: Enhanced glucose uptake creates a hyperglycaemic environment that contributes to the oral carcinogenetic cascade but has received less attention and has not been fully elucidated. This study aimed to assess the levels of free and bound carbohydrates in saliva and serum among healthy individuals, subjects with potentially malignant disorders, and oral cancer/oral squamous cell carcinoma (OSCC) patients.

Methods: A cross-sectional comparative study was conducted among 90 subjects randomly selected based on clinical and histological criteria and allocated into three groups: Group 1, healthy individuals (n = 30); Group 2, potentially malignant disorders (n = 30); and Group 3, OSCC cases (n = 30). Saliva and serum samples were collected and subjected to biochemical analysis for carbohydrate level estimation. Descriptive statistics and the Mann–Whitney test were applied to assess differences between independent groups.

Results: Mean salivary-bound total carbohydrate levels were 12.06 mg/dL, 37.67 mg/dL, and 65.45 mg/dL for Groups 1, 2, and 3, respectively. Mean serum-bound total carbohydrate levels were 30.39 mg/dL, 68.28 mg/dL, and 88.33 mg/dL for Groups 1, 2, and 3, respectively. Mean salivary-free total carbohydrate levels were 25.58 mg/dL (Group 1), 24.28 mg/dL (Group 2), and 53.13 mg/dL (Group 3), while mean serum-free total carbohydrate levels were 62.39 mg/dL, 74.01 mg/dL, and 193.68 mg/dL for Groups 1, 2, and 3, respectively. A highly significant increase was observed ($P < 0.001$).

Conclusion: A substantial increase in serum and salivary total carbohydrate levels, particularly in bound forms, was observed across the three groups, highlighting the potential utility of carbohydrate levels as biomarkers for disease progression in oral cancer.

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Introduction

Oral squamous cell carcinoma (OSCC) remains a major global health issue. According to GLOBOCAN 2022 estimates, lip and oral cavity cancer accounted for approximately 389,846 new cases and 188,438 deaths worldwide. In India, lip and oral cavity cancer is a leading malignancy, with 143,759 new cases (10.2% of all cancers) and 79,979 deaths. (1). Hence, detection of oral cancer at an early stage is of paramount importance to decrease the disease burden worldwide.

Various cancer screening techniques that include routine clinical examination, toluidine blue staining, tissue autofluorescence, oral brush biopsy and chemiluminescence have been implemented in the past few years (2). However, the most common gold standard approach in diagnosing OC was considered to be the conventional biopsy method. Nevertheless, these methods have documented certain limitations, such as acceptability, affordability, accessibility and inadequacy of training and screening of OSCC cases by physicians, nurse practitioners, and dental health professionals resulting in possible delay in diagnosis and high probability of self-assessment without proper systematic investigations and treatment approaches (3). In recent years, alternative methods such as analysis of serum and saliva are considered to be cost-effective approach for screening and post-therapeutic monitoring (4). Moreover, despite the tremendous progress in molecular biology, evidence-based studies on objective assessment of predicting and diagnosing OSCC cases at

the earliest stage using serum and saliva as single marker are scant in literature (5).

Aberrant Glycosylation which is the most universal feature of posttranslational modification of proteins is considered as one of the new hallmarks of carcinogenetic process that play a significant role in tumor formation and metastasis. The availability and composition of sugars in the tumor microenvironment may affect cell glycosylation. Moreover, enhanced glucose uptake during carcinogenesis, thereby creating a hyperglycaemic environment have received less attention and has not been fully elucidated (6). Various meta-analytical studies have been conducted to correlate the levels of serum total carbohydrates with malignancy (4,7). However, no studies have yet been conducted to correlate oral cancer with serum and salivary total carbohydrate levels. There are compelling reasons to use saliva as a diagnostic fluid to monitor health and diseases. As a clinical medium, saliva has many advantages over serum. Saliva is easy to collect, store and transfer and can be obtained in sufficient quantities at low cost for analysis. Therefore, the need for this study has been identified. The study is designed to estimate serum and salivary total carbohydrate levels in the free and bound forms in patients with oral precancerous states and carcinomas and compare them with normal controls. Based on this rationale, we decided to conduct a cross-sectional comparative study to assess the levels of free & bound carbohydrates in saliva & serum among healthy individuals, potentially malignant disorders, & oral cancer subjects.

Materials and Methods

A cross-sectional comparative study was conducted during the period of November 2011 to June 2013 at the Department of Oral Medicine & Radiology, Yenepoya Dental College & Hospital and nearby cancer centers, Mangalore. The study was initiated after obtaining the ethical committee approval bearing the protocol number YDC / 69 / 70. The inclusion criteria was individuals with clinically diagnosed oral potentially malignant disorders (OMPD's) & OSCC cases. The exclusion criteria included any other pathologies of the oral cavity involving odontogenic/inflammatory/ cystic/infectious lesions of head and neck region. A total of ninety (n=90) subjects who were randomly selected based on clinical and histological criteria & allotted into three groups; Group 1: Normal healthy individuals (n=30), Group 2: potentially malignant disorders (n=30) & Group 3: OSCC cases (n=30). Age and sex-matched healthy volunteers without tobacco-related oral habits or oral lesions from the university campus were selected for the control group designated as Group 1. A total of 5 ml of peripheral blood sample was collected from each subject with disposable syringes under aseptic conditions through venipuncture. The serum was separated by centrifugation at 3000 rpm for 15 minutes. 1.5 to 2 ml of unstimulated whole saliva was also collected under resting conditions during the hours 10 am -12 noon, 2 hours after the subject's usual breakfast time, according to the method of Navazesh (8). Serum and saliva samples thus obtained were stored at -80°C until total carbohydrate and fructose analysis was done. The biochemical analysis of the sample was performed by preparing protein free filtrate of serum and saliva for estimating free and bound fructose and total carbohydrates in saliva and serum as per Rao and Pattabiraman (6) & Vishu Kumar method (9). About 1.9ml of 3.5% trichloroacetic acid, 0.1ml of sample was added and mixed. After 10 minutes, the sample was centrifuged for 5 minutes in a table centrifuge. Aliquots of supernatant were used to estimate free total carbohydrate and free fructose. The precipitate was dissolved in 1ml of 0.1N NaOH and used to estimate the total carbohydrate and fructose bound.

To estimate the total carbohydrate content, 1ml of the sample's aqueous solution & 3ml of concentrated sulphuric acid was added rapidly. The mixture was allowed to stand at room temperature (28-30°C) for 30 minutes. Ethanolic solution of o-cresol (0.1ml, 10%) was added and mixed. The pinkish-orange color was measured after 30 minutes at 500nm. Chromogens formed from HMF, fructose and glucose absorbed maximal at 495nm. Finally, the calculation of total carbohydrate was done applying the formula:

The biochemical values of this study were subjected to statistical analysis to specify the statistical correlation between the groups and various parameters. One-way ANOVA, Kruskal-Wallis, and Tukey HSD tests were used to compare and correlate different parameters in subgroups.

$$\text{Concentration}_{\text{Test}}(\%) = \frac{(OD_{\text{Test}} - OD_{\text{Blank}}) \times \text{Amount}_{\text{Std}} \times 100}{(OD_{\text{Std}} - OD_{\text{Blank}}) \times \text{Volume}_{\text{Undiluted est}}}$$

Results

In the present study, Serum and salivary samples were collected from Group 1, Group 2 & Group 3 cases and each sample were analyzed for total carbohydrate and fructose. The mean age and gender ratio included in the study is illustrated in Tables 1 and Table 2. The mean salivary bound carbohydrate level in the normal group is 12.06±7.62mg/dL, whereas in precancer, 37.67±18.47 mg/dl and in cancer, the mean value was 65.45±36.71mg/dL. A comparison of the groups' results using the Mann-Whitney test showed that the level difference was statistically highly significant (P<0.001). (Table 3) The mean serum-bound total carbohydrate level in the normal group is 30.39±11.20mg/dL, whereas in precancer, 68.28±21.01 mg/dl and in cancer, the mean value was 88.33±61.10mg/dL. A comparison of the groups'

results using the Mann-Whitney test showed that the level difference was statistically highly significant (P<0.001). (Table 3) The levels of total bound carbohydrates in saliva and serum are shown in the histogram (Figure 1). The increase in the levels of total bound carbohydrates in serum is also reflected in an increase in saliva.

Table 1. Depicts gender ratio in the study groups

	Control		Pre-cancer		Cancer		Total	
Sex	(n)	%	(n)	%	(n)	%	(n)	%
Male	18	60%	23	92%	23	77%	64	75%
Female	12	40%	7	23%	7	23%	21	25%
Total	30	100%	30	100%	30	100%	90	100%

Table 2. Depicts Mean Age in the study groups

Study group	Age range (in years)	Mean age (in years)
OSCC	25-75	51
OPMDs	18-60	35
Control	21-52	33

Table 3. Depicts bound total carbohydrate levels in saliva and serum in normal, precancer and cancer groups.

		N	Mean	Std. Deviation	Minimum	Maximum	P
Total Carbohydrate bound - saliva	Normal	30	12.061333	7.6267138	.0000	40.2000	
	Precancer	30	37.670667	18.4715671	2.9500	74.1100	<0.0005
	Cancer	30	65.453667	36.7102496	3.3600	162.7800	
Total Carbohydrate bound -serum	Normal	30	30.390000	11.2020688	4.0500	60.2800	
	Precancer	30	68.289333	21.0168609	21.2500	111.8200	<0.0005
	Cancer	30	88.334667	61.1079255	1.8100	257.5600	

Level of statistical Significance: p value ≤0.05 was considered statistically significant; p ≤ 0.001 was considered highly significant.

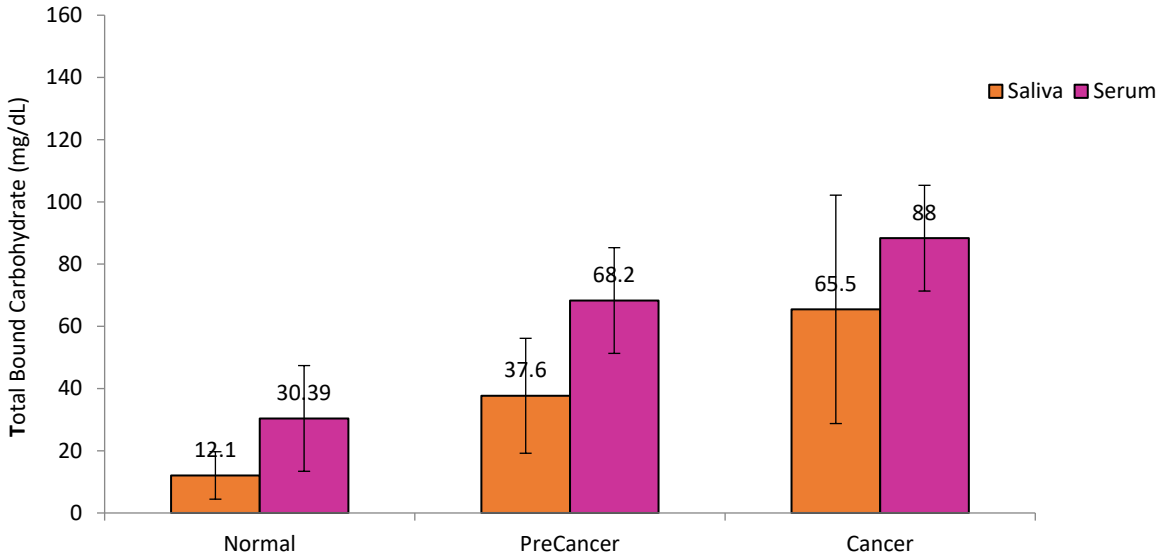

Fig. 1. Illustrates serum and salivary level of bound carbohydrate in normal, pre-cancer and oral cancer groups

Multiple group comparison of the result was done using the Tukey HSD multiple comparison test, which showed that the difference in levels was found to be very highly significant (P<0.001) between the normal and pre-cancer group, normal and OSCC group and between the pre-cancer and OSCC group in saliva. In contrast, in serum statistically significant difference was found only between normal and OSCC groups. (Table 4)

The salivary-free carbohydrate in the normal group ranged from 2.65 to 112.75mg/dL with a mean value of 25.58 ± 19.8mg/dL. The salivary free carbohydrate level (supernatant) in the pre-cancer group ranged from 2.66 to 73.9mg/dL with a mean value of 24.9 ± 17.52mg/dL, whereas in the OSCC group, it ranged from 5.6 to 82.8mg/dL with a mean value of 53.13 ± 19.32mg/dL. The difference in salivary free carbohydrate level in all the study groups was statistically significant (P<0.0005) (Table5).

The serum-free carbohydrate in the normal group ranged from 30.7 to 114.4mg/dL with a mean value of 62.3 ± 20.9mg/dL. The serum-free carbohydrate level in the pre-cancer group ranged from 40.25 to 111.9mg/dL with a mean value of 74.01 ± 20.9mg/dL, whereas in the OSCC group, it ranged from 35.5 to 437.5mg/dL with a mean value of 193 ± 101.6mg/dL. The difference in salivary-free carbohydrate levels in all the study groups was statistically significant (P<0.0005) (Table 5). The levels of free carbohydrates in saliva and serum are shown in the histogram (Figure 2).

Table 4. Depicts Tukey HSD multiple group comparisons for bound total carbohydrate levels in saliva and serum in normal, precancer and cancer

			Mean Difference	P	Significance
Total bound carbohydrates saliva	Normal	PreCancer	-25.6093*	<0.0005	Highly significant
		Cancer	-53.3923*	<0.0005	Highly significant
	Precancer	Cancer	-27.7830*	<0.0005	Highly significant
Total Bound carbohydrates serum	Normal	PreCancer	-37.8993*	.001	Highly significant
		Cancer	-57.9446*	<0.0005	Highly significant
	PreCancer	Cancer	-20.0453	.106	No significance

*. The mean difference is significant when p ≤ 0.05 and highly significant when p≤ 0.001

Table 5. Depicts free carbohydrate level in saliva and serum of normal, precancer and cancer groups.

		N	Mean	Std. Deviation	Minimum	Maximum	P
Free carbohydrates saliva	Normal	30	25.582000	19.8429509	2.6500	112.7500	<0.0005
	PreCancer	30	24.281667	17.5282619	2.6600	73.0800	
	Cancer	30	53.135000	19.3216853	5.6200	82.8200	
Free carbohydrates serum	Normal	30	62.388667	20.9288774	30.7400	114.4300	<0.0005
	PreCancer	30	74.014000	20.3265735	40.2500	111.9900	
	Cancer	30	193.67620	101.6024779	35.5500	437.5000	

Level of statistical Significance: p value ≤ 0.05 was considered statistically significant; p value ≤ 0.001 was considered highly significant.

Table 6. Depicts Tukey HSD multiple comparisons between the normal, precancer and oral cancer groups.

			Mean Difference	P	Significance
Free carbohydrates saliva	Normal	PreCancer	-27.5530*	<0.0005	Highly Significant
		Cancer	1.3003	.962	Not Significant
	PreCancer	Cancer	28.8533*	<0.0005	Highly Significant
Free carohydrates serum	Normal	PreCancer	-11.6253	.742	Not Significant
		Cancer	131.2876*	<0.0005	Highly Significant
	PreCancer	Cancer	119.6622*	<0.0005	Highly Significant

* The mean difference is significant when p ≤ 0.05 and highly significant when p≤ 0.001

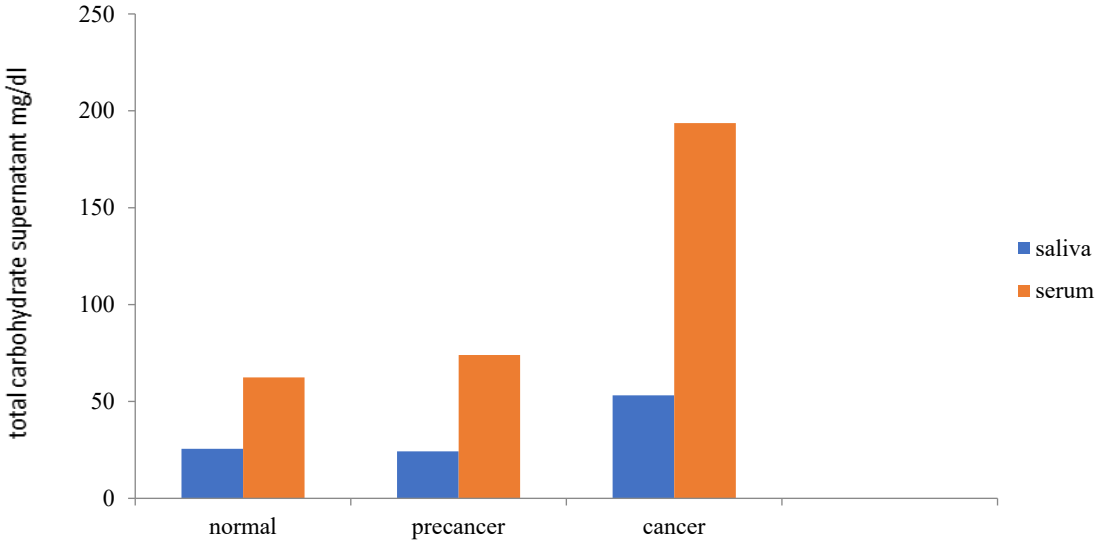

Fig. 2. Illustrates serum and salivary free total carbohydrate levels in normal, precancer and oral cancer groups.

Discussion

OSCC is one of the most common & challenging epithelial malignancies that has reported high mortality and morbidity index across the globe. Prompt diagnosis & prevention of OSCC can aid in improving the Quality of life (QoL) and survival index of patients, thereby contributing to early detection of cancer at its initial stages & prediction of its treatment outcomes. This can be further achieved by accurate screening methods that include routine biopsy procedures, clinical examination, toluidine blue staining, tissue autofluorescence, oral brush biopsy and chemiluminescence. The gold standard method for definitive diagnosis was considered to be tissue biopsy (9), however it imposed certain limitations such as invasive procedures, accessibility & affordability issues that resulted in possible delay in diagnosis and high probability of self-assessment without proper systematic investigations and treatment approaches. Therefore, there is an urgent need to develop new non invasive diagnostic tools involving salivary and serum diagnostic procedures including tumor markers (10). Glycoproteins and glycolipids form an important element of the cell membrane. The cell membrane is an intricate aggregation of lipids, proteins, and other complexes such as glycoproteins with a definite asymmetry in its distribution in some of these macromolecules on the two surfaces of the cell membrane (11). Altered cell membrane surface is the key feature of malignant cells (10).

The biology of glycoproteins, which form a vital cell surface component, has been studied extensively since its role became evident during malignant transformation. Numerous investigators have reported marked differences in cell surface carbohydrate structure in tumour cells (12). The majority of the presently known tumour markers are glycoprotein in nature (13). Glycoproteins belong to the conjugated class of proteins and are complexes of oligosaccharides with protein. The oligosaccharide may be branched with monosaccharides (mannose, glucose, galactose, xylose) and derivatives of monosaccharides such as deoxy sugars (fucose) and sialic acid.

These glycoconjugates are released into the circulation through increased turnover, secretion and shedding from malignant cells. Increased levels of different components of glycoproteins have been associated with other types of malignancies, such as malignant melanomas, breast cancer, cancer of stomach, gall bladder cancer, colorectal cancer, endometrial cancer and laryngeal carcinoma (14-17). The use of carbohydrate markers for clinically meaningful prognostic purposes is well developed, with monoclonal antibodies to sialosyl-Tn markers being used in colonic carcinoma and the agglutinins from *Helix pomatia* and *Datura stramonium* being used in breast cancer (18-20). Ever since the original report of spontaneous hyperglycemia in patients with cancer appeared, the question of the association between altered carbohydrate metabolism and cancer has generated varied interest and controversy in cancer research (21).

The original report of Freund (1890) showed hyperglycemia in sixty-two out of seventy patients with cancer, which was later confirmed by Trinkler (1890) in his report, which concluded that the blood of cancer patients shows a relatively large percentage of reducing substances, mainly glucose (21).

Tuffier (1888) summarised in his report that the simultaneity of cancer and diabetes was not rare but certainly was not a uniform occurrence (22). Theis and Stone reported that 26 per cent of 180 cancer patients (known diabetics excluded) showed an elevated fasting

blood sugar, while only 13 per cent were below normal (23).

In an analysis of 154 cases, Langston suggested that carbohydrate metabolism was disturbed by cancer growth, like in endocrine disturbances, but could not find a characteristic glucose-tolerance curve for cancer patients (24). Another perspective that attracted little attention from early researchers was the effect of therapy on altered carbohydrate metabolism. Slosse and Keding, reporting on hyperglycemia in patients with cancer and PC lesions, found that radiation therapy produced a profound and lasting effect on blood sugar regulation (25).

Highlights of the present study

In our study, although there is an increase in the levels of total free carbohydrates in serum, the increase in saliva is not proportionate. However, the salivary levels are seen to be increased only in the OSCC group and not in the PC group.

When the result was compared between the groups using the Tukey HSD multiple comparison tests, the difference in levels was found to be very highly significant ($P<0.0005$) between the normal and precancer groups and between the precancer and OSCC groups in saliva.

In contrast, in serum, the difference in level was found between normal and OSCC groups and between pre-cancer and OSCC groups.

Future scope: To confirm this hypothesis, more studies are required in oral cancer and potentially malignant disorders. Further evaluation of the results in a different setting, such as multi-centre trials, would involve cross-population analysis. One of our limitations was the adequate sample size based on the population prevalence of oral cancer and potentially malignant disorders.

Conclusion

Substantial increase in serum & salivary total carbohydrate levels in all the three groups was observed, highlighting the potential utility of carbohydrate levels as biomarkers for disease progression in oral cancer.

Acknowledgments

None

Authors' Contributors

I.M. conceptualized the study, conducted the investigation, collected primary data, performed formal analysis, and wrote the original draft of the manuscript V.P. contributed to methodology development, data curation, formal analysis, and review & editing of the manuscript. V.R.P. provided expertise in biochemical analysis, supervised the laboratory procedures, contributed to methodology, and participated in review & editing. M.J. assisted with data collection, investigation, validation, and review & editing. J.D. contributed to resources, biochemical analysis, data curation, and review & editing. S.H. supervised the overall project, acquired funding, administered the project, and contributed to conceptualization, review & editing. All authors read and approved the final manuscript.

Data Availability

The datasets generated and analyzed during the current study are not publicly available; however, the data can be shared for research and authentication purposes upon reasonable request.

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Ethics Approval

All patients became familiar with the content of the study from the moment they entered the study plan, and written informed consent was obtained from them. The patients were assured that at any time during the research, if they did not agree with the study plan, their treatment process would continue as before. The study protocol is in accordance with the Declaration of Helsinki. It has been approved by the Research Ethics Committee Yenepoya University Ethics Committee, protocol YDC/69/70.

Conflict of Interest

The authors declared no conflict of interest.

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