10.5005/jp-journals-10031-1125

ORIGINAL ARTICLE

Serum Albumin, Globulin and Albumin/Globulin Ratio in Oral Squamous Cell Carcinoma: A Prospective Study

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ABSTRACT

Background: Detection of oral squamous cell carcinoma (OSCC) at an early stage would be a paramount for any successful clinical treatment, and thus better prognosis. Serum proteomics, a minimally invasive procedure being simple, safe and accessible, is one of the methods that are used for detection of various biomarkers that could be of diagnostic and prognostic importance for diseases including OSCC. The aim of this prospective study was to determine the role of serum albumin, globulin levels and albumin/globulin (A/G) ratio as a reliable diagnostic and prognostic biomarker in OSCC.

Materials and methods: The study was conducted on 30 clinically diagnosed OSCC patients and 10 normal healthy patients of the control group. Blood samples were collected from all patients under necessary precautions and processed further to obtain serum. Biopsies were obtained from OSCC patients and were histopathologically graded into well, moderate and poorly differentiated OSCC. Serum sample from both groups was evaluated and statistically analyzed for albumin, globulin and A/G ratio.

Results: Serum albumin, globulin and A/G ratio levels did not show any statistically significant increase in OSCC patients as compared to the control group. However, A/G ratio decreased with the advancement of disease.

Conclusion: The results obtained suggested that serum albumin, globulin and A/G ratio cannot be used as serum markers for diagnosis of OSCC. However, there have been studies suggesting significant increase in the levels, hence we emphasize on the need for more studies with larger sample sizes to be conducted for determining the role.

Keywords: Albumin/globulin ratio and serum proteomics, Albumin, Globulin, Oral squamous cell carcinoma.

How to cite this article: Hosalkar RM, Patel S, Pathak J, Swain N, Poonja L. Serum Albumin, Globulin and Albumin/Globulin Ratio in Oral Squamous Cell Carcinoma: A Prospective Study. J Contemp Dent 2015;5(3):149-152.

Source of support: Nil

Conflict of interest: None

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INTRODUCTION

The term 'oral squamous cell carcinoma (OSCC)' or more frequently used term 'oral cancer' in general depicts any malignancy arising from the oral cavity. Oral cancer still poses a major health problem in many parts of the world and is also a leading cause of death among the most common cancers.[1]

In diseases including OSCC, due to continuous perfusion, blood proteomes show constant changes within. These changes could result in serum protein levels to over-express and/or abnormally shed, add, subtract and modify as the disease advances. Alterations in the blood proteomes could be implored through various methods of which serum-based proteomic pattern analysis is a minimally invasive procedure being simple, safe and accessible.[2]

Many researchers have studied the implications of various serum markers for OSCC including serum albumin, globulin and albumin/globulin A/G ratio.[3-5] In the present study, we evaluated the serum albumin, globulin levels and A/G ratio in different grades of OSCC to determine if they could be used as diagnostic or prognostic markers.

MATERIALS AND METHODS

The study was carried out in department of oral and maxillofacial pathology for a period of 1 year after obtaining ethical clearance from college and hospital ethical committee. The study was conducted on 30 clinically as well as histopathologically diagnosed OSCC cases comprising the diseased group and 10 normal healthy patients forming the control group all aged between 32 and 80 years. The exclusion criteria included previously treated cases of carcinoma or sarcomas, metastatic tumors to the jaw, recurrent OSCC and no other systemic diseases, such as renal, hepatic or muscle related, etc.

Five milliliters venous blood was collected from all patients under aseptic conditions. Blood was centrifuged for obtaining serum which was used then used for analysis. An informed consent was taken from patient prior to conducting the study. The serum obtained from the blood sample was analyzed for albumin, globulin levels and A/G ratio using colorimeter by biuret test. The serum levels were calculated and expressed in gm/dl.

The tissue obtained from 30 clinically diagnosed OSSC patients were subjected to routine histological processing and staining. These were graded histopathologically into well differentiated (11 cases), moderately differentiated (10 cases) and poorly differentiated (09 cases) OSCC based on descriptive criteria given by World Health Organization, 2005 and Royal College of Pathologist.[6,7]

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) 16.0 software (SPSS Inc. Chicago, IL, USA). Normality of the data was analyzed with help of one sample Kolmogorov-Smirnov test. Statistical significance was studied using one-way ANOVA followed by post hoc test (Dunnett's t-test). $p < 0.05$ was considered as statistically significant.

RESULTS

Serum albumin, globulin levels and A/G ratio was evaluated for four groups; control group, well differentiated oral squamous cell carcinoma (WDOSCC), moderately differentiated oral squamous cell carcinoma (MDOSCC) and poorly differentiated oral squamous cell carcinoma (PDOSCC). Mean, median, maximum and minimum levels were calculated (Tables 1 to 3). The descriptive statistics revealed that mean serum albumin (gm/dl) was systematically decreasing from WDOSCC to PDOSCC group. Mean serum globulin (gm/dl) increased from WDOSCC to MDOSCC and decreased in PDOSCC. It seemed that all four groups did not have comparable variance as the differences obtained were less significant even when difference in the means levels and standard deviation differed.

Comparison of mean serum albumin, globulin levels and A/G ratio was performed within the four groups using one-way ANOVA test. Results of the test indicated that F-value associated with four means of both albumin, globulin levels did not seem to be statistically significant ($F(3, 37) = 0.576$, $p > 0.0005$) ($F(3, 37) = 0.063$, $p > 0.0005$) (Tables 4 and 5). However, we observed that A/G ratio showed that one of the means could be statistically significant from the other three ($F(3, 37) = 0.058$, $p < 0.0005$) (Table 6). For confirmation of our observation, we further did multiple comparisons by post hoc test (Dunnett's t-test) between the four groups for albumin, globulin and A/G ratio. We found that only mean serum A/G ratio between MDOSCC and control group showed statistically significant difference (Table 7).

Table 1: Descriptive statistical comparison of mean serum albumin level of control group with different histopathological grades of OSCC

Groups	*N*	*Mean*	*Median*	*Std. dev.*	*Minimum*	*Maximum*
Control	11	4.382	4.5	0.5115	3.6	5.3
Well	11	4.5	4.3	0.8556	3.4	6
Moderate	10	4.43	4.3	0.7514	3.1	6.1
Poorly	9	4.1	4.1	0.6874	3	5.2

Table 2: Descriptive statistical comparison of mean serum globulin level of control group with different histopathological grades of OSCC

Groups	*N*	*Mean*	*Median*	*Std. dev.*	*Minimum*	*Maximum*
Control	11	2.9	2.9	0.4561	3.6	5.3
Well	11	3.418	3	1.0581	2.2	5.9
Moderate	10	3.58	3.2	0.8522	2.5	5.4
Poorly	9	2.744	2.8	0.5593	2	3.8

Table 3: Descriptive statistical comparison of mean serum A/G ratio of control group with different histopathological grades of OSCC

Groups	*N*	*Mean*	*Median*	*Std. dev.*	*Minimum*	*Maximum*
Control	11	1.5491	1.38	0.35593	1.12	2.12
Well	11	1.3618	1.41	0.18967	1.07	1.63
Moderate	10	1.262	1.225	0.2107	1	1.72
Poorly	9	1.5156	1.56	0.5427	1.09	1.77

Table 4: Multiple comparisons by one-way ANOVA test of mean serum albumin level of control group with different histopathological grades of OSCC

Source of variance	*Sum of squares*	*DF*	*Mean square*	*F*	*Significance*
Between groups	0.878	3	0.293		
Within groups	18.797	37	0.508	0.576	0.634
Total	19.675	40			

Table 5: Multiple comparisons by one-way ANOVA test of mean serum globulin level of control group with different histopathological grades of OSCC

Source of variance	*Sum of squares*	*DF*	*Mean square*	*F*	*Significance*
Between groups	4.79	3	1.597		
Within groups	22.315	37	0.603	2.648	0.063
Total	27.105	40			

Table 6: Multiple comparisons by one-way ANOVA test of mean serum A/G ratio of control group with different histopathological grades of OSCC

Source of variance	*Sum of squares*	*DF*	*Mean square*	*F*	*Significance*
Between groups	0.552	3	0.184		
Within groups	2.497	37	0.067	2.727	0.058
Total	3.05	40			

Table 7: Comparison by Dunnett's t-test of mean A/G ratio of control group with different histopathological grades of OSCC

Groups					*95% confidence interval*	
I	*J*	*Mean difference (I-J)*	*Std. error*	*Significance*	*Lower bound*	*Upper bound*
Well	Control	0.5182	0.3311	0.291	– 0.295	1.331
Moderate	Control	0.68	0.3393	0.131	– 0.153	1.513
Poor	Control	– 0.1556	0.3491	0.946	– 1.012	0.701

DISCUSSION

Oropharyngeal carcinoma ranks 11th in the World with the highest oral cavity cancer rates found in Melanesia, South-Central Asia, and Central and Eastern Europe and the lowest in Africa, Central America and Eastern Asia for both males and females. In Asia, India along with Sri Lanka and Pakistan show highest incidence of oral cancer cases. The survival rate of oral cancer is poor owing to diagnosis at late stage with limited access to standard and timely therapeutic needs. The burden of cancer can be lessened by implementing awareness programes with early detection and treatment.[8,9] Screening and following of the cancer patient by serum proteomics is an alluring prospective due to minimal invasiveness, ease, economics and simplicity. Cancer can be thought to be a proteomic disease in a functional sense as the genetic mutations modify the protein signaling pathways and it also extends to the tumor host interface. Studies have suggested that the tumor host interface comprises of enzymatic events and sharing of certain growth factors, such that its microenvironment could be a source for biomarkers that ultimately shed into the serum proteome.[2] Alterations within the serum proteome can help in evolution of new diagnostic and prognostic markers. Proteins are present in all the cells throughout the body and most of them have a physiological function in serum. Human serum constitutes serum proteins albumin (3.2–4.5 gm/dl), globulins (2.3–3.5 gm/dl) and fibrinogen. Albumin is the most abundant plasma protein and constitutes 55 to 60% while globulin accounts for 8% of the measured serum proteins. The normal A/G ratio is around 1.3/1.5:1.[10] Lawal et al[11] discussed that low serum albumin may reduce its role of mopping up free radicals, and thus increase the potential for toxic cellular injuries that could trigger the process of carcinogenesis. Albumin acts as an extracellular antioxidant, but unlike antioxidant vitamins that scavenge reactive oxygen radicals, it scavenges mainly carbon-centerd free radicals.[12] Low serum albumin may thus reduce the role of albumin in mopping up free radicals, and thus increase the potential for toxic cellular injuries that could trigger the process of carcinogenesis. Low serum albumin may also be an indication of malnutrition, which is known to be associated with general immunosuppression and impaired salivary gland function, and thus reduced oral mucosal immunity. The primary cause of low albumin, particularly in cancer patients, is a specific inhibition of albumin gene transcription by the tumor necrosis factor, which leads to fall in level of messenger RNA in the liver as much as 90%. This is normally part of the acute-phase reaction, brought about by cytokines, the primary one being interleukin-6.[13]

Reduced serum albumin level is partly compensated by increase in serum globulin. The compensation for reduced serum albumin levels causes loss in efficiency of globular protein, thus further reducing the serum globulin levels and also loss of its function. This in turn affects the overall A/G ratio, decreasing it as the cancer progresses.[5]

Nayyar et al[14] in their study showed serum albumin levels to be statistically significant with levels as low as 1.7 gm/dl in WDOSCC as against a minimum of 3 gm/dl in the control group. Another study conducted by Nayyar et al[3] showed that serum albumin levels was significantly lowered from a minimum of 3.00 gm/dl in controls to below 1.7 gm/dl in PDOSCC, and thus confirmed its role as an efficient antioxidant. Metgud and Patel[15] in their study confirmed that serum albumin levels decreased in oral premalignancy and oral malignancy cases as compared to normal healthy individuals. Study conducted by Lawal et al[11] showed mean serum albumin level significantly lower in the oral cancer patients than in the control group ($p < 0.001$). In the present study, serum albumin showed decrease in OSCC groups as compared to control group. However, the decrease was not statistically significant.

Shabana[16] in the study on OSCC showed significant reduction in the expression of beta-2 microglobulin. Carcinoma cells and the associated nonmalignant surface epithelial cells showed aberrant expression of beta-2 microglobulin in the form of cytoplasmic localization and depletion at the cell membrane. This localization found in the study indicated that these cells maintained the synthesis of the protein. The absence of detectable surface beta-2 microglobulin might be a mechanism by which the malignant cell escapes the immune surveillance. Silvia et al[4] in their study showed significant rise in serum beta-2 microglobulin of oral carcinoma patients. They suggested that beta-2 microglobulin is a cell membrane protein of human leukocyte antigen and accelerated membrane turnover or cell division could cause increase in the shedding of the protein. In present study, serum globulin of OSCC group showed increase in the levels as compared to control group. However, the increase was not statistically significant.

Du et al[17] showed in their study that low serum A/G ratio was significantly associated with advanced stage of nasopharyngeal carcinoma. Suh et al[18] showed that low A/G ratio was significantly associated with the incidence of cancer. Disturbance in the normal serum levels of albumin and globulin causes alteration in the normal A/G ratio of the host, indicating advancement of the disease.[19] In the present study A/G ratio showed decrease as the diseases advanced, however, the decrease in A/G ratio between MDOSCC and control appeared statistically significant.

Separate studies have evaluated the role of serum albumin, globulin and A/G ratio in OSCC and suggested that serum albumin levels constituting the major part of serum proteins have decreased significantly as the disease progressed, thus affecting the serum globulin levels by increasing it and in turn the A/G ratio. These results have led the authors to conclude that serum albumin and globulin can be used as diagnostic markers while serum A/G ratio could be a prognostic marker. The present study showed no significant changes in serum levels of albumin and globulin in different histopathological grades of OSCC. However, A/G ratio did show increase in MDOSCC. Nevertheless, we assume that this significant change observed was due to compensatory reaction of serum levels for each other as the disease progressed. Hence, we conclude that in present study there was no significant change in serum albumin, globulin levels and A/G and thus cannot be used as reliable markers in OSCC. However, limited sample size may have been a deterrent in establishing these serum levels as potential serum biomarkers.

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