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Serum Albumin: Implications in Oral Squamous Cell Carcinoma

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Abstract: Serum albumin is considered to be the most potent and abundant extra-cellular anti-oxidant that might have a protective role in the ongoing process of transition of the various oral pre-cancerous lesions and conditions into frank malignant degenerations. The aim of this study was to check the reliability of serum albumin as one of the diagnostic anti-oxidant parameter. The study revealed variations in sera levels of albumin to be statistically significant emphasizing the need for more studies with larger sample sizes to be conducted before a conclusive role could be drawn in favor of the results obtained.

Key words: Reactive oxygen species · Carcinogenesis · Free radicals · Transformation · Pre-cancerous

INTRODUCTION

Oral squamous cell carcinoma has a much higher prevalence among the elderly people as compared with the younger population. [1, 2] This high prevalence among the elderly population might result from an age related increase in the magnitude of the attack of free radicals including the so-called reactive oxygen and nitrogen species-ROS and RNS-causing various DNA mutations and/or, aberrations. It might also result from an age related reduction in the body's antioxidant defenses and/or, both. Ma and colleagues recently demonstrated that oxidative and nitrative stresses contribute to the development of frank oral squamous cell carcinoma from one of the well known oral pre-cancerous/pre-malignant lesion, leukoplakia. [3, 4]

In fact, it has been found that whereas reactive oxygen and nitrogen species are involved in the initiation and promotion of the multi-step carcinogenesis, both are inhibited by the antioxidant defenses present in the saliva and the serum of the patient. [2, 3] This is only when the equilibrium is disturbed that the damage to the DNA is brought about and cancer evolves. [5-7]

Serum proteins have long been implicated to have anti-oxidant properties owing to their rich concentration of free thiol groups. Amongst them, albumin is seen as the most potent and abundant extra-cellular anti-oxidant.

The role of serum albumin as plasma's potent anti-oxidant defense, if comes out to convincing enough to be used as a reliable marker of oxidative stress in the body, could be helpful in the early identification and even before that, in determining the pre-disposition of the various oral pre-cancerous lesions and conditions towards their transformation into frank oral squamous cell carcinoma as against the other invasive and not so cost-effective diagnostic adjuncts.

Hence, the present study is being planned to assess the implications of serum albumin in oral squamous cell carcinoma by comparing the sera levels of albumin in the normal healthy adults as against the patients with clinically diagnosed and histologically proven poorly differentiated, oral squamous cell carcinoma.

MATERIALS AND METHODS

The study was conducted in the Dept. of Oral Medicine and Radiology, Govt. Dental College and Research Institute, Bangalore over a period of 3 months from Jan 2011 to March 2011. The study consisted of 30 new cases of clinically diagnosed and histologically proven poorly differentiated, oral squamous cell carcinoma and 30 age and sex matched healthy controls. None of the patients were on any therapeutic modality prior to the inclusion in the study or, suffering from any

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systemic condition, especially hepatic or, renal disorders that could have affected the sera albumin levels. The sera of the subjects were obtained taking full precautions to prevent hemolysis. Bio-chemical analysis of sera levels of albumin was done in the Dept. of Clinical Biochemistry, Bangalore Medical College and Research Institute and associated Hospitals, Bangalore.

Collection of blood and serum separation-For this, following an overnight fasting period, 5 ml of venous blood was taken from selected patients from the antecubital vein using a sterile disposable syringe in the sitting position between 8 A.M. and 10 A.M. Serum was immediately separated by ultracentrifugation taking full precautions to prevent hemolysis. The supernatant was discarded and the rest of the sample was stored at -20 degrees Celsius.

Assay of albumin in sera-Assay of sera levels of albumin was done with the help of Biuret method. [4, 5] Serum albumin was expressed as g/dL.

Method of Statistical Analysis-The results were analyzed using student t-test and were averaged as (mean +/- standard deviation) for continuous data. In above test, P values less than 0.05 were taken to be statistically significant. The normality of data was checked before the statistical analysis was performed.

RESULTS

Sera levels of albumin were statistically significant ($p<0.001$) with levels falling from a minimum of 3.00 g/dL in controls to be low as 1.7 g/dL in poorly differentiated, oral squamous cell carcinoma (Table 1). The standard error was rated to be 0.3 between controls and histologically established poorly differentiated, oral squamous cell carcinoma. The mean level of sera albumin was found to be 4.956+/-1.0579 in controls as against 3.6933 +/- 1.2177 in patients with histologically proven poorly differentiated, oral squamous cell carcinoma [table.1]. The significance calculated was found to be less than 0.001 in between controls and poorly differentiated, oral squamous cell carcinoma (Table 1).

Table 1: Table depicting serum albumin in study groups along with the mean, standard deviation, minimum and maximum values and P values

Control [n=30]		Poorly differentiated, oral squamos cell carcinoma[n=30]		'p' value
Mean [Min.3 g/dL], [Max.7.8 g/dL]	SD	Mean [Min.1.7 g/dL], [Max.7.2 g/dL]	SD	
4.956	1.0579	3.6933	1.2177	<0.001

*p<0.05

DISCUSSION

Oxidative stress is a general term used to describe the steady state level of oxidative damage in a cell, tissue or, organ, caused by the reactive oxygen species. This damage can affect a specific molecule or, the organism as a whole. [8] Reactive oxygen species such as free radicals and peroxides represent a class of molecules that are derived from the metabolism of oxygen and exist inherently in all aerobic organisms. Most reactive oxygen species are generated from the endogenous sources as byproducts of essential metabolic reactions such as energy generation from mitochondria or, the detoxification reactions involving the hepatic microsomal enzyme system. Exogenous sources include exposure to cigarette smoke, environmental pollutants such as emission from the automobiles and industries, consumption of alcohol in excess, asbestos and exposure to ionizing radiation in addition to the plethora of the bacterial, fungal and viral infections. [1, 5]

The level of oxidative stress is determined by the balance between the rate at which oxidative damage is induced and the rate at which it is efficiently repaired and/or, removed/nullified. The determinants of oxidative stress are regulated by an individual's unique hereditary factors as well as environment and characteristic lifestyle. Unfortunately, under the present day life style conditions, many people run an abnormally high level of oxidative stress that could increase their probability of early incidence of decline in optimum body functions and lead to a number of pathologies. [1, 9]

A free radical is a molecular fragment that contains an odd number of unpaired electrons in the valent shell ie. radical and is capable of existing freely i.e. free. Most free radicals are highly reactive and short lived. [4, 6] Sun has proposed that free radicals are involved in both the initiation and the promotion of multistage carcinogenesis. These free radicals have been shown to cause DNA damage, activate pro-carcinogens and alter the cellular anti-oxidant defense mechanisms. [2] Antioxidant defenses of the body have been proposed to be the inhibitors of initiation, promotion and transformational stages of carcinogenesis and to protect the cells against oxidative damage, in addition to, protecting the organism as a whole from the continuous endogenous damage to cellular DNA, the accumulation of which has been found to play a significant role in carcinogenesis. [4, 10] To counteract these lethal effects, normal living cells have multiple antioxidant defense mechanisms acting in a cascade manner. Studying biologic markers such as the

antioxidant enzyme systems and oxidative stress related markers could be helpful in the early identification of oral carcinogenesis. [2, 4, 10]

Oxidative modification of nucleic acids by reactive oxygen species is of remarkable biological importance as it results in the transformation of non-malignant cells into malignant ones. The structure and functions of cell surfaces are also altered by changes in membrane lipids, considered to be important aspects of malignant transformation. Lipids, particularly, polyunsaturated fatty acids, are the major class of bio-molecules susceptible to oxidative damage by reactive oxygen species. Free radical mediated lipid per-oxidation has recently been proposed as a basic mechanism of injury responsible for a wide variety of diseases and conditions including cancers affecting the activity of various enzymes including the Na-K ATP ase pump, Ca-ATP ase pump and several others in the cell. [4, 6]

Oxidative stress is however not always detrimental. Selective oxidative stress, sometimes, is desirable and can be utilized therapeutically. Certain drugs including anti-malarials like chloroquin, quinine, mefloquine, primaquin, artemisinin, antibiotic like ciprofloxacin and the numerous anti-cancer drugs including bleomyin, calcitriol, the hormonal form of vitamin D as well as iron chelators that can deplete iron or, cause oxidative stress in the tumor due to redox perturbations in its environment are included in such category of drugs that utilize oxidative stress for deriving therapeutic advantage. [7]

Plasma is known to contain a wide range of important antioxidants including albumin, ascorbic acid and uric acid. In plasma, free thiol groups are quantitatively the most important scavengers of the various free radicals and are known to be largely located on various serum proteins, one amongst them being albumin. While ascorbate is an important extra-cellular antioxidant, albumin via its thiol groups, provides quantitatively almost ten folds greater antioxidant protection against the various reactive oxygen and nitrogen species held responsible for the genetic damage eventually leading to the development of cancers. [5, 6, 11, 12-15]

In humans, albumin is the most abundant plasma protein accounting for about 55-60% of the measured serum proteins. It consists of a single polypeptide chain of 585 amino acids with a molecular weight of around 66,500 Da. [9] Albumin synthesis takes place only in the liver and secreted into the portal circulation. In healthy young adults, the rate of synthesis is about 12-25 g of albumin/day, varying with various nutritional and disease states. [9, 16-18] Amongst the numerous plasma proteins that possess anti-oxidant properties owing to their rich concentrations of free thiol groups, albumin is unusual in having a free sulfhydryl group in addition. The usual half-life of albumin is 20 days. [9, 19, 20]

With normal concentrations lying between 3.5-5.5 g/dL, only a small number of factors are known to result in variation in serum albumin. [9, 21, 22] The serum concentration of albumin is a function of its rate of synthesis and degradation and its distribution between the intra-(42%) and extra-vascular compartments. Besides analbuminaemia, a rare congenital disease, the main pathological situation known to lower albumin concentration, is the nephrotic syndrome, which is the subject of most studies. [20, 21]

Several lines of evidence suggest strongly that a reduced serum albumin concentration, although within the normal range, is associated with increased mortality risk. [9] From studies performed with healthy subjects and patients, it has been reported that the estimated increase in the odds of death ranges from 24 to 56 % for each 2.5 g/L decrement in serum albumin concentration. The serum albumin level thus appears to be an independent predictor of mortality risk with a direct protective effect of the albumin molecule being suggested by the persistence of the association after adjustment for other risk factors. Albumin may thus represent quantitatively the most important component that plays a role in the efficient antioxidant defense; organisms have developed to protect against the various oxidant mediated disease processes including cancers. [9, 15, 20]

Albumin in our study came out to be statistically significant with values as low as 1.7 g/dL in patients afflicted with clinically diagnosed and histologically proven poorly differentiated, oral squamous cell carcinoma to as high as 7.8 g/dL in the healthy control (Table 1). The exact role of albumin in assessing the prognosis is, therefore, warranted by larger, follow-up studies correlating the level of serum albumin in these groups of patients with the overall 5-year survival rates.

CONCLUSION

Reactive oxygen and nitrogen stresses have long been implicated in the genesis of oral cancers. There is enough literature available that shows convincing evidence in the use of anti-oxidants as chemo-preventive agents to halt the transformation of various oral pre-cancerous lesions and conditions into frank oral cancers.

The results obtained emphasize the need for more studies with larger sample sizes to be conducted in this regard for the assessment of sera levels of albumin to accept their utility and to assess their role in the pathogenesis and their impact on the prognosis of oral squamous cell carcinoma providing a scientific ground for the use of diverse chemo-preventive strategies in controlling damage at genetic and molecular levels to prevent the ongoing transition of the various oral pre-cancerous lesions and conditions into frank malignant degenerations

Contributions from the authors: Literature search, manuscript preparation, manuscript editing and manuscript review.

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Ethical Declaration: The study has been approved by the ethical committee appointed by the Government Dental College and Research Institute, Bangalore and Bangalore Medical College and Research Institute, Bangalore and has therefore been performed in accordance with the ethical standards laid down in the 1975 declaration of Helsinki and its later amendments in 2000 after a written informed consent from the patients for their inclusion in the study. Details that might disclose the identity of the patient have been omitted.

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