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

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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±1.31, 5.65±0.85 and 4.99±1.34 mg/dL, respectively, compared to 5.16±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 ± 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±1.66, 3.79±1.23, 5.65±0.86 and 5.16±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±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±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±97 µmol/L) than in the non-smokers (250±132 µmol/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±0.07 mmol/L) than in the non-smokers (0.27±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
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
The mean serum uric acid level in the OSCC cohort was 4.19±1.66 mg/dL, which was lower when compared to the controls (5.16±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±1.96 mg/dL, which was lower than that of the control group (7.09±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±2.26 mg/dL) when compared to the control group (5.66±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±1.29 and 3±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±1.49, 3.3±0.83 and 3.59±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±1.04, 5.02±1.71 and 3.67±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 ± SD levels of serum uric acid compared to the clinical & histopathological diagnosis and grading in OL, OSMF, and OSCC groups

<table>
<thead>
<tr>
<th>Study group</th>
<th>Staging</th>
<th>Serum uric acid (mg/dL)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral leukoplakia</td>
<td>Clinical presentation</td>
<td></td>
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<tr>
<td></td>
<td>Homogenous leukoplakia</td>
<td>3.99±1.29</td>
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<tr>
<td></td>
<td>Non-homogenous leukoplakia</td>
<td>3±0.39</td>
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<td></td>
<td>Histopathological grading</td>
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<tr>
<td></td>
<td>No dysplasia</td>
<td>4.15±1.49</td>
<td>0.5</td>
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<tr>
<td></td>
<td>Mild OED</td>
<td>3.3±0.83</td>
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<tr>
<td></td>
<td>Moderate OED</td>
<td>3.59±0.64</td>
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<tr>
<td></td>
<td>Severe OED</td>
<td>3.43±0.78</td>
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<tr>
<td>Oral submucous fibrosis</td>
<td>Clinical staging</td>
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<td></td>
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<tr>
<td></td>
<td>Stage I</td>
<td>5.89±1.39</td>
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<tr>
<td></td>
<td>Stage II</td>
<td>5.64±0.84</td>
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<tr>
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<td>Histopathological staging</td>
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<tr>
<td></td>
<td>Stage I</td>
<td>6.95±0</td>
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<td></td>
<td>Stage II</td>
<td>5.80±0.83</td>
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<td>Stage III</td>
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<tr>
<td>Oral squamous cell carcinoma</td>
<td>TNM staging</td>
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<tr>
<td></td>
<td>Stage I</td>
<td>–</td>
<td>0.004*</td>
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<tr>
<td></td>
<td>Stage II</td>
<td>6.96±1.04</td>
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<tr>
<td></td>
<td>Stage III</td>
<td>5.02±1.71</td>
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<td></td>
<td>Stage IV</td>
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<td></td>
<td>Histopathological staging</td>
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<td>Well differentiated</td>
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<td>Moderately differentiated</td>
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<tr>
<td></td>
<td>Poorly differentiated</td>
<td>5.19±1.58</td>
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</table>

*, 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 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.

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