



# Serum uric acid levels in patients with oral cancer, leukoplakia and submucous fibrosis: a cross-sectional study

Karthik D. Yadav<sup>1</sup>, Bharati A. Patil<sup>1</sup>, Syed Ahmed Raheel<sup>2</sup>, Abdulwahab Abuderman<sup>3</sup>, Shankargouda Patil<sup>4</sup>, Kamis Gaballah<sup>5</sup>, Omar Kujan<sup>6</sup>

<sup>1</sup>Department of Oral Medicine and Radiology, The Oxford Dental College and Research Center, Bangalore, India; <sup>2</sup>Department of Oral Medicine and Radiology, KGF College of Dental Sciences, Kolar, Karnataka, India; <sup>3</sup>Department of Basic Medical Sciences, College of Medicine, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia; <sup>4</sup>Department of Oral and Maxillofacial Surgery and Diagnostic Sciences, Division of Oral Pathology, College of Dentistry, Jazan University, Jazan, Saudi Arabia; <sup>5</sup>Department of Oral and Maxillofacial Surgery, College of Dentistry, Ajman University, Ajman, United Arab Emirates; <sup>6</sup>UWA Dental School, The University of Western Australia, Perth, Australia

**Contributions:** (I) Conception and design: KD Yadav, BA Patil, SA Raheel, O Kujan; (II) Administrative support: SA Raheel, A Abuderman, S Patil, K Gaballah; (III) Provision of study materials or patients: KD Yadav, BA Patil, SA Raheel; (IV) Collection and assembly of data: KD Yadav, BA Patil, SA Raheel, O Kujan; (V) Data analysis and interpretation: KD Yadav, BA Patil, SA Raheel, O Kujan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Dr. Omar Kujan. UWA Dental School, The University of Western Australia, 17 Monash Avenue, Nedlands WA 6009, Australia. Email: omar.kujan@uwa.edu.au.

**Background:** This cross-sectional cohort study aimed to assess the associations between the serum uric acid levels and oral leukoplakia (OL), submucous fibrosis (OSMF) and squamous cell carcinoma (OSCC), and to correlate these with the clinical and histopathological features of these lesions.

**Methods:** Fifty-two patients with oral potentially malignant disorders (OPMD) (25 OL and 27 OSMF cases) and 33 OSCC patients with complete clinical and histopathological characteristics were included. A healthy control group was also investigated. The serum uric acid concentration was assessed using the uricase method from a blood sample without hemolysis.

**Results:** The level means of serum uric acid in the OL, OSMF and OSCC patients were  $3.86 \pm 1.31$ ,  $5.65 \pm 0.85$  and  $4.99 \pm 1.34$  mg/dL, respectively, compared to  $5.16 \pm 0.97$  mg/dL in the healthy controls.

**Conclusions:** The serum uric acid levels were reduced in the OL and OSCC patients but they were increased in the OSMF patients when compared to the healthy controls. No significant differences were seen in the clinical and histopathological features of the OL and OSMF patients. Future studies with larger sample sizes may improve the understanding of the contributory role of uric acid in the risk stratification of OPMDs. Although measuring the serum uric acid level involves a simple and economical assay, the data from this cross-sectional cohort does not support the clinical utility of evaluating the uric acid levels in OPMD and OSCC patients.

**Keywords:** Antioxidants; leukoplakia; oral; potentially malignant disorders; squamous cell carcinoma; submucous fibrosis; uric acid

Submitted Sep 16, 2019. Accepted for publication Jan 06, 2020.

doi: 10.21037/tcr.2020.01.08

View this article at: <http://dx.doi.org/10.21037/tcr.2020.01.08>

## Introduction

Oral squamous cell carcinoma (OSCC) is an aggressive malignant tumour characterized by a relatively low rate of prognosis (1). OSCC may arise from accumulated process

of genetic, epigenetic and metabolic changes resulting mostly from exposure to extrinsic sources (carcinogens). It includes the initial presence of a precursor or precancerous lesion (2), with the latter being a well-established form

that is called an oral potentially malignant disorder (OPMD) (3). Oral leukoplakia (OL) and oral submucous fibrosis (OSMF) are the most common OPMDs, with reported malignant transformation rates ranging from 0.13% to 34% and from 1.9% to 9.13%, respectively (4,5). Lifestyle factors, including tobacco, alcohol and areca nut/betel quid chewing, are the most common factors contributing to OPMD and OSCC development. To a lesser extent, the sexually acquired human papilloma virus is also a contributing factor (1,6). Moreover, specific medical conditions can contribute to the OPMD prevalence (7).

The cell's ability to block malignant transformation and return to a normal state is highly influenced by antioxidants (8). Antioxidants can be taken exogenously, and they are produced endogenously in our body. They help to maintain the cell integrity by harmonizing the oxidant-antioxidant levels in the body. An increase in the oxidant levels is described as 'oxidative stress', which can lead to the production of free radicals, especially reactive oxygen species (ROS). These can cause serious irreversible cell damage, ultimately leading to a malignant transformation (9-11). However, antioxidants neutralize the deleterious effects of ROS and free radicals via several intracellular and extracellular antioxidative systems (12).

Uric acid is the final product of purine metabolism in humans. It has been shown to be an important antioxidant, and it is responsible for approximately 60% of the free radical scavenging activity in humans (13,14). Uric acid forms a stable nitric oxide donor through the interaction with peroxynitrite. This leads to increase vasodilatation and decreasing the potential for peroxynitrite-induced oxidative damage (15).

Whenever there is increased oxidative stress (responsible for cell damage), antioxidants act against the oxidants in order to try to eliminate them and reduce the oxidative stress within a cell (15). In this process, uric acid gets consumed, and the oxidant levels are reduced in the serum, which is indicative of an active disease process (16). Uric acid, being a major antioxidant in the human plasma, both correlates and predicts the development of obesity, hypertension and cardiovascular disease, conditions that are associated with oxidative stress, and thus, it may prevent cancer by preventing cellular and genetic injury (16-18). Uric acid, as an antioxidant, was carefully chosen for this assessment because it is the major antioxidant in our body; it is produced endogenously and can be taken exogenously. In addition, uric acid participates in redox reactions, and it exhibits protective action against oxidation. The uric acid

level was correlated with the clinical and histopathological data for a better understanding of its role. Moreover, uric acid testing is economical, so it can be used for mass screening if it is shown to correlate with the disease process.

This study was designed to assess and correlate the uric acid levels in the serum of patients diagnosed with OL, OSMF and OSCC and to compare these to healthy controls.

## Methods

This is a cross-sectional cohort study that was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (19). This study received ethical approval from the Institutional Review Board of the KGF College of Dental Sciences and Hospital (Karnataka, India). All of the included participants signed informed consent forms, and all of the procedures were undertaken in accordance with the principles of the Helsinki Declaration.

The study commenced in January of 2018 and recruited 115 subjects over 18 months. The study group was comprised of patients clinically diagnosed with OSCC (n=33) and OPMD (n=52), in addition to 30 healthy controls. The OPMD group was further subdivided into 2 subgroups consisting of 25 OL and 27 OSMF patients. A full medical history was taken from each participant in order to validate their eligibility for study enrolment. The following criteria were used for enrolling the participants:

- (I) Inclusion criteria: patients clinically and histopathologically diagnosed with OSCC, OL or OSMF. The healthy volunteers should have had no previous history of tobacco or alcohol use.
- (II) Exclusion criteria: individuals suffering from systemic diseases (such as gout, rheumatological disorders, hypertension, renal disease, diabetes mellitus or metabolic disorders), patients on medication for hyperuricemia and/or hypertension, patients diagnosed with any other malignancies or who had received chemotherapy and/or radiotherapy, subjects who had taken any vitamin supplements in the previous 3 months and participants who refused to provide consent.

A fasting blood sample of 5mL for standard clinical biochemistry was obtained. The uricase method was used to measure the serum uric acid levels from blood samples without hemolysis, as described previously (20).

The subjects included in this study received full mouth

examinations by an oral medicine specialist after obtaining a full patient history with details about their social habits, including their tobacco, betel quid/areca nut and alcohol use. An incisional biopsy was taken as part of the patient management, and the histopathological evaluation was reported using the World Health Organization grading system for oral epithelial dysplasia (OED) and OSCC (21). OSMF was clinically and histopathologically diagnosed using the new classification proposed by Arakeri *et al.* (22). OL is a clinical diagnosis, characterised histopathologically as keratosis/hyperkeratosis with or without OED (4).

### Statistical analysis

The data were expressed as the mean  $\pm$  the standard deviation. The Student's *t*-test and an analysis of variance were used. Pearson's chi-squared test was used to determine the associations between the variables. IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA) was used for the analysis, and  $P < 0.05$  was set as the statistical significance level.

### Results

*Table 1* summarizes the sociodemographic details of the healthy control group and the clinical and histopathological diagnoses of the subjects. OSCC, OL and OSMF were diagnosed predominantly in males (72.9%,  $P = 0.006$ ). Tobacco habits and betel quid/areca nut chewing were significantly associated with the oral lesions reported ( $P = 0.012$ ). Alcohol drinking was significantly reported in the OSCC patients ( $P = 0.04$ ). Remarkably, the buccal mucosa was the most affected anatomical site ( $P = 0.003$ ). Nearly 70% of the patients with OSCC were diagnosed at an advanced stage (stage IV). All of the OL lesions had single presentations, and clinically, 72% of them presented with a homogenous appearance. The histopathological diagnosis of OL was keratosis/hyperkeratosis with and without OED. Specifically, OED was evident in 60% of the OL cases. Approximately 92% of the OSMF patients were clinically diagnosed with stage II.

The serum uric acid level means were  $4.19 \pm 1.66$ ,  $3.79 \pm 1.23$ ,  $5.65 \pm 0.86$  and  $5.16 \pm 0.97$  mg/dL in the OSCC, OL and OSMF patients and the control group, respectively (*Table 2*). A statistically significant association between the mean serum uric acid level and OSCC was only found when it was compared to the control group ( $P = 0.007$ ).

The results of the comparisons of the serum uric

acid level means with the clinical and histopathological diagnoses of OL, OSMF and OSCC and their statistical significances are shown in *Table 3*. There was only a significant association between the tumour, node, metastasis (TNM) staging of the OSCC cases and their mean serum uric acid level ( $P = 0.004$ ).

### Discussion

It is important to note that oxygen radicals may cause cell damage that ultimately contributes to oral carcinogenesis through several molecular mechanisms including DNA damage, oxidation of important enzymes, protein damage, and activation of specific cytokines. Uric acid acts as antioxidant and is affected by several factors including alcohol consumption and dietary intake (23).

In our study, the mean serum uric acid level in the OL patients was  $3.79 \pm 1.23$  mg/dL, which was found to be lower than that of the controls, who had a mean serum uric acid level of  $5.16 \pm 0.97$  mg/dL. This difference was found to be statistically significant (*Table 2*).

Our study is the first to report a serum uric acid level estimation in OL patients using blood specimens. In the literature, there was only one paper that examined the salivary uric acid levels in OL patients, and it reported no significant difference between the OL patients and the controls (23). More importantly, those researchers found that the salivary uric acid levels were influenced by alcohol and tobacco consumption (23). Specifically, alcohol was lightly consumed by the subjects recruited in our study, but tobacco habits were predominantly prevalent. These findings are consistent with those reported in previous studies from the Indian subcontinent (22,24). Moreover, several previous studies have estimated the serum uric acid levels in patients with tobacco use habits (18,25). For example, Hanna *et al.* examined the potential effects of smoking on the serum uric acid levels among 60 smokers and 60 non-smokers within the same social class, and their findings showed that the serum uric acid level was significantly lower in the smokers ( $199 \pm 97$   $\mu\text{mol/L}$ ) than in the non-smokers ( $250 \pm 132$   $\mu\text{mol/L}$ ) (18). Another study examining the effects of cigarette smoking on the plasma uric acid concentration was conducted among 162 smokers, and it showed that the plasma uric acid concentration was lower in the smokers ( $0.22 \pm 0.07$  mmol/L) than in the non-smokers ( $0.27 \pm 0.05$  mmol/L) (25). Hanna *et al.* attributed the low serum uric acid levels in the smokers to reduced endogenous production as a result of chronic exposure to

**Table 1** Sociodemographic details of the participants and the clinical and histopathological diagnosis of oral lesions

Characteristics	Study cohorts				P value
	OSCC, N (%)	OL, N (%)	OSMF, N (%)	Healthy control, N (%)	
Sample size	33 (27.5)	25 (20.8)	27 (22.5)	30 (25.0)	0.746
Gender (male %)	24 (72.7)	19 (76.0)	19 (70.3)	17 (56.7)	0.006*
Mean age (years)	51	42.8	34	37	0.021*
Tobacco smoking	8 (24.2)	20 (80.0)	10 (37.0)	–	0.237
Tobacco chewing	9 (27.3)	4 (16.0)	4 (14.8)	–	0.053
Non-tobacco user	3 (9)	–	–	–	
Betel quid/areca nut user	13 (39.4)	1 (4.0)	13 (48)	–	0.143
Tobacco & betel quid user	29 (87.8)	19 (76.0)	23 (85.2)	–	0.012*
Alcohol drinking	20 (60.6)	11 (44.0)	10 (37.0)	–	0.040*
Site	Buccal mucosa 15 (45.5)	Buccal mucosa 15 (60.0)	L & R buccal mucosa 1 (3.7)	–	0.003*
	Alveolus 8 (24.2)	Lateral tongue 6 (24.0)	L & R buccal mucosa, tongue, & lips 26 (96.3)	–	
	Retromolar area 7 (21.1)	Retromolar area 4 (16.0)		–	
	Lateral tongue 3 (9)			–	
Clinical presentation/staging	Stage I 0 (0)	Homogenous OL 18 (72.0)	Stage I 2 (7.4)	–	0.008*
	Stage II 2 (6)		Stage II 25 (92.6)	–	
	Stage III 8 (24.2)	Non-homogenous OL 7 (28.0)	Stage III 0 (0)	–	
	Stage IV 23 (69.7)			–	
Histopathological diagnosis/staging	Well differentiated SCC 11 (33.3)	Keratosis with no OED 10 (40.0)	Grade I 1 (3.7)	–	0.548
		Keratosis with mild OED 8 (32.0)	Grade II 12 (44.4)	–	
	Moderately differentiated SCC 19 (57.6)	Keratosis with moderate OED 5 (20.0)	Grade III 13 (48.1)	–	
	Poorly differentiated SCC 3 (9)	Keratosis with severe OED 2 (8.0)	Grade IV 1 (3.7)	–	

\*, statistically significant (P<0.05). OSCC, oral squamous cell carcinoma; OL, oral leukoplakia; OSMF, oral submucous fibrosis; N, number; OED, oral epithelial dysplasia.

cigarette smoke (18).

The mean level of serum uric acid in the OSMF patients was 5.65±0.86 mg/dL, which was slightly higher than in the controls, and the difference was found to be statistically significant. One previous study estimated the levels of urea, uric acid and creatinine in the pathogenesis of OSMF, and their results showed that the serum uric acid, urea and creatinine levels were altered in the OSMF patients (26). The serum uric acid level means in the OSMF patients

and the control group were 7.12±1.7 and 7.99±3.0 mg/dL, respectively (26). The values for both the OSMF and control groups were comparatively higher than those found in our study. Contrary to their results, we found higher serum uric acid values in the OSMF patients than in the controls.

The mean serum uric acid level in the OPMD patients was 4.99±1.34 mg/dL, which was slightly lower when compared to the controls (5.16±0.97 mg/dL); however, the

**Table 2** Mean  $\pm$  SD serum uric acid levels in control, oral squamous cell carcinoma and potentially malignant disorders patients

Groups	Control	OPMD		OSCC
		Oral leukoplakia	OSMF	
No. of patients	30	25	27	33
Serum uric acid (mg/dL)	5.16 $\pm$ 0.98	3.79 $\pm$ 1.23	5.65 $\pm$ 0.86	4.19 $\pm$ 1.66
		4.99 $\pm$ 1.34		
P value		0.55 <sup>A</sup>		0.007 <sup>B*</sup>

\*, statistically significant ( $P < 0.05$ ); <sup>A</sup>, statistical significance between OPMD & healthy control; <sup>B</sup>, statistical significance between OSCC & healthy control. OPMD, oral potentially malignant disorder; OSCC, oral squamous cell carcinoma; OSMF, oral submucous fibrosis.

difference was not statistically significant (*Table 2*).

The mean serum uric acid level in the OSCC cohort was 4.19 $\pm$ 1.66 mg/dL, which was lower when compared to the controls (5.16 $\pm$ 0.97 mg/dL), and the difference was statistically significant ( $P = 0.007$ ). It has been reported in various studies that there is a significant drop in serum uric acid levels of patients with oral cancer when compared to healthy controls (27,28). One such study was conducted at a tertiary institution in Nigeria, and the study showed similar results. The mean serum uric acid level in the oral cancer patients was 5.18 $\pm$ 1.96 mg/dL, which was lower than that of the control group (7.09 $\pm$ 1.84 mg/dL), and the researchers concluded that the low serum uric acid level was associated with a 3.98 times increased risk of oral cancer development (27). Similarly, Ara *et al.* showed lower serum uric acid levels in patients with OSCC (3.80 $\pm$ 2.26 mg/dL) when compared to the control group (5.66 $\pm$ 1.82 mg/dL), and this difference was statistically significant ( $P < 0.001$ ) (28).

We found that the serum uric acid levels in the homogenous OL and non-homogenous OL groups were 3.99 $\pm$ 1.29 and 3 $\pm$ 0.39 mg/dL, respectively, and the difference was not statistically significant ( $P = 0.22$ ). Moreover, the serum uric acid level means in the patients with no OED, mild OED and moderate OED were 4.15 $\pm$ 1.49, 3.3 $\pm$ 0.83 and 3.59 $\pm$ 0.64 mg/dL, respectively. We observed a decrease in the mean serum uric acid level as the severity of the dysplastic changes increased; however, the difference was not statistically significant ( $P = 0.5$ ) (*Table 3*). The possible explanation to this observation is the small number of participants included in each subgroup making it difficult to find statistical significant difference. Thus a larger sample size is warranted.

Our study did not reveal any significant changes in

the serum uric acid level means across the clinical and histopathological stages of OSMF (*Table 3*). A study conducted by Shekhawat *et al.*, which was designed to assess the oxidative stress in OSMF by assessing the total serum and salivary antioxidant capacities, showed that as the severity of the OSMF increased, the total antioxidant capacity level decreased (29). The main cause of OSMF is betel quid/areca nut chewing that results in marked fibrosis. As a result, the blood supply is compromised resulting in decreasing the flow of nutrients and ultimately this will impact on the level of the antioxidants such as uric acid (23,29).

The overall means of serum uric acid level in the OSCC cases according to the TNM staging and grading for stage II, stage III and stage IV were 6.96 $\pm$ 1.04, 5.02 $\pm$ 1.71 and 3.67 $\pm$ 1.35 mg/dL, respectively (*Table 3*). Here, we can see a decrease in the serum uric acid level with an increase in the clinical staging and grading. The salivary superoxide dismutase level showed a progressive increase between the well to poorly differentiated OSCC cases, although it was not statistically significant (30).

## Conclusions

The limitations of our current study were that the only antioxidant studied was the serum uric acid and that our sample size was relatively small. Further research involving both the oxidative markers and total antioxidant capacity in a larger study sample of OPMD cases may explain the contributory role of oxidative stress and antioxidants in the development of OPMDs and their malignant transformation. This may help us to better understand and develop a more effective preventive strategy to control OSCC.

**Table 3** Mean  $\pm$  SD levels of serum uric acid compared to the clinical & histopathological diagnosis and grading in OL, OSMF, and OSCC groups

Study group	Staging	Serum uric acid (mg/dL)	Statistical significance
Oral leukoplakia	Clinical presentation		
	Homogenous leukoplakia	3.99 $\pm$ 1.29	0.22
	Non-homogenous leukoplakia	3 $\pm$ 0.39	
	Histopathological grading		
	No dysplasia	4.15 $\pm$ 1.49	0.5
	Mild OED	3.3 $\pm$ 0.83	
	Moderate OED	3.59 $\pm$ 0.64	
Oral submucous fibrosis	Clinical staging		
	Stage I	5.89 $\pm$ 1.39	0.7
	Stage II	5.64 $\pm$ 0.84	
	Histopathological staging		
	Stage I	6.95 $\pm$ 0	0.06
	Stage II	5.80 $\pm$ 0.83	
	Stage III	5.44 $\pm$ 0.83	
Oral squamous cell carcinoma	TNM staging		
	Stage I	–	0.004*
	Stage II	6.96 $\pm$ 1.04	
	Stage III	5.02 $\pm$ 1.71	
	Stage IV	3.67 $\pm$ 1.35	
	Histopathological staging		
	Well differentiated	4.02 $\pm$ 1.53	0.56
Moderately differentiated	4.14 $\pm$ 1.78		
Poorly differentiated	5.19 $\pm$ 1.58		

\*, statistically significant (P<0.05). OSCC, oral squamous cell carcinoma; OSMF, oral submucous fibrosis; OL, oral leukoplakia; OED, oral epithelial dysplasia; TNM staging, tumour, nodes, and metastasis staging.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editor (Shankargouda Patil) for the series “Oral Pre-cancer and Cancer” published in *Translational Cancer Research*. The article was sent for external peer review

organized by the Guest Editor and the editorial office.

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.01.08>). The series “Oral Pre-cancer and Cancer” was commissioned by the editorial office without any funding or sponsorship. SP served as an unpaid Guest Editor of the series. He also serves as the unpaid an unpaid Editorial Board Member of *Translational Cancer Research* from Jul 2018–Jun 2020. The authors have no



other conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of the KGF College of Dental Sciences (No. 432/2018) and written informed consent was obtained from all individuals participated in the study.

**Open Access Statement:** This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

- Chi AC, Day TA, Neville BW. Oral cavity and oropharyngeal squamous cell carcinoma--an update. *CA Cancer J Clin* 2015;65:401-21.
- Farah CS, Shearston K, Nguyen AP, et al. Oral Carcinogenesis and Malignant Transformation. Premalignant Conditions of the Oral Cavity. Singapore: Springer Singapore, 2019:27-66.
- Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med* 2007;36:575-80.
- Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018;125:612-27.
- Warnakulasuriya S, Ariyawardana A. Malignant transformation of oral leukoplakia: a systematic review of observational studies. *J Oral Pathol Med* 2016;45:155-66.
- Porter S, Gueiros LA, Leao JC, et al. Risk factors and etiopathogenesis of potentially premalignant oral epithelial lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018;125:603-11.
- Frydrych AM, Kujan O, Farah CS. Chronic disease comorbidity in patients with oral leukoplakia. *Oral Cancer* 2019;3:17-26.
- Lobo V, Patil A, Phatak A, et al. Free radicals, antioxidants and functional foods: Impact on human health. *Pharmacogn Rev* 2010;4:118-26.
- Gokul S, Patil VS, Jailkhani R, et al. Oxidant-antioxidant status in blood and tumor tissue of oral squamous cell carcinoma patients. *Oral Dis* 2010;16:29-33.
- Alamir AWH, Arakeri G, Patil S, et al. Association of nitric oxide with oral lichen planus. *J Oral Pathol Med* 2019;48:345-50.
- Iannitti T, Rottigni V, Palmieri B. Role of free radicals and antioxidant defences in oral cavity-related pathologies. *J Oral Pathol Med* 2012;41:649-61.
- Metgud R, Bajaj S. Evaluation of salivary and serum lipid peroxidation, and glutathione in oral leukoplakia and oral squamous cell carcinoma. *J Oral Sci* 2014;56:135-42.
- Waring WS, Webb DJ, Maxwell SR. Systemic uric acid administration increases serum antioxidant capacity in healthy volunteers. *J Cardiovasc Pharmacol* 2001;38:365-71.
- Kurutas EB. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. *Nutr J* 2016;15:71.
- Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. *Physiol Rev* 2007;87:315-424.
- Skak-Nielsen H, Torp-Pedersen C, Finer N, et al. Uric acid as a risk factor for cardiovascular disease and mortality in overweight/obese individuals. *PLoS One* 2013;8:e59121.
- Tomita M, Mizuno S, Yokota K. Increased levels of serum uric acid among ex-smokers. *J Epidemiol* 2008;18:132-4.
- Hanna BE, Hamed JM, Touhala LM. Serum uric Acid in smokers. *Oman Med J* 2008;23:269-74.
- von Elm E, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806-8.
- Wu CY, Hu HY, Chou YJ, et al. High Serum Uric Acid Levels Are Associated with All-Cause and Cardiovascular, but Not Cancer, Mortality in Elderly Adults. *J Am Geriatr Soc* 2015;63:1829-36.
- El-Naggar AK CJ, Grandis JR, Takata T, et al. WHO Classification of Head and Neck Tumours. 4th ed. Lyon: 2017.
- Arakeri G, Thomas D, Aljabab AS, et al. TFM classification and staging of oral submucous fibrosis: A new proposal. *J Oral Pathol Med* 2018;47:403-9.
- Babiuch K, Bednarczyk A, Gawlik K, et al. Evaluation

- of enzymatic and non-enzymatic antioxidant status and biomarkers of oxidative stress in saliva of patients with oral squamous cell carcinoma and oral leukoplakia: a pilot study. *Acta Odontol Scand* 2019;77:408-18.
24. Kumar GK, Abidullah M, Elbadawi L, et al. Epidemiological profile and clinical characteristics of oral potentially malignant disorders and oral squamous cell carcinoma: A pilot study in Bidar and Gulbarga Districts, Karnataka, India. *J Oral Maxillofac Pathol* 2019;23:90-6.
  25. Haj Mouhamed D, Ezzaher A, Neffati F, et al. Effect of cigarette smoking on plasma uric acid concentrations. *Environ Health Prev Med* 2011;16:307-12.
  26. Narang D, Rathod V, Khan F, et al. Estimation of urea, uric acid and creatinine in pathogenesis of OSMF: a randomized blind trial. *Int J Bioassays* 2015;4:4582-5.
  27. Lawal AO, Kolude B, Adeyemi BF. Serum uric Acid levels in oral cancer patients seen at tertiary institution in Nigeria. *Ann Ib Postgrad Med* 2012;10:9-12.
  28. Ara SA, Ashraf S, Patil BM. Evaluation of serum uric acid levels in patients with oral squamous cell carcinoma. *Indian J Dent Res* 2016;27:178-83.
  29. Shekhawat C, Gopakumar R, Shetty S, et al. Oxidative Stress in Oral Submucous Fibrosis- A Clinical and Biochemical Study. *Oral Health and Dental Management* 2016;15:22-6.
  30. Singh H, Shetty P, Patidar M, et al. Analysis of salivary antioxidant levels in different clinical staging and histological grading of oral squamous cell carcinoma: noninvasive technique in dentistry. *J Clin Diagn Res* 2014;8:ZC08-11.

**Cite this article as:** Yadav KD, Patil BA, Raheel SA, Abuderman A, Patil S, Gaballah K, Kujan O. Serum uric acid levels in patients with oral cancer, leukoplakia and submucous fibrosis: a cross-sectional study. *Transl Cancer Res* 2020;9(4):3084-3091. doi: 10.21037/tcr.2020.01.08