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Original Article

# Investigating the relationship between stimulated salivary markers and the history of opioid use: a case-control study

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## Abstract

***Background & Aims*:** Opioids cause dry mouth, tooth decay, discoloration of oral tissues, and periodontal diseases. Adequate saliva flow is a prerequisite for a healthy periodontium, and the salivary urea concentration is an important parameter for the tooth and gum health. The purpose of the present study was to investigate salivary urea concentration in opioid users.

***Materials & Methods*:** This case-control study was conducted on 240 people in 2021. The case group included 120 people referred to addiction treatment centers of Birjand. The control group also consisted of 120 people with no history of addiction and was selected from clients referred to the Faculty of Dentistry of Birjand University of Medical Sciences and Samen Dental Clinic in Birjand. The control and case groups were age matched, and their demographic information and periodontal clinical data were collected. The obtained data were then analyzed using SPSS ver. 19.

***Results*:** The amount of stimulated saliva in the case group was significantly lower than the control group ($P$=0.000), while the salivary urea concentration in methadone and opium users was significantly higher than the control group ($P$ = 0.000).

***Conclusion*:** Drug addiction causes dry mouth and increased salivary urea concentration. Poor oral and dental hygiene and increase in chronic periodontitis are also observed in drug addicts, and chronic periodontitis causes a raise in salivary urea concentration. Hence, the reason for enhanced salivary urea concentration in drug addicts could increase chronic periodontitis.

***Keywords*:** Salivary urea concentration, Stimulated saliva, Opioids, Salivary biomarkers

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## Introduction

Opioids, particularly opium, heroin, and codeine, are the most common addictive substances in Iran and are used orally, inhaled and injected. Addiction reduces motivation and self-confidence; as a result, oral hygiene and daily dental care are severely reduced (1). Addiction causes dry mouth or xerostomia, which gives rise to a decrease in the pH of saliva and an increase in dental plaque and calculus, ultimately

leading to a raise in the incidence of tooth decay and periodontal diseases (2, 3).

Saliva is a fluid secreted by the salivary glands and includes serum components, gingival crevicular fluid, and oral mucosal secretions. It is used as a diagnostic fluid and indicates the level of circulating biomarkers. Saliva collection is safe, non-invasive and simple, and saliva samples can be collected many times with minimal patient discomfort (4). The flow rate of saliva depends on various factors such as stimulation, circadian rhythm, diet, and age (5). Saliva is very important in the formation of oral biofilm and immunity and has a significant effect on the progress of periodontal diseases and tooth decay (6, 7). Adequate saliva flow is a prerequisite for a healthy periodontium, and the salivary urea concentration is an important parameter for the tooth and gum health (8). The hydrolysis of saliva urea by bacterial urease enzymes induces ammonia and carbon dioxide ($CO_2$), which could be very destructive to periodontal tissues;as a result, the analysis of salivary urea level reflects the activity and severity of periodontal disease (9).

Despite several epidemiological studies on the relationship between dry mouth and drug use (10, 11), there is little information on the association of salivary urea concentration with drug use. Therefore, this study investigated the level of salivary urea, as one of the salivary biomarkers affecting periodontium and teeth, among drug users and control group.

## Materials & Methods

In the present case-control study, 120 people were assigned to the case group and selected from clients referred to addiction treatment centers. Also, 120 people were assigned to the control group and were selected from clients who visited the Faculty of Dentistry of Birjand University of Medical Sciences and Samen Dental Clinic in Birjand in 2021. Inclusion criteria included the mean age of 20-40 years and addiction to opioids in the case group for at least one year. Exclusion criteria also entailed patients with underlying diseases such as diabetes, immunodeficiency, leukemia, hepatitis, HIV, upper respiratory infection, necrotizing ulcerative gingivitis, mucosal lesions, and invasive periodontitis. Patients undergoing periodontitis treatment, using antibacterial or anti-inflammatory drugs in the last three months, and taking vitamin supplements, as well as cases with a history of chemotherapy and radiotherapy that caused xerostomia and regular use of mouthwashes were also excluded. A consent letter was obtained from each patient who participated in the study, and their general data were recorded in an information form. The form included patients' demographic information (age, gender, residence place, occupation, and education level), opioid addiction, type of opioid (methadone, opium extract, opium, and methamphetamine), route of abuse (smoking and non-smoking), and duration of opioid addiction (1-2 years, 2-4 years, and more than 4 years).

In order to collect stimulated saliva, each participant was asked to chew a piece of unflavored rubber dam for one minute to collect his/her saliva in a calibrated falcon tube at the same time. The amount of stimulated saliva was observed and recorded on the calibrated falcon and sent to the laboratory to determine the salivary urea concentration. The test was performed by a laboratory technician, and the results were recorded in the information form and was entered into SPSS ver. 19. In addition, the salivary urea concentration was investigated among addicts and non-addicts with varying degrees of periodontitis.

## Results

The present research was conducted on 240 volunteers, including 120 addicted people and 120 people without a history of addiction, in the age range of 20-40 years, with an average age of 36±4.95 in the case group and an average age of 34±6.03 in the control group. The data were analyzed by SPSS version 19 at a significance level of 0.05.

According to the Tukey's post hoc test and ANOVA, there was a significant difference in the salivary urea between methadone and opium users compared to the control group, but this difference was not significant for methamphetamine (Table 1). Also,

the amount of stimulated saliva in drug addicts of different types of drugs did not show a significant difference compared to the control group, but in general, the amount of stimulated saliva in the case group was significantly lower than the control group ($P$ =0.000). Besides, the salivary urea concentration in the case group was significantly more than the control group ($P$ =0.022).

**Table 1**. Comparison of the average amount of stimulated saliva and salivary urea concentration between different drug users and the control group

| | Group | Number | Mean ± SD | | P value |
|---|---|---|---|---|---|
| Urea (mg/ml) | Methadone | 84 | 31.95 ± 4.47 | Opium | 0.671 |
| | | | | Methamphetamine | 0.516 |
| | | | | control group | 0.000* |
| | Opium | 32 | 33.65 ± 5.62 | Methamphetamine | 0.287 |
| | | | | Control group | 0.000* |
| | Methamphetamine | 4 | 32.25 ± 11.22 | Control group | 0.213 |
| | Total | 120 | 32.41 ± 9.47 | Control group | 0.022* |
| Saliva (ml/min) | Methadone | 84 | 1.66 ± 0.67 | Opium | 0. 917 |
| | | | | Methamphetamine | 1.000 |
| | | | | Control group | 0.196 |
| | Opium | 32 | 1.49 ± 0.59 | Methamphetamine | 0.994 |
| | | | | Control group | 0.164 |
| | Methamphetamine | 4 | 2.25 ± 1.08 | Control group | 0.943 |
| | Total | 120 | 1.64 ± 0.72 | Control group | 0.000* |

* shows a statistically significant difference

The Tukey's post hoc test and ANOVA did not show a significant difference in the salivary urea concentration between drug users with a duration of 1-2 years and 2-4 years compared to the control group, but in drug users for more than 4 years, salivary urea concentration was significantly different from the control group ($P$ = 0.036). Also, the amount of stimulated saliva showed a significant difference in all drug users with different durations of use compared to the control group, ($P$ =0.000). These results are indicated in Table 2.

**Table 2.** Comparison of the average amount of stimulated saliva and salivary urea concentration between different number of years of drug use and control group

| | Group | Number | Mean ± SD | | P value |
|---|---|---|---|---|---|
| Urea (mg/ml) | 1-2 years | 17 | 29.47 ± 8.47 | 2-4 years | 0.993 |
| | | | | > 4 years | 0.586 |
| | | | | Control group | 0.996 |
| | 2-4 years | 20 | 30.15 ± 12.37 | > 4 years | 0.768 |
| | | | | Control group | 0.930 |
| | > 4 years | 83 | 33.56 ± 9.97 | Control group | 0.036* |
| Saliva (ml/min) | 1-2 years | 17 | 1.58 ± 0.55 | 2-4 years | 0.998 |
| | | | | > 4 years | 1.000 |
| | | | | Control group | 0.000* |
| | 2-4 years | 20 | 1.60 ± 0.37 | > 4 years | 0.995 |
| | | | | Control group | 0.000* |
| | > 4 years | 83 | 1.66 ± 0.07 | Control group | 0.000* |

* shows a statistically significant difference

The two above-mentioned tests showed that the salivary urea concentration in smoking and non-smoking drug users was not significantly different compared to the control group, but the amount of stimulated saliva in both users was significantly

different compared to the control group ($P$ = 0.000), as illustrated in Table 3.

**Table 3.** Comparison of the average amount of stimulated saliva and salivary urea concentration between smoking and non-smoking drug use and the control group

| | Group | Number | Mean ± SD | | P value |
|---|---|---|---|---|---|
| Urea (mg/ml) | Smoking | 31 | 33.93 ± 14.02 | Non-smoking | 0.875 |
| | | | | control group | 0.121 |
| | Non-smoking | 85 | 32.21 ± 13.71 | control group | 0.099 |
| Saliva (ml/min) | Smoking | 31 | 1.54 ± 0.73 | Non-smoking | 0.776 |
| | | | | control group | 0.000* |
| | Non-smoking | 85 | 1.67 ± 0.93 | control group | 0.000* |

* shows a statistically significant difference

## Discussion

Saliva is a fluid secreted by the salivary glands and contains serum components, gingival crevicular fluid, and oral mucosal secretions. It is used as a potential diagnostic fluid that reflects the level of circulating biomarkers. Saliva collection is safe, non-invasive and simple, and saliva samples can be collected many times with minimal patient discomfort (4).

According to the results of the present study, there was no significant difference in the amount of stimulated saliva flow between methadone, opium, and methamphetamine users, but in general, the amount of stimulated saliva flow in the case group was significantly lower than the control group. There was no significant difference in the amount of stimulated saliva flow between different years of drug use, but a significant difference was observed in saliva reduction when comparing different years of drug use with the control group. Also, there was no significant difference in the amount of stimulated saliva between smoking and non-smoking drug users. Akbari's study showed that drug addiction causes a decrease in saliva (1).

Regarding the use of methamphetamine, it is assumed that the activation of alpha-adrenergic receptors in the vessels of the salivary glands causes vasoconstriction and a decrease in saliva flow. Another hypothesis is the stimulating effect of methamphetamine on the inhibitory alpha-3 adrenoreceptors in the salivary glands and a decrease in the amount of saliva flow (1). It is also supposed that the use of some drugs changes the composition of saliva and leads to dry mouth. Dehydration caused by drug addiction elevates metabolism, and increasing physical activity leads to dry mouth (1). Nekui et al. concluded that the use of opium led to dry mouth (10). Also, in the study of Saini et al., opioids and amphetamines reduced the production of saliva (11). According to the study of Reza et al. in Indonesia, methadone causes dry mouth (12). Moreover, by interfering with environmental signals in parasympathetic muscarinic receptors, methadone has the ability to suppress the secretory function of saliva and causes dry mouth (12).

In the present study, salivary urea concentration in methadone and opium users was significantly higher than the control group, which was similar to the results obtained in the study of Patil et al. who found a statistically significant increase in the salivary urea concentration among smokers with severe periodontitis compared to other groups (non-smokers, non-smokers with gingivitis, and smokers with moderate periodontitis (9). Saini et al. observed a high prevalence of periodontal diseases with heavy calculus among drug users (11). Most addicts have a high level of dental plaque and calculus due to poor oral hygiene, dry mouth, and changes in the microbial profile. Also, the use of drugs such as opioids leads to the suppression of pain responses and causes the patient to ignore the symptoms of tooth decay, periodontal diseases, and access to dental care (11). In Bezerra et al.'s and Nomura et al.'s studies, an increase in the salivary urea concentration was reported in

periodontitis (13, 14). Hydrolysis of urea by bacterial urease enzymes produces ammonia and carbon dioxide ($CO_2$), which is an important way to increase pH in the oral cavity. Ammonia, which is potentially cytotoxic, increases the permeability of the epithelium to other antigenic and toxic substances and plays an essential role in the initiation of gingivitis (13).

## Conclusion

Drug addiction causes dry mouth and enhanced salivary urea concentration. Poor oral and dental hygiene and increase in chronic periodontitis are also observed in drug addicts, and chronic periodontitis causes a raise in salivary urea concentration. Hence, a reason for increased salivary urea concentration in drug addicts could be elevation in chronic periodontitis.

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