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Investigating the relationship between hyposalivation and mucosal wetness

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6 **Investigating the relationship between hyposalivation and mucosal**
7 **wetness**
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Title: Investigating the relationship between hyposalivation and mucosal wetness
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ABSTRACT

Mucosal wetness (MW) reflects the layer of residual saliva that covers the oral mucosal surfaces. Objectives: to determine MW at different oral mucosa sites and to investigate the relationship between MW, **Unstimulated Whole salivary flow rates (UWS)** and clinical oral dryness score (CODS). Method: 100 dry mouth patients and 50 healthy subjects. MW was sampled with filter paper strips at four sites inside the mouth; Anterior Hard Palate (AHP), Buccal mucosa (BUC), Anterior Tongue (AT), Lower Lip (LL) and measured with a micro-moisture meter. Reproducibility was assessed by repeated sampling and diurnal variation was examined. Results: MW in healthy subjects showed site variation and means \pm SD were; AHP ($11 \pm 11.7 \mu\text{m}$), BUC ($32 \pm 14.8 \mu\text{m}$), AT ($65 \pm 17.2 \mu\text{m}$), and LL ($25 \pm 13.5 \mu\text{m}$). Dry mouth patients with reduced UWS showed increased CODS. MW at all four sites was significantly reduced ($p < 0.05$) in dry mouth patients compared with the healthy subjects. Reproducibility of MW measurement using the intra-class correlation coefficient showed agreement at different visits within subject. MW of the AT showed a positive correlation with **UWS** ($p < 0.05$). Conclusion: MW is a reliable measure of oral dryness and had a positive correlation with UWS.

Key words: xerostomia, mucosal wetness, salivary secretion.

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1. INTRODUCTION

Dry mouth is most commonly caused by alterations in salivary gland function, dehydration, and cognitive alteration. Anxiety or depression and stress can be a cause of both subjective (xerostomia) (Fox *et al.*, 1985) and objective (hyposalivation) feelings of dry mouth (Bergdahl & Bergdahl, 2000). It is known that drugs are the most common cause of the dry mouth condition and complaints of xerostomia are a frequent side effect of many drugs (reviewed by Scully, 2003). Hyposalivation is especially known in those drugs used to treat anxiety, depression, and stress but is usually reversible. Salivary gland diseases associated with hyposalivation include primary or secondary Sjögren's syndrome, (Sjögren, 1933; Navazesh *et al.*, 1996; Price & Venables, 2002; Kassin & Moutsopoulos, 2004; Atkinson *et al.*, 2005), and Sialadenitis, Nodal Osteoarthritis, Xerostomia syndrome (SNOX; Kassimos *et al.*, 1995). Sjögren's syndrome affects approximately 0.4% of the population and has a male: female ratio of 1: 10 (Fox 2005). Other conditions and systemic diseases where dry mouth could be a relevant complaint include diabetes, thyroid disorders, connective tissue diseases and graft versus host disease (Atkinson *et al.*, 1994; Scully, 2003). The prevalence of xerostomia in the general population ranges between 10-20% in different published studies (Fox *et al.*, 1985; Pujol, 1998). Prevalence is greater in females and increases with increased medication (Nederfors, 1997; Schein *et al.*, 1999). In the elderly (60+ years) population prevalence is approximately 20% (Ben-Aryeh *et al.*, 1985; Nederfors *et al.*, 1997; Nayak *et al.*, 2004).

As with most symptoms, it has been difficult to quantify dry mouth complaints precisely and reproducibly. Investigators have used a variety of methods to assess oral dryness including: questionnaires, Visual Analog-Scales (VAS), simple functional measures such as observing if a tongue blade adheres to the buccal mucosa or if a patient can chew and swallow dried biscuits without water (Fox, 2005). Dry mouth can also be assessed by measuring the volume of residual saliva on mucosal surfaces using filter paper and micro-moisture meter

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3 and calculating thickness (DiSabato-Mordarski & Kleinberg, 1996; Won *et al.*,
4 2001; Lee *et al.* , 2002; and Eliasson *et al.* , 2005) and more recently mucosal
5 wetness devices have been used (Kakinoki *et al.*, 2004; Takahashi *et al.*, 2005).
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9 Collins & Dawes (1987) calculated the average surface area of the mouth to be
10 214.7 cm² and calculated the thickness of the salivary film in the mouth to be 44
11 μm, by dividing the mean residual saliva in the mouth by surface area. The
12 thickness of the salivary film is governed it part by the rheological properties of
13 saliva. It is apparent that the thickness and composition of the salivary film will
14 vary in different parts of the mouth depending upon the position in relation to
15 salivary glands.
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18 The current study aims are to determine the normal variation of Mucosal
19 Wetness (MW) at different oral mucosa sites and secondly to determine the
20 relationship between mucosal wetness, unstimulated whole mouth (UWS)
21 salivary flow rate, Clinical Oral Dryness Score (CODS).
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2. MATERIAL & METHOD

2.1. Study subjects

Samples were collected from a total of 100 patients with a mean age of 62 ± 11 years (range 22-82 years) attending Oral Medicine clinics at Guy's Hospital. They all complained of dry mouth and were divided into five groups according to their diagnosis: primary and secondary Sjögren's syndrome (SS1 & SS2); Drug induced Hyposalivation (DIH); non-Sjögren's but presence of sialadenitis, nodular osteoarthritis, xerostomia (SNOX); none of the above (NOS).

Fifty healthy age matched subjects who did not complain of dry mouth were selected as controls and had a mean age of 60 ± 15 years (range 22-83). They were recruited from members of staff and from a residential home for the elderly. All patients and participants were given an explanation and information sheet of the study and all gave their informed consent prior to the procedure. The study was performed under ethical approval of Guy's & St Thomas' Hospitals (Local) Research Committee. Ten healthy volunteers with mean age \pm SD is 35 ± 9.5 years (n=10) from the 50 controls were used to validate the reproducibility of mucosal wetness measurements.

2.2. Assessment of patients and collection of samples

a. Clinical oral dryness score

The signs of dryness in the mouth were examined using a scoring system (the Clinical Oral Dryness Score, CODS) which is composed of ten features: 1) Mirror sticks to buccal mucosa, 2) Mirror sticks to tongue, 3) Saliva frothy, 4) No saliva pooling in floor of mouth, 5) Tongue shows loss of papillae, 6) Altered gingival architecture/ smooth (especially anterior), 7) Glassy appearance to oral mucosa (especially palate), 8) Tongue lobulated / deeply fissured, 9) Cervical caries (more than two teeth), 10) Mucosal debris on palate (excluding under dentures). This technique was validated and the data presented elsewhere (Challacombe *et al*, 2008).

b. Unstimulated whole mouth (UWS) salivary flow

UWS was measured for 10 minutes and the subject was asked to spit into a pre-weighed vessel and not to swallow any saliva. UWS flow rate was calculated and expressed ml/min, taking 1g saliva =1ml.

c. Mucosal wetness (MW) measurements

The thickness of residual saliva (oral mucosal wetness) was measured in dry mouth patients (n =100) and aged matched healthy subjects (n = 50) using a filter paper strip (Oraflow Inc, USA) and micro-moisture meter (Periotron® 8000; Oraflow Inc, USA). A filter paper strip with a diameter 7.5 mm covering an area of 44 mm² was placed immediately on the mucosa after swallowing and was gently pressed flat with a finger of a gloved hand. After 10 sec the paper strip was transferred to the sensors of the micro-moisture meter. Four mucosal sites were measured; Anterior Hard palate (AHP), Buccal (BUC), Anterior Tongue (AT), and Lower Lip (LL) (Figure 1). A calibration curve previously constructed using volumes of UWS saliva was used to calculate the volumes (µl) of residual saliva collected from mucosal surfaces and then mucosal thickness (µm) was calculated. For the validation of mucosal wetness measurements 10 volunteer subjects were assessed over 10 visits, 5 morning (9-12 am) and 5 afternoon (2-5 pm) visits. **UWS** was also measured on each occasion.

2.3. Statistics

Statistical analysis was carried out using SPSS computer software version 15. An analysis of variance (ANOVA) and intra-class correlation coefficient (ICC) were used in order to validate the mucosal wetness measurement between and within subjects. For the purpose of analysis, dry mouth patients' data was grouped according to either diagnostic or to **UWS** flow rate groups. All groups were compared with age matched controls. Correlations between MW and UWS salivary flow rate were determined using Pearson (parametric) correlation analysis.

3. RESULTS

3.1. Validation of mucosal wetness measurement

Measurement of MW using filter paper strips and the micro-moisture meter showed good reproducibility. Intra-class correlation coefficients (ICC) for MW measurements from the same subjects (n =10) at different visits for AHP, BUC, AT and LL were 0.49, 0.48, 0.58, 0.53 respectively ($P < 0.02$ for all surfaces). No significant difference was found between morning and afternoon for oral mucosal wetness values for AHP, BUC, AT, and LL (Figure 2) and UWS salivary flow rate.

3.2. Mucosal wetness of dry mouth patients and controls

In dry mouth patients, the means \pm SD MW of all four surfaces were significantly reduced by approximately 50% compared with age-matched controls (Figure 3) but the trend was the same. That is AHP had the thinnest and AT tongue had the thickest MW amongst both patients and controls (Figure 3).

3.3. Correlation between UWS salivary flow and mucosal wetness

Overall **UWS** was significantly ($p < 0.05$) directly correlated with MW at all four sites. Pearson correlation coefficients for each site were $r = 0.22$ (AHP), $r = 0.18$ (BUC), $r = 0.4$ (AT), $r = 0.3$ (LL) respectively.

Subjects were grouped according to UWS salivary flow rate as follows: three patient groups with low flow (**0-0.1** ml/min, n = 57), moderate flow (0.1- 0.2 ml/min, n=25), high flow (>0.2 ml/min, n=18) and a fourth group of controls (mean flow = 0.45 ml/min, range 0.2-1.0 ml/min, n = 50). The group with lowest flow (< 0.1ml/min) showed a significant ($p < 0.05$) reduction in MW at all four sites (AHP, BUC, AT and LL) compared with controls (Figure 4a). The AHP, BUC and LL mucosal surfaces showed no significant differences between the low and high **UWS** patient groups whilst AT showed a significant ($p < 0.05$) reduction in MW between all UWS flow rate patient groups.

In addition, when a patient group (n = 14) with UWS flow rate > 0.2- 0.3 ml/min with a mean \pm SD (0.24 \pm 0.01 ml/min) was compared with a similar UWS flow

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3 rate (mean = 0.26 ± 0.01 ml/min, n=10) control group there was a significant ($p <$
4 0.05) reduction of MW at BUC and AT surfaces (Figure 4b). The AHP showed
5 no difference in wetness whilst the LL showed a significant difference only by a
6 one-tailed t-test ($p < 0.05$). The different flow rate groups of control subjects did
7 not show any statistically significant differences in MW of different oral surfaces.
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14 **3.4 The relationship between CODS and UWS salivary flow rate**

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17 There was inverse correlation between CODS and UWS salivary flow rate of dry
18 mouth patients and healthy subjects (aged matched controls). Even in dry mouth
19 patients with low CODS (1-3) has a significant ($p < 0.01$) reduction in there UWS
20 compared with the controls (Figure 5).
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4. DISCUSSION

The findings show that the mucosal wetness differ on oral surfaces; AHP, BUC, AT and LL. The trend of MW follows the same trend in healthy subjects as well as dry mouth patients. In both groups the wettest surface was AT, followed by BUC, LL then AHP. Our findings are similar to those in previous studies (DiSabato-Mordarski & Kleinberg, 1996; Won et al., 2001; Lee *et al.*, 2002). For AHP the values of at least 10 μm on the palate appeared necessary to avoid complaints of dry mouth (Wolff and Kleinberg, 1998). Previous studies suggest that the percentage contribution of different glandular salivas to the total saliva on different oral surfaces varies. Thus the percentage contribution of parotid saliva to the total saliva on different oral surfaces is not the same (Sas & Dawes, 1997). For example, the surface vestibular to the upper right molars appears to have a 50-60% contribution from parotid saliva whilst the surfaces vestibular or lingual to the lower incisors have only a 5-7% contribution. These differences in composition along with differing densities of minor salivary glands in the submucosae of oral surfaces will also presumably contribute in determining the wetness of the different surfaces measured in the present study.

Measurement of MW by filter paper sampling and micro-moisture meter measurement showed good reproducibility and consistency at all four sites. AT and BUC surfaces were very consistent sites while anterior hard palate showed variations between individuals. Previously it has been reported that unstimulated whole salivary flow rates show a circadian rhythm (Dawes, 1972). However, in the present study, neither mucosal wetness nor UWS flow rate showed a significant difference between samples taken in the morning (9-12) or in the afternoon (2-5). This suggests that mucosal wetness and UWS flow rate can be measured during the hours of normal clinics.

In dry mouth patients, MW at four sites (AHP, BUC, AT, LL) was significantly reduced by approximately 50% compared with controls. Other studies on

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3 subjects with oral dryness have reported similar findings (Wolff & Kleinberg,
4 1998; Won et al., 2001; Lee *et al.*, 2002; Eliasson *et al.*, 2005). In addition, the
5 distribution pattern of the MW on the four mucosal surfaces was the same in
6 patients and controls. i.e., the AT had the thickest and anterior AHP had the
7 thinnest layers of MW which is in agreement with Lee *et al.*, (2002). Whilst Wolff
8 and Kleinberg (1998) found that the posterior tongue had the thickest layer of
9 mucosal wetness. Although there appeared to be a decrease in wetness of the
10 AHP in the dry mouth patients compared to controls there was more variation
11 between individuals with means of $7 \pm 7.2 \mu\text{m}$ and $11 \pm 11.3 \mu\text{m}$ for patients and
12 controls respectively. In the present study all of the patient groups showed a
13 mean MW of $<10 \mu\text{m}$ but the normal control group showed a mean thickness of
14 only $11 \mu\text{m}$. Others have shown that there was no significant difference in palatal
15 saliva secretion between Sjögren's syndrome patients and healthy control
16 (Marton *et al.*, 2004).
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30 Oral dryness assessed using CODS was significantly increased in all patients
31 complaining of dry mouth. Subjects with lower UWS salivary flow rates showed
32 the highest CODS values. Since mucosal wetness of all surfaces (AHP, AT,
33 BUC, LL) showed a significant decrease with a reduction in UWS salivary flow
34 rate it can be inferred that CODS and mucosal wetness also show an inverse
35 relationship. Thus reduced MW is linked with increased CODS and clinical
36 features of oral dryness. A positive correlation between MW and UWS salivary
37 flow rate has also been previously reported (Wolff & Kleinberg 1998). The anterior
38 tongue showed a different pattern to the other surfaces with a 'stepped' decrease
39 in wetness that mirrored the decrease in UWS flow rate. An explanation for this
40 is that the tongue is the mobile part in the mouth and its fluid coating is derived
41 from all contributions to the whole mouth saliva volume.
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53 Patients with higher UWS flow rates ($>0.2-0.3 \text{ ml/min}$) still showed a significant
54 reduction in MW of the BUC and AT surfaces compared to controls with similar
55 UWS flow rates. Others have observed a decrease in labial mucosal wetness in
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3 subjects with a subjective complaint of dry mouth (Eliasson *et al* 1996;
4 Niedermeier *et al* 1989; Shern *et al* 1990). Therefore measuring mucosal
5 wetness is an important investigation in the management of dry mouth patients
6 since it is a direct measure of wetness that can discriminate between normal
7 subjects and dry mouth patients. Our findings suggested that the reduction in
8 mucosal wetness could be an early sign of dry mouth observed before UWS flow
9 rate is obviously reduced. However, this needs to be substantiated on a larger
10 numbers of samples. It may be that this group of patients (UWS > 0.2-0.3
11 ml/min) had a more than 50% reduction in their baseline UWS salivary flow rate
12 and consequently had reduced mucosal wetness. It has been reported that a
13 subject needs at least a 50% reduction in baseline resting (unstimulated) salivary
14 flow rate before dry mouth is experienced and this may coincide with a decrease
15 in oral mucosal wetness (Dawes, 1987; Wolff and Kleinberg, 1999). It may also
16 be that the patients with higher **UWS** flows but reduced mucosal wetness have
17 saliva with altered mucosal coating properties due to changes in composition.
18 There is evidence of reduced mucin sulphation in Sjögren's syndrome and this
19 may impact on surface coating properties or water retention (Allende *et al.*,
20 2008). Changed composition could result from a relatively greater reduction in
21 submandibular secretion which might reduce mucin levels in whole mouth saliva,
22 although results from a previous study do not support this idea (van den Berg *et*
23 *al.*, 2007). It would be interesting to examine the rheological and wetting
24 properties and mucin content of salivas from such patients. When control
25 subjects were divided into UWS flow rate groupings it is evident that there was
26 little difference in wetness of the oral surfaces with increase **UWS** flow rate. It
27 can be suggested that above a **UWS** flow rate of 0.2ml/ min there is no further
28 significant retention of residual fluid on oral surfaces.
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51 In conclusion, mucosal wetness can potentially be used as an index of oral
52 dryness. It is a reliable, simple method which can be used at the chair side to
53 measure oral dryness. There is a positive correlation between oral mucosal
54 wetness and **unstimulated salivary flow rate**.
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Legends Figures and tables

Figure 1. Periotron® 8000 micro-moisture meter, filter paper strip Sialopaper strip™ and four mucosal wetness surfaces inside the mouth, (a) Anterior hard palate (AHP), (b) Buccal (BUC), (c) Anterior Tongue (AT), (d) Lower Lip (LL) surfaces on a healthy subjects.

Figure 2. Mean values of mucosal wetness in μm from four oral surfaces (AHP, BUC, AT, LL) were measured from 10 subjects in the morning (am, light bars)) and the afternoon (pm, dark bars) and 5 visits for each time point of the same subjects. It showed there are no significant ($P < 0.05$) differences in wetness of all the four surfaces between morning and afternoon.

Keys: AHP= Anterior Hard Palate, BUC= Buccal, AT= Anterior Tongue, LL= Lower Lip. Error bars represent SEM.

Figure 3. Mean values of mucosal wetness at four surfaces (AHP, BUC, AT, LL) from dry mouth patients ($n=100$, dark bars) and healthy subjects as controls ($n=50$, light bars). There is a significant ($p < 0.05$) reduction in wetness on all mucosal sites from dry mouth patients compared with controls.

Keys: AHP= Anterior Hard Palate, BUC= Buccal, AT= Anterior Tongue, LL= Lower lip. *= statistically significant ($P < 0.05$). Error bars represent SEM

Figure 4. A relationship between mucosal wetness (MW) and unstimulated whole salivary flow rates (UWS) groups. (a) It shows 4 groups of UWS; 3 groups from dry mouth patients (3 groups; 0-0.1, > 0.1-0.2, > 0.2-0.3 ml/min) and controls (one group > 0.2-1.0 ml/min, $n=50$). All four sites; AHP, BUC, AT, LL in patients with different flow groups were significantly ($P < 0.01$) less than controls. AT shows a statistically significant ($P < 0.05$) increase in MW (μm) with increase in UWS salivary flow. (b) The patient group (UWS > 0.2-0.3 ml/min) with a mean of 0.24 ± 0.01 ml/min had a significant reduction in MW at BUC ($p < 0.001$), AT ($p < 0.05$) and were the same at AHP and LL compared with controls of a similar

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3 (UWS > 0.2-0.3 ml/min) flow rate with a mean of 0.26 ± 0.01 ml/min. **Keys:**
4 AHP= Anterior Hard Palate, BUC= Buccal, AT= Anterior Tongue, LL= Lower Lip.
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7 ¹ = statistically significant different between patients (3 groups) and controls. ² =
8 statistically significant between the three flow rate (0-0.1, > 0.1-0.2, > 0.2-0.3
9 ml/min) patients groups at the AT site only. ³ = BUC is statistically significant
10 different between patient group > 0.2-0.3 ml/min and controls (3 groups). ⁴ = AT
11 is statistically significant different between patient group > 0.2 and controls (3
12 groups). Error bars represent SEM.
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19 **Figure 5.** The relationship between Clinical Oral Dryness Score (CODS) and
20 Unstimulated Whole salivary flow rate (UWS) of dry mouth patients and healthy
21 subjects (aged matched controls). Patients in the lowest UWS flow rate group
22 have the highest CODS. The CODS was significantly ($p < 0.01$) increased in all
23 three patients groups compared with the controls.
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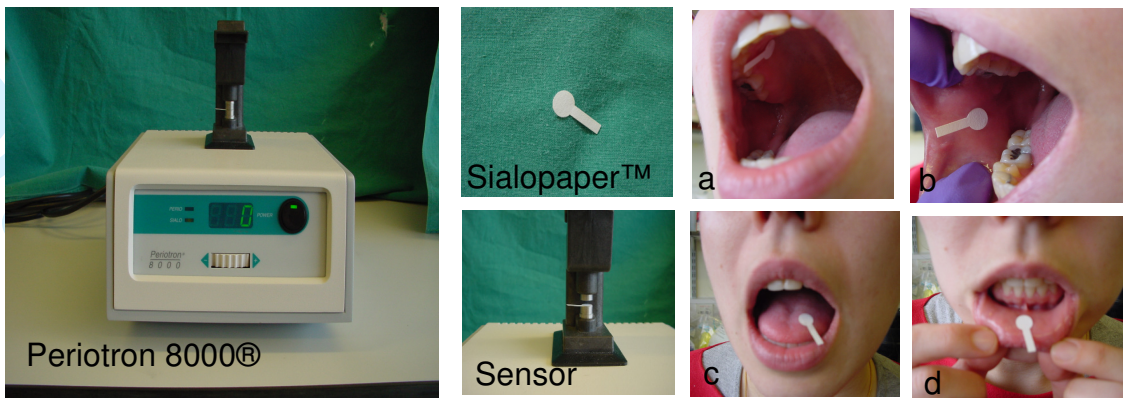
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28 **Keys:**

29 ¹ = significantly different in all three patients groups compared with the controls.

30 ² = statistically significant between patients group 0-0.1 and >0.1-0.2 ml/min.

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32 ³ = statistically significant between 0-0.1 and > 0.2-0.3 ml/min. Error bars
33 represent SEM.
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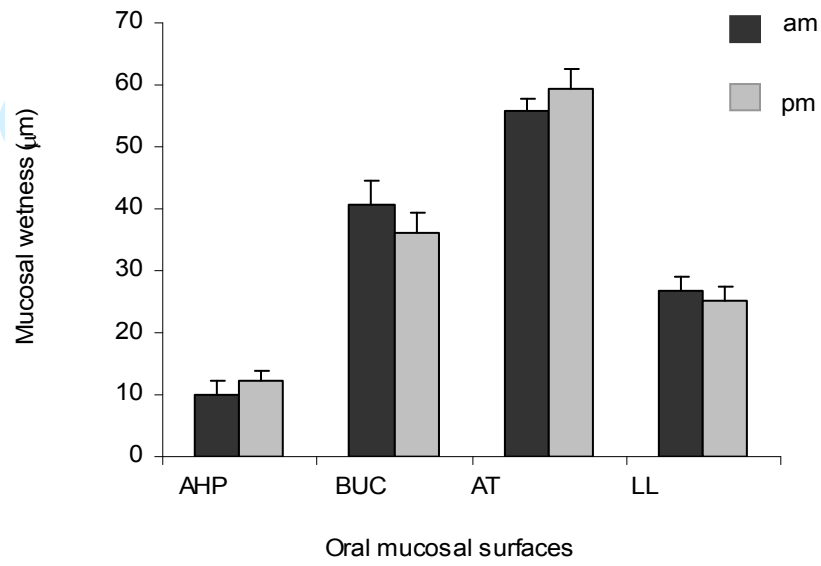


Figure2

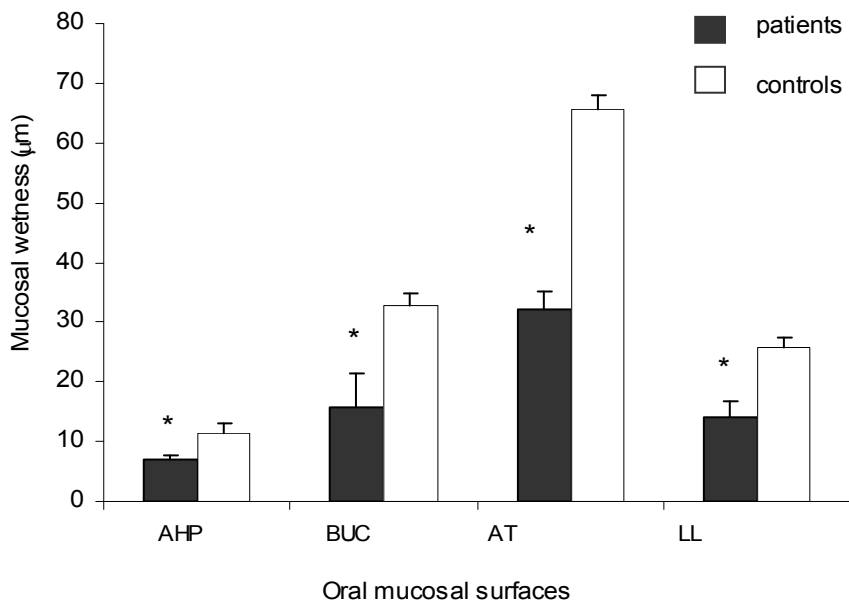
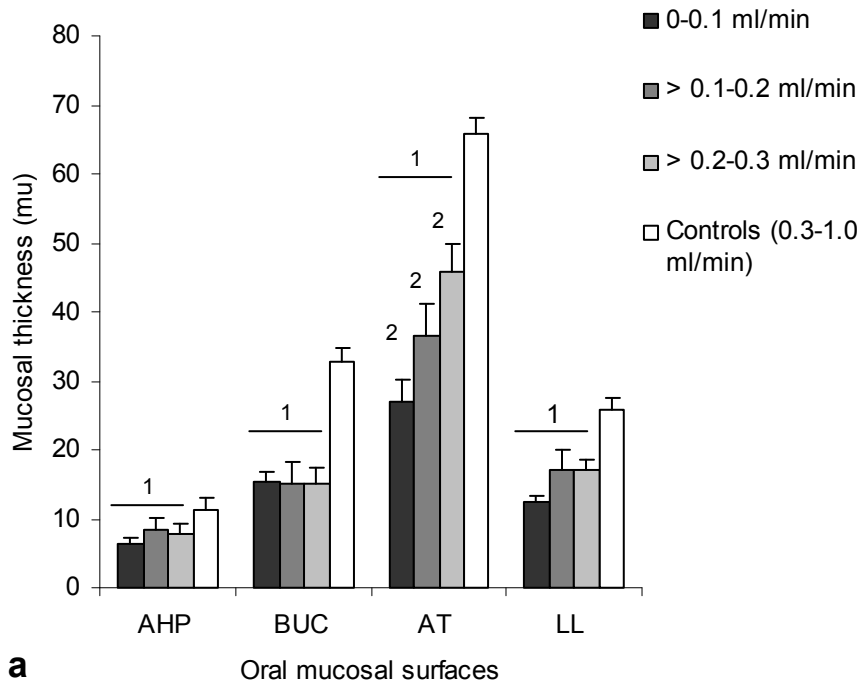


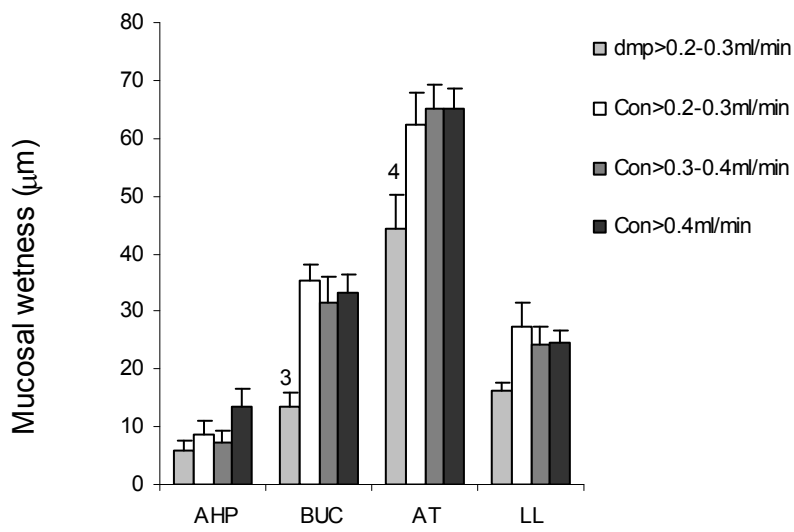
Figure3



a

Oral mucosal surfaces

Figure4a



b

Oral mucosal surfaces

Figure4b

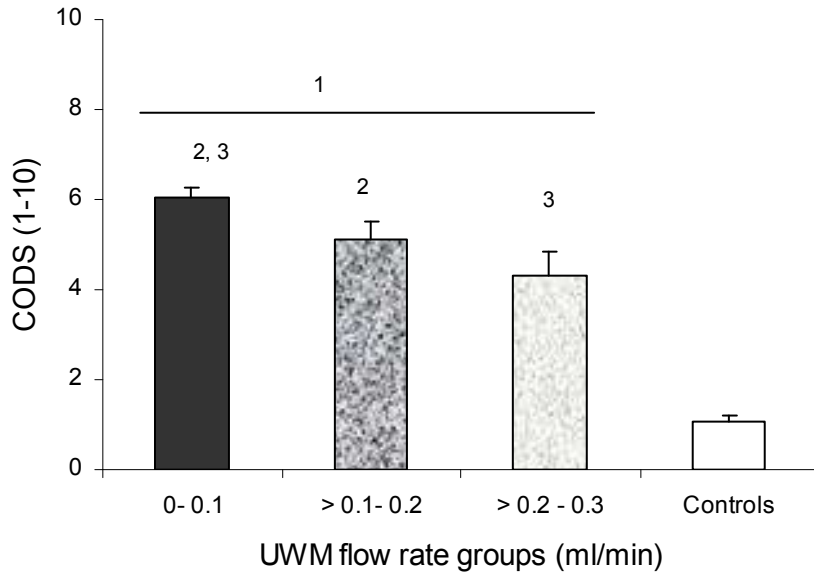


Figure5

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3 1-April-2010
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5 Dear Prof Baum
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8 Manuscript ODI-08-09-OM-1372.R2, entitled "Investigating
9 the relationship between hyposalivation and mucosal
10 wetness", which you submitted to Oral Diseases, has now
11 been change according to the reviewers' comments
12

13
14 Kind regards
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16
17 Yours sincerely,
18

19 Dr Samira Osailan
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23 Reviewers' Comments to Author:
24

25 Reviewer: 1
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27
28 The paper has further improved. However, the authors still
29 fail to be consistent with the nomenclature:
30

- 31 • Page 6, line 28/29: add years to 35±9.5.

32 **Response: The word years was added**

- 33 • Page 6, line 41/42: either use <0.1 ml/min (bold
34 first time it is use as was done for 0.1-0.2 and >0.2) or
35 0-0.1 and >0.1-0.2 and >0.2. Now still the manuscript and
36 figures are not similar. E.g., to what group belongs 0.1?

37 **Response: page 9 line 41/42, it is changed to 0-0.1**

- 38 • References: please apply the instructions to the
39 authors. Now the abbreviations of the journals are not
40 always correct, e.g. J Den Res in stead of J Dent Res,
41 Archs oral Biol in stead of Archs Oral Biol as well as that
42 dots are added to the abbreviations of the journals e.g. J.
43 Dent. Res. at some spot and not at other spots. Please
44 review carefully the instructions to the authors.

45 **Response: References were checked and changed according to
46 the reviewer's recommendation**

- 47 • Add the volume number and page number to the
48 reference of Challacombe in J Dent Res.

49 **Response: this is an abstract publication**

50 (http://iadr.confex.com/iadr/2008Toronto/techprogram/abstract_106439.htm)
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5 Reviewer: 2
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7 I strongly recommend not using the term Unstimulated Whole
8 Mouth salivary flow rate as it is very rare in the
9 literature. Using sometimes UWM salivary flow rate, on
10 other occasions UWM flow, on others UWM flow rate and still
11 on others solely UWM for the same concept is confusing. It
12 will be much simpler and straight forward to use
13 Unstimulated Whole Salivary Flow Rate and the abbreviation
14 UWS throughout the entire paper.
15

16 **Response: Unstimulated Whole Mouth salivary flow rate is**
17 **now change to Unstimulated Whole Salivary Flow Rate with**
18 **abbreviation UWS throughout the whole paper as recommended.**
19

20
21 Associate Editor:
22

23 Please use consistent nomenclature throughout the paper.
24 The AE urges strongly the use of unstimulated whole saliva
25 (UWS) or unstimulated whole salivary flow rate in the
26 manuscript.
27

28 **Response: UWS abbreviation is now used for unstimulated**
29 **whole salivary flow rate through out the whole paper**
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