



The Effect of Systemic Corticosteroid Use on the pH and Viscosity of Saliva

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Received 2020 February 19; Revised 2020 March 28; Accepted 2020 March 28.

Abstract

Background: Systemic corticosteroid use is undeniable for many patients, and many require long-term use of such drugs. Corticosteroids have adverse and irreversible effects on all organs of the body. One of these complications that have not been studied fully is the drug effect on salivary gland function and the quantity and quality of saliva. Some of the many properties of saliva affected by these drugs are saliva pH and viscosity changes and, therefore, its effect on oral health.

Methods: This study was performed on 90 cumulative saliva samples containing three groups of corticosteroid users, including more than 15 mg/day, corticosteroid users less than 15 mg/day, and healthy and non-drug users. Each group contained 30 samples. The unstimulated cumulative saliva of volunteers was collected by spitting method for 5 minutes, and the pH of the samples were measured by digital pH meter, and the viscosity of the samples was calculated based on the comparison of the amount of movement of saliva in the capillary tube in millimeter per second with the control fluids. Statistical analysis was performed by Statistical Package for Social Sciences (SPSS V. 18) software and the analysis of variances (ANOVA), Tukey's multiple comparisons, or their non-parametric equivalents tests were used.

Results: The viscosity of saliva in patients with corticosteroid > 15 mg/day was higher than the healthy subjects ($P = 0.028$). Also, salivary pH in patients taking corticosteroid < 15mg/day was lower than healthy ones ($P = 0.017$). There was no significant relationship between gender with pH and salivary viscosity ($P = 0.933$).

Conclusions: Long-term consumption of corticosteroids reduces the pH of saliva and increases its viscosity. Therefore Corticosteroids can cause quantitative and qualitative changes in saliva. It also can affect oral and dental health. Hence, the oral health of people taking corticosteroids should be more noticed.

Keywords: Cumulative saliva, Salivary pH, Salivary Viscosity, Systemic Corticosteroid

1. Background

In the modern era and with the aging population, daily medication use is very common among individuals. One of these medications is corticosteroids that are used for allergies, autoimmune diseases, and inflammatory diseases (1). Long term consumption of corticosteroids has several complications, including adrenal gland suppression, fats distribution discrepancies, metabolic disorders, osteoporosis, hypertension, and many other complications (2).

As we know, to maintain oral health, the quantity, and quality of saliva most not be altered greatly.

The literature shows that systemic disease and medication can alter the properties of the secreted saliva (3). One of the most important properties of saliva is viscosity, which has a direct link to the protein content, inorganic

compounds, and mucous proteins in the saliva (4). Salivary pH is also an important element in oral health, so, alternation in the buffering capacity of saliva can affect oral health deeply. Among the several complications of corticosteroids, its effect on saliva has not been studied fully.

2. Objectives

Thus, this study aimed to evaluate the relationship between corticosteroid use with pH and viscosity of saliva.

3. Methods

This study was conducted on patients referred to Shahid Sadoughi Dermatology Clinic with pemphigus vulgaris, lichen planus, or mucous membrane pemphigoid,

who had been consuming prednisolone for at least three months.

The individuals with other systemic diseases, including renal, pulmonary, hepatic, and diabetic disease, as well as who were using other medications, were excluded from the study.

A total of 90 cumulative saliva samples were collected by using the spitting method. For this purpose, 30 saliva samples of patients who took systemic corticosteroid with doses more than 15 milligrams per day (> 15 mg/day) (5) and 30 saliva samples from patients who took corticosteroid with doses less than 15 milligrams per day (< 15 mg/day), along with 30 saliva samples taken from healthy individuals who were matched to the other two groups regarding their age and gender were collected.

The patients were asked to avoid drinking, eating, or smoking at least 90 minutes before sample collection. Then they were asked to swallow all of the saliva present in their mouth for 30 seconds and then discharged all of the cumulative saliva inside the mouth into a sterilized sampling container provided by the researcher.

Saliva sampling of all people was carried out at 9 - 11 a.m., since the volume of saliva may differ across different hours of the day (6).

The pH of the samples was measured by a digital pH meter device. The viscosity of samples was obtained based on comparing the movement of saliva in the calibrated capillary tube in terms of millimeters per seconds (mm/s) with control liquids. To measure the saliva movement in the capillary tube, the capillary tube was placed inside the container holding the saliva sample for ten seconds. The extent of saliva movement inside the capillary tube was measured in terms of mm. For all samples, the ten seconds was constant. To decrease the researcher error, this was done three times for each saliva sample, and the average was recorded.

The viscosity of control liquids, including glycerin and water at 25°C, is 1000 cp and 830 cp, respectively. In this study, the extent of the mobility of control liquids was calculated during the ten seconds in the capillary tube. The movement of water and glycerin in the capillary tube was 21 and six millimeters, respectively. They were then employed as control across all viscosity measurements for the studied samples.

The collected data were analyzed by the Statistical Package for Social Sciences (SPSS V. 18), and the analysis of variances (ANOVA) along with Tukey's multiple comparisons tests or their nonparametric equivalents were used.

Written informed consent was taken from the patients and healthy controls for participating in the study. The Research Ethics Committee of Shahid Sadoughi University of Medical Sciences approved this study with the ethics code of IR.SSU.REC.1395.177.

4. Results

In this study, 90 cumulative saliva samples were examined in terms of their viscosity and pH across three groups:

1. The subjects in the case group consuming systemic corticosteroid more than 15 mg/d.
2. The subjects in the control group 1 consuming systemic corticosteroid less than 15 mg/d.
3. Subjects in the control group 2, who consumed no medication (healthy individuals).

The mean saliva movement in the capillary tube in ten seconds is shown in Table 1. Therefore, it can be concluded that saliva viscosity in the two groups consuming corticosteroid (groups one and two) has increased, which means a higher saliva concentration ($P = 0.025$). Also, the mean pH of saliva is shown in Table 1. Accordingly, it can be concluded that the saliva pH diminished in the two groups consuming corticosteroid (groups one and two), suggesting acidification of saliva ($P = 0.02$) (Table 2). According to the obtained results, the mean movement of saliva in the capillary tube in terms of mm/10 seconds and pH had significant differences for some of the studied groups ($P < 0.05$). To investigate the significant groups, Tukey's paired comparison test was employed. According to the results (Table 2), the mean value of saliva mobility in the capillary tube was less in the first group than in the second group, and was lower in the second group than in the third group. Statistically, this difference was significant between the first group (< 15 mg/d) and the third group (healthy individuals) ($P = 0.028$). Also, the mean pH was lower in the first and second groups compared to the third group. This difference was significant between the second group (> 15 mg/d) and the third group (healthy individuals) ($P = 0.017$) (Table 2).

5. Discussion

Studies suggest that hormonal and metabolic changes, as well as the altered general health of the body, affect saliva properties. As the buffering and protective mechanisms of saliva are mostly provided through suitable pH and viscosity, some studies have been performed about the effect of different diseases including diabetes, hyper or hypothyroidism, hypertension, and autoimmune diseases on saliva properties (7).

With long term use of corticosteroids in the modern age for diseases that were not treated before, the side effects of this medication are seen much more (2). Due to the lack of studies investigating the effect of these medications on salivary glands and saliva properties, we performed this study on patients with pemphigus, mucous membranes pemphigoid, or lichen planus who were under systemic

Table 1. Comparison of the Mean and Standard Deviation of Salivary Movement in the Capillary Tube and Salivary pH in the Three Studied Groups^a

Dependent Variable, Group	No.	Mean	Std. Deviation	Lower Bound	Upper Bound
Salivary movement in the capillary tube (mm/10 s)					
Group 1: consuming systemic corticosteroid > 15 mg/d	24	10.88	1.17	10.38	11.37
Group 2: consuming systemic corticosteroid < 15 mg/d	26	11.08	1.14	10.61	11.54
Group 3: health individuals	30	11.68	1.06	11.29	12.08
Total	80	11.24	1.16	10.98	11.50
pH					
Group 1: consuming systemic corticosteroid > 15 mg/d	24	6.47	0.45	6.28	6.67
Group 2: consuming systemic corticosteroid < 15 mg/d	26	6.24	0.45	6.06	6.43
Group 3: health individuals	30	6.56	0.35	6.43	6.69
Total	80	6.43	0.43	6.33	6.53

^aP value < 0.05.**Table 2.** Comparison of the Two-Way Mean Difference for the Amounts of Saliva Movement in the Capillary Tube and pH in the Three Studied Groups^a

Dependent Variable	Group	Mean Difference	P Value	
Salivary movement in the capillary tube (mm/10 s)	Group 1: consuming systemic corticosteroid > 15 mg/d	2	-0.202	0.801
		3	-0.808	0.028
	Group 2: consuming systemic corticosteroid < 15 mg/d	1	0.202	0.801
		3	-0.606	0.116
	Group 3: health individuals	1	0.808	0.028
		2	0.606	0.116
pH	Group 1: consuming systemic corticosteroid > 15 mg/d	2	0.231	0.133
		3	-0.084	0.744
	Group 2: consuming systemic corticosteroid < 15 mg/d	1	-0.231	0.133
		3	-0.316	0.017
	Group 3: health individuals	1	0.084	0.744
		2	0.316	0.017

^aTukey test (P < 0.05).

corticosteroid treatment and their salivary pH and viscosity were measured. The results show that the pH and viscosity differed significantly in some of the studied groups.

The Tukey's test showed that the mean saliva pH differed significantly between the group consuming less than 15 mg/d corticosteroid (Group 2) and healthy group (Group 3) (P = 0.017). Also, the pH decreased, and the saliva was more acidic in both groups who consumed corticosteroids. It has been shown that in long term corticosteroid consumers, opportunistic infections such as Candida can also be involved in the development of acidic pH on the oral cavity in these individuals, resulting in a more compromised oral health (8).

The mean inter-group viscosity of the patients who consumed corticosteroid above 15 mg/d (Group 1) was sig-

nificantly different from that of the healthy group (Group 3) (P = 0.028). In addition, the viscosity increased in the group of patients consuming corticosteroid, suggesting that the saliva concentration of these patients has become higher compared to healthy individuals.

The results of this study were in line with the findings obtained by previous researchers. For example, the study by Ersin et al. in 2006 for examining oral and dental manifestations associated with pharmacotherapy, intensity, and duration of disease in young patients suffering from asthma concluded that disease conditions and pharmacotherapy cause diminished flow rate of saliva and pH (9). It can be stated that, in patients with asthma, and patients taking systemic corticosteroid treatment in the present study, reduction of pH and elevation of viscosity

is due to the use of corticosteroids as a long-term medications in both studied groups. This effect on saliva properties could be due to the underlying disease itself and the medication used to treat it.

Helenius et al. concluded that patients with connective tissue autoimmune disorders have a slower saliva flow rate (10). As with the present study, autoimmune disorders can cause elevated salivary viscosity in the patients. This reduction of saliva flow and increased viscosity can be attributed to the effect of autoimmune disease on the acinar structure of salivary glands. This means that having autoimmune diseases for a long time and with the formation of immune complexes and their precipitation in salivary glands can lead to diminished glandular function, reduced saliva flow, and increased viscosity regardless of the medication used by the patient.

In a study by Inger et al., the function and changes of salivary glands in patients with oral lichen planus was studied. They found that the extent of secretion of non-stimulatory saliva diminished across a large percentage of patients, though the pH and buffering capacity of saliva did not change significantly, which is not consistent with our study due to different study groups. This diminished saliva secretion can be attributed to the lichen planus disease itself. Accordingly, the results obtained from the present study can also be due to the effect of autoimmune disease on the structure of salivary glands in addition to the effect of drugs consumed, including systemic corticosteroids (11).

Different drugs have varying effects on the secretion of saliva from salivary glands. These include the diminished saliva flow rate (medications which have cholinergic and anticholinergic effects, antipsychotics, alpha- and beta-adrenergic drugs cause diminished saliva flow rate), increased saliva flow, pain in the salivary glands, changes in the morphology of salivary glands, and altered taste or smell in the mouth (12).

The drugs consumed daily by the patients have a different effect on salivary glands. Most of them result in the diminished function of glands, so corticosteroids are not an exception. Nevertheless, there are some contradictions regarding their effects. It can be stated that their effect on salivary glands is dose-dependent. For example, in the study by Izumi et al. on patients with Sjogren's disease, they found that steroid therapy with different doses in these patients not only failed to decrease the saliva flow, it also resulted in improvement of saliva flow in these patients, improving xerostomia. It seems that corticosteroids have both anti-inflammatory effects and inhibitory effects against the activity of T-cells, reducing the entrance of T-cells into parotid glands and inflammation in this salivary gland. Therefore, the gland can recover parts of its normal secretory function (13). However, return to the initial value

rarely occurs, as the primary autoimmune disease causes structural changes in the acini of salivary glands (14). On the other hand, in the present study, it was observed that the patients in the first group consuming more than 15 mg/d corticosteroid did not have impaired salivary properties compared to the group consuming corticosteroid with a lower dose. It can be concluded that the effects of corticosteroid on salivary glands may not be dose-dependent, and more consumption of corticosteroid does not necessarily lead to diminished saliva flow and alteration of other salivary properties.

In a study by Mohiti et al. in 2015 on the effect of the presence of antibodies in saliva, it was found that the pH and viscosity were higher in the group of patients with antithyroid antibodies. Due to the alkaline structure of antithyroid antibody proteins in the saliva, which can generate ammonium compounds after degradation, the saliva pH tends to become more alkaline. As the chance of getting autoimmune diseases grows in these patients compared to similar patients without the antibody, the presence of these proteins in saliva results in increased viscosity and diminished saliva function (15). Considering the study by Agha-Hosseini et al. in 2016 for investigating changes in saliva flow and its other properties in patients with Hashimoto, autoimmune diseases, including thyroid autoimmune diseases, can cause impaired function of salivary glands and the saliva (16). Also, in a study by Mohiti et al in 2016 on diabetic type two patients, it was demonstrated that saliva pH and viscosity differed between controlled and non-controlled diabetic patients suggesting that other systemic diseases can alter saliva properties as well as autoimmune diseases (7).

The nervous regulation for the secretion mechanism of salivary glands is controlled by sympathetic and parasympathetic nerves. Therefore, all drugs affecting the peripheral and central nervous system can also affect saliva secretion. As the secretions resulting from stimulation of both systems are different, and stimulation of either sympathetic or parasympathetic nervous system results in different secretions chemically and physically in saliva. For example, drugs with cholinergic as well as alpha and beta-adrenergic effects, lead to diminished saliva flow and increased viscosity (12). Therefore, it can be stated that systemic corticosteroids can also have a systemic effect on salivary glands in addition to their local effect on salivary glands. This systemic effect can change the saliva properties by influencing the autonomous nervous system.

Santos et al. evaluated the non-stimulatory saliva flow rate in teenagers with asthma who consumed inhaled corticosteroids. They found that there is a relationship between consuming inhaled corticosteroids and increased risk of dental decay and bacterial plaque in patients with asthma. However, the level of non-stimulatory saliva flow

is similar in both groups, suggesting that inhaled corticosteroid consumption does not affect saliva flow (17), which is not in line with our results. This is because, in the present study, we found that systemic corticosteroid causes diminished saliva flow. The cause of this difference may be attributed to the fact that in our study, the patients consumed systemic corticosteroid, whereas in Santos et al's research, asthmatic patients used inhaled corticosteroid locally. Furthermore, it can be stated that the damaging nature of the autoimmune disease itself (pemphigus, mucous membrane pemphigoid, and Lichen Planus) also affects salivary glands, causing the diminished function of these glands, thereby reducing saliva flow in these patients.

Paganini et al. studied the status of dental decay and properties of the stimulatory saliva among children and teenagers with asthma. They found that there is no significant relationship between the frequency of drug consumption ($P > 0.05$) as well as the type of drug ($P > 0.05$) with the saliva flow level. Furthermore, the buffering capacity of saliva is the same for both patient and healthy groups (18). These different results can be due to using non-stimulatory saliva samples in our study. To measure salivary properties, cumulative saliva is a better source than stimulatory saliva. This is because diminished saliva flow in non-stimulatory saliva is more common than stimulatory saliva, which was also observed in other studies. As non-stimulatory saliva is associated with xerostomia, and stimulatory saliva is mostly used to measure the function of salivary glands, and it does not have the necessary stability for studies dealing with examining qualitative and quantitative properties of saliva (19).

5.1. Conclusions

Long-term consumption of corticosteroid causes diminished saliva pH and increased viscosity. Therefore, corticosteroids cause qualitative and quantitative changes in the saliva, affecting oral and dental health. Considering the adverse effects of increased saliva viscosity on the oral and dental environment, various oral complications can occur observed in the patients who use corticosteroids. As we know, the pH of saliva, especially the pH of non-stimulatory saliva, is closely associated with the buffering capacity of the mouth and risk of decay. Accordingly, given the adverse effects of pH reduction on oral and dental health and its damaging effect on the quality of life, these effects should be examined more carefully in patients consuming systemic corticosteroids. Regular follow-up of oral health in these individuals should be taken into account. Many of adverse effects of systemic corticosteroids are taken into consideration when prescribing them. Evaluations are needed to reduce those adverse effects. Since the

adverse effect of these medications on saliva is not understood very well, no precise preventive measures are currently in place to prevent adverse effects on the oral cavity health. Our results demonstrate that corticosteroids can compromise the salivary function and oral health, leading to a severe decrease in the patients' quality of life. Hence, controlling these effects could be in the physicians' routine treatment plans while prescribing corticosteroids.

Footnotes

Authors' Contribution: Mitra Amooei wrote the article and did the fieldwork. Mohammad Ebrahimzadeh Ardakani provided the patients. Azra Mohiti provided the idea and helped in writing and sample gathering.

Conflict of Interests: The authors declared no conflict of interest.

Ethical Approval: IR.SSU.REC.1395.177.

Funding/Support: Shahid Sadoghi University of Medical Science funded this research.

Informed Consent: The subjects were given a written consent form and if participated in the study they signed the form.

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