Salivary Status in Patients Treated for Head and Neck Cancer

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Abstract

The objective of this study was to compare unstimulated salivary flow rate and residual salivary volume (the volume of saliva retained in the mouth after swallowing) in a group of 23 control subjects and a group of 25 patients who had received radiation treatment or had undergone removal of the salivary glands (or both) for head and neck cancer. As expected, the mean flow rate (± standard deviation) in the patient group was significantly less than that in the control group (0.07 ± 0.11 and 0.45 ± 0.27 mL/min, respectively). However, the mean residual volumes were not significantly different between the 2 groups (0.70 ± 0.28 and 0.82 ± 0.26 mL, respectively). The 25 patients were subdivided according to their self-reported assessment of the mouth as being not dry (3), somewhat dry (12) or very dry (10); mean residual volume of saliva was significantly lower, at 71% the level in control subjects, for the group with very dry mouth ($p < 0.02$). These results suggest that people who report that the mouth is dry may not have a complete lack of fluid in the mouth; rather, there may be localized areas of dryness, notably on the hard palate, where the salivary film is particularly thin and subject to fluid absorption or evaporation because of mouth breathing.

MeSH Key Words: *head & neck neoplasms/radiotherapy; salivary glands/radiation effects; xerostomia/etiology*

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Treatment of cancer of the head and neck region can result in permanent damage to the salivary glands. When the cancer is located in the salivary tissue, the gland is usually excised. However, more patients experience damage as a result of radiation therapy to an area that encompasses salivary tissue. One or more glands may be affected by such therapy, and the possibility of recovery depends on the radiation dosage sustained by the glands.

A variety of symptoms resulting from damage to the salivary glands have been recorded, including difficulty in speaking, chewing and swallowing, increased caries rates, candidiasis and difficulties with dentures. Individual tolerance of physical damage varies greatly, and factors such as the number of glands affected are also important in determining patient outcomes.

This study was designed to assess reported symptoms and actual salivary flow rates and volumes in patients who had been treated for head and neck cancer for comparison with an age- and sex-matched control group.

Materials and Methods

Twenty-five patients who had been treated for head and neck cancer at the Manitoba CancerCare Centre were enrolled, along with 23 control subjects who were matched as closely as possible for sex and age. The control subjects were screened to exclude anyone with medical problems that would affect saliva secretion, such as Sjögren's syndrome or medication use. The study was approved by the Health Research Ethics Board of the University of Manitoba and all participants gave informed consent. Both control subjects and patients were paid for their participation.

The participants were asked not to eat, drink or chew gum for at least 1 hour before saliva collection. At the time of sample collection, patients swallowed and then collected unstimulated whole saliva for 5 minutes (controls) or 10 minutes (patients) by drooling into a funnel placed in a graduated centrifuge tube. At the end of the collection period each participant spat into the funnel any saliva remaining in the mouth. The volume was recorded and the flow rate calculated. After an interval of at least 5 minutes,

Table 1 **Demographic characteristics of control participants and patients who had been treated for head and neck cancer**

Group	No. of subjects			Mean age (and range) (years)
	Total	Men	Women	
Controls	23	14	9	57.2 (41–77)
Patients	25	16	9	57.4 (42–75)

during which normal swallowing was permitted, the participants swallowed and then rinsed the mouth for about 5 seconds with about 5 mL of distilled water taken from a paper cup and then expectorated into a different paper cup. The paper cup that had contained the distilled water was weighed before and after the water was taken into the mouth to determine the precise volume used (V). The unstimulated saliva and the expectorate were assayed for potassium concentration (C_s and C_e, respectively) by atomic absorption spectroscopy,[1] and the residual volume of saliva (RV) was calculated as $RV = (V \times C_e)/(C_s - C_e)$, as described previously.[1]

The patient group also completed a questionnaire regarding the cause and duration of salivary damage and any symptoms they were experiencing. Patient records were checked to determine the treatment previously provided and the salivary glands that might have been affected by the treatment.

Results

The control participants and the patients were similar in age and sex ratio (**Table 1**). The questionnaire data allowed a breakdown of the patient group into 3 categories of xerostomia (**Table 2**): mouth not perceived as dry (3 patients), mouth perceived as somewhat dry (12) and mouth perceived as very dry (10). On a scale of 0 to 10, where 0 = very good appetite and 10 = no appetite, most patients (15) claimed to have a very good appetite (mean score 2.0). On a scale of 0 to 10, where 0 = no difficulty in swallowing and 10 = great difficulty in swallowing, only 6 patients reported no difficulty in swallowing. The mean swallowing scores for the patients whose mouths felt not dry, somewhat dry or very dry were 0.6, 2.3 and 4.5, respectively. No subjects in the control group reported a poor appetite or a dry mouth.

Of the 3 patients who reported no oral dryness, 2 had lost 1 gland only to surgery, whereas the other patient had had 2 glands exposed to radiation and may have experienced some recovery of the tissue. Of the 12 patients with a somewhat dry mouth, 5 had lost 1 gland and 6 had lost 2 glands; for the other patient, 4 glands had been in the radiation field. Of the 10 patients with a very dry mouth, 8 had been treated with external radiation as the primary management modality. The 2 other patients had wide surgical fields with subsequent high-dose radiation, including the area of 2 major salivary glands.

Table 2 **Treatments, salivary glands affected by treatment and self-reported degree of mouth dryness among 25 patients who had been treated for head and neck cancer**

	No. of patients
Treatment	
Gland removal only	2
Radiation only	12
Radiation plus gland removal	11
Salivary glands affected	
1 parotid	2
1 submandibular	5
1 parotid and 1 submandibular	3
2 submandibular	9
2 parotid and 2 submandibular	6
Self-reported dryness of mouth	
Not dry	3
Somewhat dry	12
Very dry	10

The flow rates of unstimulated whole saliva, residual saliva volumes and salivary potassium concentrations are presented in **Table 3**. The mean salivary potassium concentrations (± SD) in the 3 groups of patients who reported that their mouths were not dry, somewhat dry or very dry were 29.4 ± 8.2, 29.5 ± 10.7 and 23.9 ± 9.3 mmol/L, respectively. One-way analysis of variance showed no significant differences ($p > 0.05$) in potassium concentrations between the control subjects and the 3 patient subgroups. The method for estimating residual volume used the potassium concentration of each person's saliva. Although this method has not been validated for patients who have undergone therapy for head and neck cancer, there is no reason to believe that it would not be applicable to the patient groups in this study, given that the mean salivary potassium concentrations in these groups were not significantly different from that of the control group (**Table 3**).

The individual and mean unstimulated flow rates and residual saliva volumes for the control subjects and the 3 groups of patients are shown in **Figs. 1** and **2**, respectively. Analysis of variance and a Duncan new multiple-range test revealed significantly lower flow rates in the patient groups than the control group (**Fig. 1**; $p < 0.001$), but the differences among the 3 patient groups were not statistically significant ($p > 0.05$). When the residual volumes of the 3 patients who did not have a dry mouth were pooled with those for the control subjects, analysis of variance revealed significant differences between the controls and the other 2 patient groups. A Duncan new multiple-range test showed that the mean residual volume for patients whose

Table 3 **Unstimulated salivary flow rates, residual salivary volumes and salivary potassium concentrations for control participants and patients who had been treated for head and neck cancer[a]**

Group	No. of participants	Flow rate (mL/min)	Residual volume (mL)	K concentration (mmol/L)
Controls	23	0.45 ± 0.27	0.82 ± 0.26	23.9 ± 5.9
Patients	25	0.07 ± 0.11	0.70 ± 0.28	27.3 ± 9.9

[a]*Data are presented as mean ± standard deviation.*

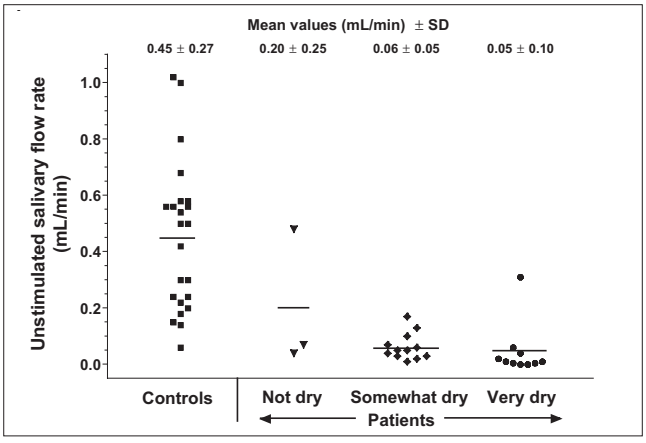

Figure 1: *Unstimulated salivary flow rates in control subjects and in 3 subgroups of patients. The horizontal lines indicate the mean values.*

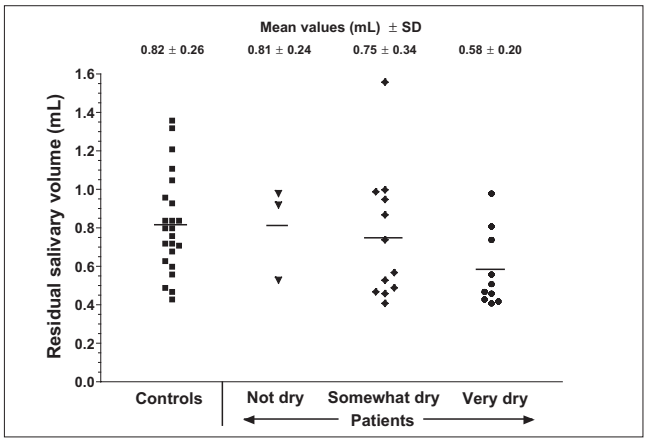

Figure 2: *Residual salivary volume in control subjects and in 3 subgroups of patients. The horizontal lines indicate the mean values.*

mouths felt somewhat dry was not significantly different from that for the control group or the patients whose mouths felt very dry. However, the mean residual volumes of the latter 2 groups were significantly different from each other, and the mean residual volume for patients who stated that their mouth felt very dry was only 71% of that for the control group (**Fig. 2;** $p < 0.02$).

Discussion

Xerostomia is the subjective sensation of dry mouth and should be distinguished from hyposalivation, the objective measurement of a low salivary flow rate.[2] The normal unstimulated salivary flow rate averages just over 0.3 mL/min, and a flow rate of < 0.1 mL/min is usually considered evidence of hyposalivation.[3]

A certain volume of saliva, termed the residual volume, is left in the mouth after swallowing; this has been reported to average 0.77 mL (range 0.38–1.73 mL) in healthy people with no salivary gland disorders.[1] The volume of saliva in the mouth is increased by in-flow of fresh saliva until swallowing is again induced, by which time the volume averages 1.07 mL (range 0.52–2.14 mL).[1] Thus, in healthy individuals, the volume of saliva in the mouth when food or drink is not being consumed fluctuates between about 0.77 and about 1.07 mL.

As well as by swallowing, salivary fluid can be lost by evaporation and by absorption through the oral mucosa.[4] In the absence of these 2 processes, individuals with even a very low salivary flow rate would not be expected to experience xerostomia. The residual volume would be the same and they would simply swallow less frequently, because with a low salivary flow rate it would take longer to reach the volume at which swallowing is triggered. However, if evaporation and mucosal fluid absorption are clinically significant factors in removal of saliva from the mouth, then people with xerostomia might be expected to have lower-than-normal residual volumes.

In this study, the very low unstimulated salivary flow rates in most of the patients (**Fig. 1**) were not unexpected, particularly for those who had received wide-field radiation treatment. The mean residual volume in the control subjects (0.82 mL) was very similar to the value of 0.77 mL reported previously.[1] It was only in the patients who stated that their mouths felt very dry that the mean residual salivary volume was significantly less, by 29%, than that in the control group (**Fig. 2**). In fact no patient had a residual volume less than 50% of the mean value in the control subjects.

The residual volume of saliva is normally present in the mouth as a thin film, averaging about 72 µm in thickness and separating the oral surfaces that would otherwise be in direct contact with each other.[5] Estimation of the mean film thickness in a particular individual necessitates knowledge of the residual volume and the surface area of the

mouth, and the latter was not available in this study. However, with a mean reduction of 29% in the residual volume for patients whose mouth felt very dry, a significant reduction in thickness of the salivary film would certainly be expected. When individual oral surfaces such as the tongue and palate are separated from each other, the mean retained film thickness after swallowing will average about 36 μm, half the total film thickness. However, DiSabato-Mordarski and Kleinberg[6] found marked site-specific variation in the thickness of the surface fluid layer, with mean values ranging from 70 μm on the posterior dorsum of the tongue to 10 μm on the hard palate. In addition, Wolff and Kleinberg[7] reported that in patients with dry mouth and unstimulated flow rates of less than 0.1 mL/min, the mean mucosal salivary film thickness was only 22.4 μm, the site specificity of the film thickness was maintained, and salivary films of < 10 μm on the hard palate were associated with complaints of dry mouth.

These previous studies, as well as the current data on residual salivary volume in xerostomic patients, suggest that people who report dryness of the mouth do not have a complete lack of fluid in their mouth but rather a reduced residual volume, which probably creates localized areas of dryness, especially on the hard palate, where dryness is readily perceived. A salivary film of less than 10 μm thickness on the hard palate would be particularly susceptible to evaporation if there is any mouth breathing. As discussed elsewhere in more detail,[4] saliva evaporation and mucosal fluid absorption appear to be important factors in the development of xerostomia. The findings of this study suggest that more severe symptoms (e.g., feelings of dryness and difficulty in eating, leading in turn to loss of appetite) occur when all 4 major salivary glands have been damaged. This situation is most likely to arise after external-beam wide-field radiation treatment.

For patients who have undergone hemifacial treatment, symptoms are less severe, and improvement over time suggests that adaptation occurs. Nevertheless, all patients who have undergone treatment for head and neck cancer require close dental monitoring in the early recovery stage, and patients with very dry mouth can be expected to encounter lifelong dental problems.

Pilocarpine, which stimulates salivary flow, is effective in relieving dry mouth in some patients. However, several clinical trials[8,9] have shown that pilocarpine has undesirable side effects, such as increased sweating, and may be contraindicated in persons with asthma or glaucoma. Nonpharmacologic ways for patients with dry mouth to alleviate the severity of symptoms include drinking plenty of water to maintain the maximum unstimulated salivary flow rate; avoiding mouth breathing to reduce evaporation of saliva; using a humidifier in the winter to increase the relative humidity, especially in the bedroom, as mouth breathing commonly occurs during sleep; avoiding tobacco, caffeine and alcohol, which have a drying or diuretic effect; chewing sugar-free gum or candy to stimulate salivary flow; and using water or saliva substitutes. It is recommended that patients with dry mouth use specially formulated dentifrice to help prevent dental caries. ◆

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