



Estimation of urea, uric acid and creatinine in pathogenesis of OSMF: a randomized blind trial

Deepak Narang^{1*}, Vanita Rathod², Fatima Khan³, Jaideep Sur³, Rachita Jain³, Dharmen Bhansali³, Manish Pandit⁴, Deepak Thakur⁴ and Shama Shishodiya⁵

¹Oral Medicine and Radiology, Azamgarh Dental College, Chandeshwar, Azamgarh, Uttar Pradesh 276138, India.

²Oral Pathology and Microbiology, Rungta College of Dental Sciences and Research, Bhilai, Chhattisgarh, India.

³Oral Medicine and Radiology, Rungta College of Dental Sciences and Research, Bhilai, Chhattisgarh, India.

⁴Oral and Maxillofacial Surgery, Rungta College of Dental Sciences and Research, Bhilai, Chhattisgarh, India.

⁵ENT and Otolaryngology, Gangaram Medical College & Hospital, Delhi, India.

Received for publication: August 26, 2015; Accepted: September 26, 2015

Abstract: Oral Submucous fibrosis (OSMF) is a chronic debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). Present study is aimed to analyze the serum uric acid, urea, creatinine levels in Oral Submucous Fibrosis patients and compare them with those of healthy controls. Clinical study was conducted from 2014 to 2015 at Rungta College of dental sciences [Bhilai] in each of 20 clinically diagnosed and histopathologically proven patients of OSMF groups (I and II) and twenty normal patients had serum uric acid, urea and creatinine levels measured using spectrophotometer. The data obtained was analysed using the Statistical Package for the Social Sciences, version 19.0 (SPSS19). Statistical significance was determined at $P < 0.05$. No alteration was observed in serum uric acid, urea and creatinine levels in OSMF patients when compared with normal controls. This study showed that serum uric acid, urea and creatinine were altered in OSMF patients compared with healthy volunteers but were statistically non-significant. These findings suggest that pan masala tobacco users are in a state of alteration in the biochemical parameters promoting cellular damage when comparing with non-tobacco users. However, further prospective cohort studies are suggested to better understand their role in aetiology and progression of OSMF.

Key Words: Oral Submucous Fibrosis, Urea, Uric acid, Creatinine

INTRODUCTION

Oral Submucous fibrosis (OSMF) is a chronic insidious disease with precancerous potential. Since the last decade, there has been constant rise in OSMF in India. This rise in OSMF in India has been attributed to the increased consumption of areca nut, containing detectable levels of trace elements like copper, zinc, iron and magnesium. ¹The role of areca nut in the pathogenesis of OSMF has been studied in detail over last two decades. It is apparent that fibrosis and hyalinization of subepithelial tissues account for most of the clinical features encountered in this condition. Moreover, substantial amount of research appear to have been focused on changes in the extracellular matrix (ECM). It is logical to hypothesize that the increased collagen synthesis or reduced collagen degradation as possible mechanisms in the development of the disease².

The pathogenesis of the disease is still not clearly understood but it is usually considered to be an abnormal wound healing process and is often compared with fibrosis of other organs.³ Fibrosis occurring in other organs like liver is associated with a number of biochemical changes, which lead to structural and metabolic abnormalities. Impaired lipid metabolism and consequent impaired or reduced cholesterol occurs in fibrosis and cirrhosis of liver.⁴

On comparing OSMF with liver fibrosis, it can be hypothesized that biochemical parameters might also play a role in pathogenesis of the disease. However, to the best of our knowledge, no study has examined the role of urea, uric acid and creatinine in the aetiology of oral cancer. Very little information is available about the biochemical abnormalities

and changes in metabolic parameters. Hence, in the present investigation, is aimed to analyse the Urea, Uric Acid and Creatinine levels in oral cancer patients and compare them with those of normal people in order to examine the possible role of urea, uric acid and creatinine parameters associated with the pathogenesis of OSMF and to assess their role in aetiology and progression of OSMF.

MATERIALS AND METHODS

A clinical study was conducted from 2014 to 2015 at Rungta College of dental sciences [Bhilai]. The study had 20 healthy control and 20 patients of clinically diagnosed and histopathologically proven patients of Oral Submucous fibrosis (OSMF) in each group (I and II). Patients with habit of chewing areca nut or one of its commercial preparations, with the presence of burning sensation, inability to consume spices, stiffness of buccal mucosa, vesicle formation, ulceration, and blanching of oral mucosa were included in the OSMF group. Patients with any systemic disease or any major illness, and habit of chewing only tobacco were excluded. The OSMF group was clinically staged into stage I and stage II as per the staging given by Pindborg.⁵ Twenty healthy individuals, matched for gender and age, without any history of habit of chewing areca and tobacco and any major illness in recent past were included as controls. The uric acid present in serum was determined by the method of Caraway⁶. Serum creatinine was estimated by the method of Owen *et al.*,⁷

*Corresponding Author:

Dr. Deepak Narang,

Senior Lecturer,

Oral Medicine and Radiology

Azamgarh Dental College, Chandeshwar,

Azamgarh, Uttar Pradesh 276138, India.

RESULTS

The present study have been comprised of 20 patients with early symptoms of Oral Submucous fibrosis OSMF ex. burning sensation, dry mouth, blanching oral mucosa and ulceration assigned as Group I whereas Group II was with Advanced OSMF with following symptoms difficulty in mouth opening (trismus), sinking of the cheeks out of proportion to age, stiff and small depapillated tongue, blanched floor of mouth, fibrotic gingival tissues, stiff soft palate with reduced mobility and shrunken bud-like uvula, and blanched and atrophic tonsils. The values of urea, uric acid and serum creatinine of group I and II were compared with that of Normal control group.

In Comparing the values of urea study groups with the control group, the serum urea ranges of study group-I (5.20 ± 0.9) is slightly lower than group-II (5.45 ± 1.8) and control group ranged equal with group I (5.25 ± 1.5).

This study showed that serum uric acid level was non-significant and not much difference observed in advanced OSMF group with normal control group. Whereas decreased levels observed in early stages of OSMF in compared with control group. The mean serum uric acid levels in group I is 6.25 ± 2.0 and 8.00 ± 1.4 for group II whereas 7.99 ± 3.0 in the control group. There was a significant decreased levels of uric acid observed in early stages of OSMF group I oral cancer patients compared to that of the control group. It was also observed that mean serum uric acid levels in group II almost equal with normal values. Previous studies showing relationship between serum uric acid and cancer incidence have been rather inconsistent.

Where as in serum creatinine the mean values of Group II was significantly increased in compared to group I as well as normal control group.

Table: Estimation of urea, uric acid and creatinine in study groups

Parameter	Group I (Early OSMF)	Group II (Advanced OSMF)	Normal control
Urea	5.20 ± 0.9 (NS)	5.45 ± 1.8 (NS)	5.25 ± 1.5
Uric Acid	6.25 ± 2.0 (NS)	8.00 ± 1.4 (NS)	7.99 ± 3.0
Creatinine	450 ± 33 ***	509 ± 38.2 ***	345 ± 27

Values are expressed as the mean \pm SD for 20 patients in each group.

Group I and Group II were compared with normal control group.

NS: Non-Significant. *** $p < 0.001$

DISCUSSION

Oral sub mucous fibrosis (OSMF) is a chronic, insidious oral mucosal condition of the oral cavity characterized by sub mucosal fibrosis as characterized by juxta-epithelial inflammatory reaction followed by chronic change in the fibro-elasticity of the lamina propria and is associated with epithelial atrophy. This results in burning sensation in the oral cavity causing trismus thereby impairing the ability to speak. The more matter of concern over the past few decades is the malignant transformation rate, which has been reported to be around 7.6% over a 17-year period.⁹

Oral cancer is quite common in India. Several thousands of persons are affected by oral submucous

fibrosis, Oral cancer developing from a precancerous lesion is quite a common phenomenon these days. The harmful habits such as use of tobacco intake both in smoking and smokeless forms, pan masala and Gutkha chewing, and products which contain areca nut are the main causative agent for premalignant disorders. In the literature from Indian subcontinent preview, use of areca nut is the most etiologic common agent.¹⁰ Hence, we evaluated the serum levels of urea, uric acid and creatinine in oral submucous fibrosis patients and normal control. This study showed that serum uric acid, urea and creatinine were altered in OSMF patients compared with healthy volunteers but were statistically non-significant. This shows that change in biochemical values do occur in the premalignant state of the body but the values are not statistically significant. Joseph *et al.*,¹⁰ also found non-significant alteration in the creatinine phosphokinase levels in oral sub mucous fibrosis patients. In fibrosis cases, due to reduced nutrient flow, there is reduction in blood supply in the region to the region just as in systemic sclerosis as demonstrated by Partovi *et al.*,^{11,12} Over a period of time there can be complete fibrosis and loss of activity of the muscle leading to improper nutrition intake, malnutrition and therefore decrease in standard and quality of life.¹⁰ Lawa *et al.*, showed that serum uric acid was lowered in oral cancer patients in his study when compared with healthy volunteers and this low serum uric acid was associated with increased risk of oral cancer development. The lowering of Serum uric acid in oral cancer patients may be due to due to Tumour necrosis Factor (TNF) and Interleukin 6 (IL-6) produced in cancer patients which results in loss of appetite and malnutrition (Richter E, Connelly RR, Moul JW. The role of pre-treatment serum albumin to predict pathologic stage and recurrence among radical prostatectomy cases. Prostate Cancer Prostatic Dis. 2000; 3:186-190.). Serum uric acid level is also affected by alcohol consumption and various drugs such as diuretics and genetic factors.¹³ Hence biochemical alterations might be seen in premalignant disorders. It is also possible that the effect of serum uric acid on aetiology of cancer may vary from one type of cancer to another; low serum uric acid may be associated with increased risk of oral and lung cancer for instance, while high serum uric acid may be associated with increased risk of other types of cancer.

The diagnostic and prognostics value of creatine phosphokinase as biomarker in other systemic disease are well documented. Creatine phosphokinase is an enzyme which is released due to muscle damage in different systemic diseases. Hence this is used as biomarker to find out the extent of muscle damage or the progress of a disease. The importance of biomarkers in muscle damage is reported in a study done by Brancaccio *et al.*,¹⁵ The author recommends to use these biomarkers for muscle stress, and damage. The exact mechanism for enzyme release is not clear, but some sort of muscle tissue damage can change the serum value of creatine phosphokinase which can be substantiated by the above studies. Since there is the release these enzymes the muscle damage can be assessed at very earlier in different diseases. The significance of potentially malignant disorders like oral leukoplakia, oral submucous fibrosis showed statistical significance in a study done by Spoorthy *et al.*,¹⁶ In a patient developing oral submucous fibrosis due to

excessive chewing over many years can be explained against the fact of over use of the buccal musculature. This is also substantiated by the study done by Dessem *et al.*,¹⁷ where he studied the muscle response to injury or over use over a long period of time, the levels of creatine phosphokinase are altered in different muscles in different parts of the body. The primary factor for muscle damage is due to proteolysis. IL 6, IL1, ANS TNF ALPHA are found increased in submucous fibrosis patients, which are factors which help in proteolysis¹⁸. These cytokines are elevated due to activated T-lymphocytes present in the premalignant tissues.

Keeping this view in mind we designed a study to find out the significance of Urea, Uric Acid and Creatinine in Pathogenesis of oral submucous fibrosis patients. Our study had total 20 patients in each group of patients without any other systemic disease, who had habits of chewing of areca nuts. We did not get a statistical significance between Urea Uric Acid and Creatinine related to oral submucous fibrosis against as documented in other literature. However we could not trace a literature stating such variations in urea uric acid and creatinine levels in oral submucous fibrosis. This could be due to the difference in pathophysiology of oral submucous fibrosis and other diseases like myocardial infarction and colon cancer, where in the creatine phosphokinase showed a significant correlation¹⁹. But our study shows a mild difference in levels of urea, uric acid and clear variation in creatinine values between normal subjects and oral submucous fibrosis patients. In oral submucous fibrosis there is juxtaepithelial inflammatory reaction continued by activation of collagen production pathway leading to deposition of type 1 collagen fibres. Whereas in fibrosis there is reduction in blood supply in the region resulting in reduced nutrient flow, reduced immunity, to the region just as in systemic sclerosis. Over a period of time there can be complete fibrosis and loss of activity of the muscle leading to improper diet, nutrition, minerals and thereby poor quality of life.

CONCLUSION

The present study stresses on the assessment of the biochemical status for patients with oral submucous fibrosis. Determining serum urea, uric acid and creatinine as a part of biochemical assessment, which may be of proactive intervention for high-risk groups. It is therefore, suggested that the biochemical analysis can be helpful in mass screening of the OSMF patients. Further research work is required in this field to find out the exact role which these parameters play in the pathogenesis of OSMF.

ACKNOWLEDGMENTS

Author expresses his gratitude to the women's and elder people of the study area for their ethical and logistic support and acknowledge the immense help received from Dr. Divya, Dr. Fiza Khan, Dr. Ratna S, Dr. Swati, Dr. Piyanka Aggarwal, Dr. Shefali and Pandey Ji, laboratory in charge, oral pathology for their support and good wishes.

REFERENCES

1. Kode MA and Karjodkar FR. Estimation of the Serum and the Salivary Trace Elements in OSMF Patients. J Clin Diagn Res. 2013 Jun; 7(6): 1215–1218
2. Dyavanagoudar SN. Oral Submucous Fibrosis: Review on Etiopathogenesis. J Cancer Sci Ther:20091(2):072-077
3. Angadi PV, Kale AD, Hallikerimath S. Evaluation of myofibroblasts in oral submucous fibrosis: correlation with disease severity. J Oral Pathol Med. 2011 Mar;40(3):208-13
4. George J, Chandrakasan G. Biochemical abnormalities during the progression of hepatic fibrosis induced by dimethylnitrosamine. Clinic Biochem 2000; 33(7):563–570
5. Raganathan K, Gauri M. An overview of classification schemes for oral submucous fibrosis. Journal of Oral Pathology and Medicine. 2006;10:55–58
6. Caraway WT. Determination of uric acid in serum by carbonate method. Am J Clin Pathol 1955; 25: 840–5.
7. Owen JA, Iggo B, Scandrett FJ, Stewart CP. The determination of creatinine in plasma or serum and in urine: a critical examination. Biochem J 1954; 58: 426–37.
8. Bonsnes RW, Taussky HH. The colorimetric determination of creatinine by the Jaffe reaction. J Biol Chem 1945; 158: 581–91.
9. Angadi PV, Rao SS. Oral Maxillofac Surg. 2011; 15:1–9.
10. Joseph BB, George S. Level of Serum Creatine Phosphokinase in Oral Submucous Fibrosis - A Biochemical Study. Int J Cur Res Rev. 2015; 7(13):74-78.
11. Sasan Partovi, Anja-Carina Schulte, Impaired Skelet *al.*, Muscle Microcirculation Ic Systemic Sclerosis, Arthritis Research & Therapy 2012, 14:R209
12. Rasika Priyadharshani Ekanayaka. Oral Submucous Fibrosis: Review on Mechanisms of Pathogenesis and Malignant Transformation. J Carcinogene Mutagene 2013, S5.
13. Lawal AO, Kolude B and Adeyemi BF. Serum Uric Acid Levels In Oral Cancer Patients Seen At Tertiary Institution In Nigeria. Ann Ibd. Pg. Med 2012. Vol.10, No.1 9-12.
14. Anderson WAD. Kidneys in Anderson's Pathology, 5th edition (CV Mosby Company), St Louise Batlomore Philadephia Toronto (1996) 610-621.

15. Paola Brancaccio, Giuseppe Lippi, Biochemical markers of muscular damage. *Clin Chem Lab Med* 2010; 48(6).
16. Spoorthi B R, Vidya M. serum Creatinine Phosphokinase: A Potential diagnostic tool for oral premalignant lesions²-A histopathological biochemical study. *Indian J Stomatol.* 2011; 2 (2): 86-90.
17. Dean Dessem and Richard M, Lovering. Repeated Muscle Injury as a Presumptive Trigger for Chronic Masticatory Muscle Pain, Pain Research and Treatment, 2011.
18. VV Kamath, K Satelur, and Y Komali. Biochemical markers in oral submucous fibrosis: A review and update. *Dent Res J (Isfahan).* 2013 Sep-Oct; 10(5): 576–584.
19. F. Smith, D. Radford. Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. *British Heart Journal*, 1976, 38, 225-232.

CITE THIS ARTICLE AS:

Deepak Narang, Vanita Rathod, Fatima Khan, *et al.*, Estimation of urea, uric acid and creatinine in pathogenesis of OSMF: a randomized blind trial. *International Journal of Bioassays* 4.11 (2015): 4582-4585.

Source of support: Nil

Conflict of interest: None Declared