

# Relationship of unstimulated saliva cortisol level with severity of oral dryness feeling in menopausal women

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## ABSTRACT

**Background:** Menopause may be associated with some adverse changes, such as oral dryness (OD) feeling. The exact mechanisms that mediate sensation of OD in menopausal women have not been firmly established. The purpose of this study was to assess the relationship of unstimulated whole saliva cortisol level with severity of OD feeling in menopausal women. **Methods:** A case control study was carried out on 70 selected menopausal women with/without OD feeling, conducted at the Clinic of Oral Medicine, Tehran University of Medical Sciences, Iran. The xerostomia inventory (XI) score was used as an index of OD feeling severity. Unstimulated whole saliva cortisol concentration was measured by ELISA. Statistical analysis of student's t-test and Spearman correlation was used.

**Results:** The mean cortisol concentration of saliva was significantly higher in women with OD feeling than the control. There was significant positive correlation between the XI score and the concentration of unstimulated whole saliva cortisol ( $r = 0.559$ ,  $p = 0.025$ ).

**Conclusions:** Unstimulated whole saliva cortisol is higher in menopausal women with OD feeling than in controls and this correlates with the severity of OD.

**Keywords:** Menopause, oral dryness feeling, cortisol, unstimulated saliva, flow rate.

**Abbreviations and acronyms:** ACTH = adrenocorticotrophic hormone; OD = oral dryness.

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## INTRODUCTION

Menopause may be associated with some adverse changes, such as xerostomia.<sup>1–5</sup> Xerostomia is a subjective feeling of oral dryness (OD), which should be defined by the objective measurement of saliva flow rate. A flow rate less than 0.1 ml/min for unstimulated whole saliva is considered hyposalivation or true OD.<sup>6,7</sup>

Studies on salivary changes in menopausal women have resulted in valuable findings about flow rates and composition of their saliva.<sup>3,7–10</sup> A high concentration of saliva calcium is one of the suspected factors that may contribute to the feeling of dryness in the oral cavity in spite of adequate secretion.<sup>9</sup> As menopause is related to a series of hormonal changes, higher salivary calcium levels can be attributed to the effects of these changes on calcium metabolism.

Cortisol, released by adrenal glands, is the main glucocorticoid in the human hormonal system and is responsible for some critical homeostatic tasks, such as vascular reactivity.<sup>11</sup> It can decrease the intestinal

absorption of calcium and inhibit its renal reabsorption.<sup>12,13</sup> It also enhances the transportation of calcium from extracellular fluids to the cells.<sup>14</sup>

After menopause, adrenal steroid secretion provides a low level of estradiol, in response to adrenocorticotrophic hormone (ACTH) secretion.<sup>15</sup> Cortisol is also released under the influence of hypophysial ACTH.

This study investigates the relationship of unstimulated whole saliva cortisol level with severity of OD feeling in menopausal women.

## SUBJECTS AND METHODS

### Subjects

The Ethics Committee of Tehran University of Medical Sciences (TUMS), Iran, approved the study protocol. Informed consent was obtained from all participants. Menopausal women who had not had a menstruation cycle for at least 12 months were asked to participate in this case control study conducted at the Clinic of Oral Medicine, TUMS. Smokers, obese patients (body mass

index  $\geq 30$  kg/m<sup>2</sup>), patients taking xerogenic medical agents, patients with certain systemic diseases (including Sjögren's syndrome), oral candidiasis or unfavourable oral health conditions such as poor oral hygiene, local inflammation and periodontal diseases (pocket depth more than 3 mm), and patients under corticosteroid or hormone replacement therapy, were excluded.

Based on these exclusion criteria, 70 women (age range 45–77 years) participated in the study. With the help of a questionnaire (Table 1)<sup>9</sup> asking about symptoms associated with xerostomia, 35 subjects (mean age 55.2, SD  $\pm$  7.1 years) who had at least one positive answer to the questionnaire entered the case group. Another 35 women who had no positive answers formed the control group (mean age 56.7, SD  $\pm$  8.2 years).

A second questionnaire was completed by both groups in order to assess the severity of OD feeling (Table 2).<sup>16</sup> Each answer was graded as follows: never = 1, hardly = 2, occasionally = 3, fairly often = 4, very often = 5. The scores from the responses were summed, resulting in a xerostomia inventory (XI) score for each individual. The range of XI score was 11 (11  $\times$  1) to 55 (11  $\times$  5).

### Saliva collection

Unstimulated whole saliva was collected under resting conditions in a quiet room (to reduce any stressful condition which may influence cortisol secretion) between 10 am and 12 pm (near the peak of serum cortisol level) at least 90 minutes after the last intake of food or drink. The participants were asked to swallow the saliva pooled in the mouth. Thereafter, whole unstimulated saliva was collected for about 5 minutes into a pre-weighed, dry, deionized and sterilized plastic tube. By subtracting the empty tube weight from the saliva filled one, saliva sample weight was determined to calculate the salivary flow rate. The flow rate was calculated in g/min, which is almost equivalent to ml/min.<sup>17</sup> The samples were clarified by centrifugation (2500 g, 10 minutes), and immediately stored at  $-20$  °C for later determination of cortisol.

**Table 1. Questionnaire used for selection of subjects with xerostomia (oral dryness feeling)**

1. Does your mouth feel dry when eating a meal?
2. Do you have difficulty swallowing any foods?
3. Do you need to sip liquids to aid in swallowing dry foods?
4. Does the amount of saliva in your mouth seem to be reduced most of the time?
5. Does your mouth feel dry at night or on waking?
6. Does your mouth feel dry during the daytime?
7. Do you chew gum or use candy to relieve oral dryness?
8. Do you usually wake up thirsty at night?
9. Do you have problems tasting food?
10. Does your tongue burn?

Response options: yes/no

**Table 2. The xerostomia inventory (XI)**

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- I sip liquids to help swallow food.
  - My mouth feels dry when eating a meal.
  - I get up at night to drink.
  - My mouth feels dry.
  - I have difficulty in eating dry foods.
  - I suck sweets or cough lozenges to relieve dry mouth.
  - I have difficulty swallowing certain foods.
  - The skin of my face feels dry.
  - My eyes feel dry.
  - My lips feel dry.
  - The inside of my nose feels dry.

Response options: never (scoring 1), hardly (2), occasionally (3), fairly often (4) and very often (5).

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### Analysis of saliva

Cortisol concentration was analysed by ELISA technology using commercially available kits (DRG Instruments GmbH, Germany).

### Statistical analysis

For statistical analysis, the data are presented as a mean  $\pm$  SEM. The two-tailed student's unpaired t-test was used. Spearman correlation analysis was used to identify any correlation between XI score and the salivary cortisol concentration;  $p < 0.05$  was considered statistically significant.

### RESULTS

Student's unpaired t-test showed that there was a significant difference between the case and control groups concerning unstimulated whole salivary flow rate. It was lower in the case ( $250 \pm 20$   $\mu$ l/min) than in the control group ( $350 \pm 30$   $\mu$ l/min;  $p < 0.01$ ).

The mean concentration of cortisol in saliva is shown in Fig 1. Student's t-test showed that the unstimulated salivary cortisol concentration was higher in the case group than in the control group.

Spearman correlation was performed to see if any relationship existed between severity of OD feeling (XI score) and salivary concentration of cortisol (Fig 2). There was significant positive correlation between XI score and saliva cortisol concentration ( $r = 0.559$ ,  $p = 0.025$ ).

### DISCUSSION

Oral dryness feeling, or xerostomia, is a complaint reported by a large number of menopausal women. The exact mechanisms that mediate feeling of OD in menopausal women have not been conclusively identified. In this study, the relationship between unstimulated saliva cortisol and OD feeling in menopausal women was investigated. We found that unstimulated

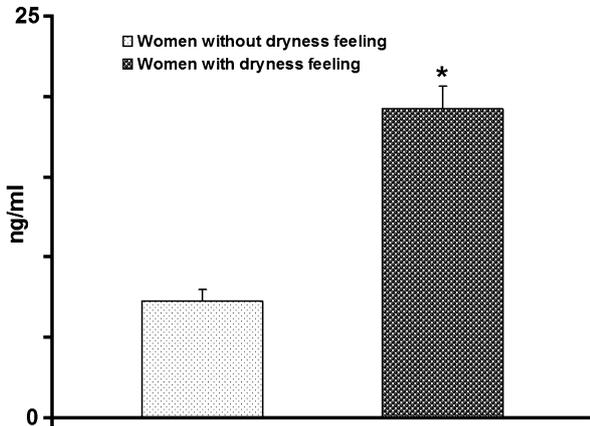


Fig 1. Unstimulated whole saliva cortisol concentration in menopausal women with/without OD feeling. \* $p < 0.05$ .

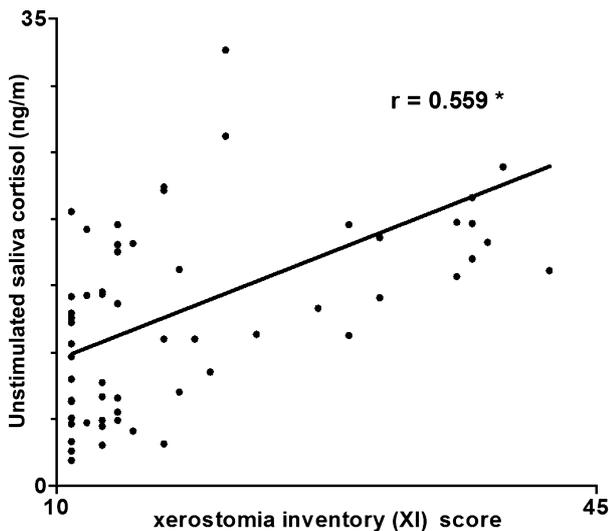


Fig 2. Relationship of xerostomia inventory (XI) score as an index of OD feeling severity with concentration of unstimulated whole saliva cortisol in menopausal women as determined by Spearman correlation coefficient. \* $p < 0.05$ .

ulated whole saliva cortisol level was significantly higher in menopausal women suffering from OD. Our data also indicated that there was a significant correlation between severity of OD feeling, and concentration of unstimulated saliva cortisol level in menopausal women.

It was shown that the subjective sensation of a dry mouth (xerostomia) is not necessarily associated with hyposalivation. Xerostomia can occur in menopausal women in spite of the existence of normal stimulated salivary flow rates.<sup>2,8,9,16,18,19</sup> We found the unstimulated salivary flow rate was significantly lower in menopausal women with OD feeling, compared with women without OD feeling, which was consistent with a study by Yalcin *et al.*<sup>5</sup> However, the measurements were higher than the lower limit of normal flow rate, and could not be considered as true hyposalivation.

In contrast, Rivera Gómez *et al.*<sup>20</sup> showed no significant difference in unstimulated saliva flow rate between menopausal women suffering xerostomia and healthy subjects. The sample size of that study ( $n = 15$ ) was small, and prior to taking the sample, the patient had a mouthwash of water in their study. It may be concluded that menopausal women with OD feeling suffer from reduced salivary flow rate in unstimulated condition.

Our data also showed that unstimulated whole saliva cortisol concentration was significantly higher in the case group, which is consistent with our previous study on stimulated saliva cortisol.<sup>19</sup> However, Rivera Gómez *et al.*<sup>20</sup> did not find statistically significant differences in the unstimulated salivary cortisol between subjects with OD feeling and the control. The rapid fall of ovarian estradiol secretion around menopause may lead to more demand for adrenal production of sexual hormones like androstenedione. This increased demand, besides the ageing induced reduction in the capacity of adrenal steroid synthesis (which is under the influence of ACTH), may result in higher secretion of serum ACTH, and eventually the cortisol released from adrenal glands.<sup>15</sup> Salivary cortisol level is shown to be a reliable indicator of serum cortisol concentration.<sup>21,22</sup> In our previous studies, we found menopausal women with OD feeling had lower serum 17- $\beta$ -estradiol and salivary progesterone than their healthy counterparts.<sup>16,23</sup> Therefore, it is reasonable that salivary cortisol levels should be higher in their salivary secretions too.

The salivary calcium and parathyroid hormone were higher in menopausal women with xerostomia than in the control group.<sup>9,18</sup> However, it has been shown that cortisol may have significant effects on overall calcium homeostasis, including PTH secretion, impairing intestinal absorption and renal re-absorption of calcium in premenopausal women; and pharmacological glucocorticoid therapy in humans is generally associated with hypercalciuria.<sup>12,13</sup> It seems that cortisol may have a role in excess salivary calcium in women suffering from OD feeling.

## CONCLUSIONS

Unstimulated salivary cortisol concentration is higher in menopausal women with subjective feeling of OD than in controls and this correlates with the severity of OD.

## REFERENCES

1. Asplund R, Aberg HE. Oral dryness, nocturia and the menopause. *Maturitas* 2005;50:86–90.
2. Frutos R, Rodriguez S, Miralles-Jorda L, Machuca G. Oral manifestations and dental treatment in menopause. *Med Oral* 2002;7:31–35.

3. Ship JA, Patton LL, Tylenda CA. An assessment of salivary function in healthy premenopausal and postmenopausal females. *J Gerontol* 1991;46:M11-15.
4. Sreebny LM. Saliva in health and disease: an appraisal and update. *Int Dent J* 2000;50:140-161.
5. Yalcin F, Gurgan S, Gurgan T. The effect of menopause, hormone replacement therapy (HRT), alendronate (ALN), and calcium supplements on saliva. *J Contemp Dent Pract* 2005;6:10-17.
6. Jorkjend L, Johansson A, Johansson AK, Bergenholtz A. Resting and stimulated whole salivary flow rates in Sjögren's syndrome patients over time: a diagnostic aid for subsidized dental care? *Acta Odontol Scand* 2004;62:264-268.
7. Ghezzi EM, Wagner-Lange LA, Schork MA, *et al.* Longitudinal influence of age, menopause, hormone replacement therapy, and other medications on parotid flow rates in healthy women. *J Gerontol A Biol Sci Med Sci* 2000;55:M34-42.
8. Ben Aryeh H, Gottlieb I, Ish-Shalom S, David A, Szargel H, Laufer D. Oral complaints related to menopause. *Maturitas* 1996;24:185-189.
9. Agha-Hosseini F, Mirzaii-Dizgah I, Moghaddam PP, Akrad ZT. Stimulated whole salivary flow rate and composition in menopausal women with oral dryness feeling. *Oral Dis* 2007;13:320-323.
10. Baum BJ. Evaluation of stimulated parotid saliva flow rate in different age groups. *J Dent Res* 1981;60:1292-1296.
11. Greenberg MS, Glick M, Ship JA. *Burket's Oral Medicine: Diagnosis and Treatment*. 11th edn. Hamilton, Ontario: BC Decker Inc, 2008:536-590.
12. Heshmati HM, Riggs BL, Burritt MF, McAlister CA, Wollan PC, Khosla S. Effects of the circadian variation in serum cortisol on markers of bone turnover and calcium homeostasis in normal postmenopausal women. *J Clin Endocrinol Metab* 1998;83:751-756.
13. Ferrari P. Cortisol and the renal handling of electrolytes: role in glucocorticoid-induced hypertension and bone disease. *Best Pract Res Clin Endocrinol Metab* 2003;17:575-589.
14. Glijer B, Peterfy C, Tenenhouse A. The effect of vitamin D deficiency on secretion of saliva by rat parotid gland in vivo. *J Physiol* 1985;363:323-334.
15. Al-Azzawi F, Palacios S. Hormonal changes during menopause. *Maturitas* 2009;63:135-137.
16. Agha-Hosseini F, Mirzaii-Dizgah I, Mansourian A, Khayamzadeh M. Relationship of stimulated saliva 17beta-estradiol and oral dryness feeling in menopause. *Maturitas* 2009;62:197-199.
17. Navazesh M. Methods for collecting saliva. *Ann N Y Acad Sci* 1993;94:72-77.
18. Agha-Hosseini F, Mirzaii-Dizgah I, Mansourian A, Zabihi-Akhtechi G. Serum and stimulated whole saliva parathyroid hormone in menopausal women with oral dry feeling. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:806-810.
19. Agha-Hosseini F, Mirzaii-Dizgah I, Mirjalili N. Relationship of stimulated whole saliva cortisol level with the severity of a feeling of dry mouth in menopausal women. *Gerodontology* 2010 Jul 15. [Epub ahead of print.] doi: 10.1111/j.1741-2358.2010.00403.x.
20. Rivera Gómez B, Hernández Vallejo G, Arriba de la Fuente L, López Cantor M, Díaz M, López Pintor RM. The relationship between the levels of salivary cortisol and the presence of xerostomia in menopausal women. A preliminary study. *Med Oral Patol Oral Cir Bucal* 2006;11:E407-412.
21. Vining RF, McGinley RA. The measurement of hormones in saliva: possibilities and pitfalls. *J Steroid Biochem* 1987;27:81-94.
22. Shigeyama C, Ansai T, Awano S, *et al.* Salivary levels of cortisol and chromogranin A in patients with dry mouth compared with age-matched controls. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;106:833-839.
23. Mirzaii-Dizgah I, Agha-Hosseini F. Stimulated and unstimulated saliva progesterone in menopausal women with oral dryness feeling. *Clin Oral Investig* 2010 Jul 21 [Epub ahead of print.] DOI 10.1007/s00784-010-0449-z.

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