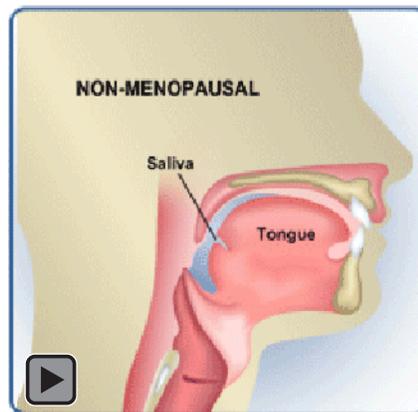


The Effect of Menopause, Hormone Replacement Therapy (HRT), Alendronate (ALN), and Calcium Supplements on Saliva

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Abstract

Purpose: In menopausal women many physiological changes take place, most of which are due to decreased estrogen production. It is known estrogen influences oral health in a number of ways and saliva undergoes variations depending upon the levels of this hormone.

Materials and Methods: The study was designed to evaluate the relationship of menopause, hormone replacement therapy (HRT), alendronate (ALN), and calcium supplements on salivary flow rate, saliva pH, and electrolytes. A group of a group of 14 osteoporotic women in menopause with an age average of 50.7 and 14 non-menopausal women with an age average of 42.4 and were selected as subjects. The oral status of the subjects was determined using the Community Periodontal Index of Treatment Needs (CPITN), the Decayed, Missing and Filled Teeth (DMFT) and the Decayed, Missing and Filled Surfaces (DMFS) indices.

The non-stimulated whole saliva samples were subsequently collected from the women in both the control and experimental groups and then analyzed biochemically. The women comprising the experimental group received HRT supplemented with ALN and calcium; saliva collecting and analyzing procedures were repeated at the third and sixth months of the treatment.

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Results: The most significant oral discomfort in women in the menopausal period was oral dryness, and this symptom was relieved after HRT with ALN and calcium supplements. The oral status of the non-menopausal women was better than the women in menopause. The salivary flow rate was decreased in the menopausal period and increased after HRT, ALN, and calcium supplementation. The saliva pH values were not affected by menopause and HRT with ALN and calcium supplementation. The level of Na⁺ was increased with menopause and did not change with HRT supplemented with ALN and calcium, whereas the K⁺ level decreased in the menopausal period and remained constant after HRT with ALN and calcium. The Cl⁻ level was not affected by menopause and the HRT supplemented with ALN and calcium. The Ca⁺⁺ level was not different in the two groups of women and did not change after HRT supplemented with ALN and calcium.

Conclusion: HRT with ALN and calcium supplementation affected some factors in saliva positively.

Keywords: Menopause, hormone replacement therapy (HRT), alendronate (ALN), saliva

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Introduction

Life expectancy for women increased significantly during the last decade, and most women spend one third of their lives after menopause. Menopause is the permanent cessation of menstruation and ovarian function characterized by lack of estrogen production. Estrogen deficiency may cause several problems such as hot flashes, sweating, osteoporosis, cardiovascular diseases, cognitive changes, urogenital infections, skin changes, etc. which may be corrected by the administration of estrogens and progestins - Hormone Replacement Therapy (HRT).¹⁻³

Recently, coadministration of HRT and bisphosphonates has been found to give more favorable results than with HRT or bisphosphonates given alone to menopausal women with established osteoporosis.^{4,5}

Bisphosphonate Alendronate (ALN) was found to be effective in the complex treatment of periodontal diseases, alveolar bone loss, and osteoporosis.⁴⁻⁷ A number of studies have been published on the influence of menopause on oral health.⁸⁻¹⁶ However, there is little information on the effect of menopause and HRT on saliva.¹⁷⁻²³

As saliva is essential for the maintenance of oral health and the number of women receiving HRT is increasing, it is important to access the

extent to which menopause and HRT affect saliva. Thus, the purpose of this study was to evaluate the relationship of menopause, HRT, ALN, and calcium supplementation on salivary flow rate, pH, and electrolytes of osteoporotic menopausal women.

Methods and Materials

The study was carried out on patients who spontaneously attended the menopause clinic at Hacettepe University Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey. The women who agreed to participate had routine gynecological examinations and tests. After the result of all the analysis, 14 voluntary osteoporotic women in the menopausal state [Bone Mineral Density (BMD) score less than -2.5 g/cm²] who had the following features were chosen for the study:

- Over 50 years of age (mean: 50.78 ± 4.3, range 42-57)
- No systemic disease
- Did not use any medicine on a regular basis
- No prior hormone treatment
- Had not menstruated for more than six months
- Had serum FSH levels >40 IU/ L and serum estradiol levels <20 pg/mL
- Non smoker
- Had at least ten teeth in their mouth

The control group consisted of 14 volunteer women aged over 40 (mean: 42.86 ± 3.18 , range 40-48), who had no systemic disease requiring regular use of medicines, had serum FSH levels < 12 IU/L, and had regular ovulatory menstrual cycles, and were non smokers.

Body Mass Index (BMI) values of all women in the test and control group were less than 25 kg/m^2 .^{2,5}

After obtaining detailed histories from all the subjects concerning dietary regimens and oral hygiene habits, they each underwent a dental examination. Their oral status was determined by Community Periodontal Index of Treatment Needs (CPITN) and Decayed, Missing and Filled Teeth (DMFT) and Decayed, Missing and Filled Surfaces (DMFS) indices on the basis of World Health Organization (WHO) criteria.²⁴ Unstimulated whole saliva was collected under standard conditions²⁵, between 8:30 and 10:30 a.m., at least 1 hour after breakfast. Unstimulated saliva was collected when the participant was positioned leaning slightly forward. After clearing the mouth by swallowing, saliva was drooled for 10 min into a glass centrifuge tube graded in 0.1 mL increments up to 10 mL. In rare cases the collection time was reduced or extended (range 5-15 min). Salivary flow rate was determined as mL/min.

Immediately after saliva collection, pH was determined electrometrically (IL test, Instrumentation Laboratory Company, Lexington MA, USA); Na^+ , K^+ , and Cl^- levels were determined by auto analyzer (Boehringer Mannheim Hitachi 911, Deutschland) using an ion-selective electrolyte method. The Ca^{++} level was obtained by use of an electrolyte analyzer (AVL list GmbH Medizintechnik 8020 Graz, Austria).

The women comprising the experimental group received continuous HRT as follows: Premarin (Conjugated estrogens 0.625 mg, Wyett, Istanbul, Turkey) and Farlutal (Medroxy progesterone acetate 5 mg, Carlo Erba, Deva, Istanbul, Turkey). Since all the patients



were osteoporotic, Fosamax (Alendronate 10 mg, Merck Sharp & Dohme, Istanbul, Turkey), Calcium Sandoz Forte (2.94 gr of calcium lactate and gluconate, and 300 mg of calcium carbonate (Novartis, Istanbul, Turkey) were added to HRT as 1 tablet/day. Saliva collection and analysis procedures were repeated 3 and 6 months after the beginning of HRT.

Statistical Analysis

The data obtained were analyzed by the Mann Whitney U Test, Friedman two-way Anova, Wilcoxon Matched Pairs-Signed Ranks tests, Spearman Correlation Coefficient, and descriptive statistics.

Results

Table 1 shows the CPITN periodontal and DMFT and DMFS caries index values. CPITN values were higher in the menopausal women ($U=15.5$, $p=0.0001$). DMFT ($U=51.4$, $p=0.031$) and DMFS ($U=51.4$, $p=0.035$) indices were also higher in menopausal women.

Oral discomfort related to menopause is shown in Table 2. The most significant oral symptom found in the menopausal women was oral dryness (78.17 %), and this symptom was relieved in some of the women after HRT.

Table 3 shows the mean salivary flow rate, pH, Na^+ , K^+ , Cl^- , and Ca^{++} values of the control group and menopausal women. Flow rate was significantly higher ($U=23.5$, $p=0.0004$) in the control group than in the menopausal women. The rate increased ($\chi^2=7.000$, $p=0.03$) from baseline during HRT in menopausal women. No significant difference was found in pH values ($U=91$, $p=0.75$) in the control group and the menopausal women. The Na^+ level was significantly higher in the menopausal women ($U=54$, $p=0.048$) and did not change with HRT ($\chi^2=1.71$, $p=0.42$). The K^+ in the saliva was lower in the menopausal women ($U=44$, $p=0.013$), and HRT did not affect the potassium level of saliva ($\chi^2=2.25$, $p=0.32$). No significant difference was found between the Cl^- values of menopausal women and the women in the control group ($U=84.5$, $p=0.53$). Also, there was no statistically significant difference between the values before HRT and after 3 or 6 months use of HRT ($\chi^2=3.46$, $p=0.17$). There was no significant

Table 1. CPITN, DMFT, and DMFS values of the control and menopause groups.

		CONTROL GROUP (n=14)	MENOPAUSE GROUP (n=14)
CPITN	Mean ± s.d*	0.81 ± 0.32	1.63 ± 0.47
	min.-max.**	0.33-1.33	0.66-2.50
	median	0.83	1.66
DMFT	Mean ± s.d*	8.21 ± 3.75	10.86 ± 3.11
	min.-max.**	4.00-17.00	6.00-16.00
	median	7.00	11.00
DMFS	Mean ± s.d*	26.36 ± 12.31	39.36 ± 17.23
	min.-max.**	10.00-48.00	12.00-58.00
	median	25.50	41.50

*s.d., standard deviation

**min.-max., minimum value-maximum value.

Table 2. Oral discomfort related to menopause.

SYMPTOMS	CONTROL GROUP (n=14)		MENOPAUSE GROUP (n=14)					
	No	%	Before Starting HRT (Baseline)		3 Months after HRT		6 Months after HRT	
			No	%	No	%	No	%
Oral dryness	-	-	11	78.57	9	64.28	6	42.85
Bad taste	-	-	2	14.28	2	14.28	1	7.14
Burning Taste	-	-	4	28.57	3	21.42	1	7.14
Halitosis	2	14.28	4	28.57	3	21.42	1	7.14

Table 3. Saliva flow rate, pH, and composition of the control and menopause groups.

		CONTROL GROUP (n=14)	MENOPAUSE GROUP (n=14)		
			Before starting HRT (Baseline)	3 months after HRT	6 months after HRT
Flow rate mL/min	Mean ± s.d*	0.28 ± 0.64	0.18 ± 0.05	0.20 ± 0.05	0.22 ± 0.06
	min-max**	0.20-0.43	0.12-0.30	0.15-0.30	0.15-0.30
	median	0.30	0.17	0.20	0.20
pH	Mean ± s.d*	6.95 ± 0.25	6.96 ± 0.13	6.99 ± 0.23	6.99 ± 0.17
	min-max**	6.39-7.34	6.75-7.25	6.66-7.50	6.80-7.30
	median	7.01	6.99	6.95	6.97
Na ⁺ mEq/l	Mean ± s.d*	9.92 ± 4.89	14.14 ± 5.48	13.14 ± 3.08	14.21 ± 3.68
	min-max**	4.00-18.00	6.00-27.00	7.00-18.00	8.00-19.00
	median	8.00	13.50	14.00	14.5
K ⁺ mEq/l	Mean ± s.d*	28.32 ± 4.40	22.92 ± 7.48	25.75 ± 8.79	23.88 ± 6.85
	min-max**	17.50-34.40	6.90-38.20	6.80-38.00	8.20-32.00
	median	28.85	23.00	27.45	24.95
Cl ⁻ mEq/l	Mean ± s.d*	19.14 ± 3.82	20.14 ± 11.99	17.71 ± 7.29	21.78 ± 6.48
	min-max**	11.00-26.00	2.00-49.00	4.00-31.00	8.00-30.00
	median	18.00	17.50	18.50	22.50
Ca ⁺⁺ mEq/l	Mean ± s.d*	1.17 ± 0.45	1.20 ± 0.21	1.34 ± 0.33	1.38 ± 0.48
	min-max**	0.58-1.89	0.80-1.60	1.00-2.20	0.83-2.60
	median	1.02	1.18	1.27	1.20

*s.d., standard deviation

**min.-max., minimum value-maximum value

difference in the Ca^{++} levels of the groups ($U=83$, $p=0.49$). The Ca^{++} level was also not influenced by HRT ($\chi^2=1.75$, $p=0.42$).

Discussion

Menopause is accompanied by a number of physical changes, some of which occur in the oral cavity.² Unfortunately, the study of menopause has received only limited attention mostly focused on gingival and mucosal discomfort during and after menopause.^{8, 10, 11, 13-16, 26} Only a few studies have been published on menopause and its treatment of HRT on salivary secretion; their results are variable.^{17, 18, 20-23}

In this study the most significant oral symptom found in the menopausal women was the feeling of oral dryness, and this symptom was relieved with the use of HRT. Oral dryness might be due to undetermined qualitative changes in the salivary composition, an unbalance between the various salivary glands, or changes in the mucosal sensory receptors. The high prevalence of oral discomfort in women at menopause was also reported by Ferguson et al.⁹ and Wardrop et al.²⁷ These complaints might be due to the hormonal alterations taking place at menopause causing vasomotor, neurological, and psychological changes.

Wardrop et al.²⁷ and also Forabosco et al.²⁸ also reported menopausal women with oral discomfort were relieved of symptoms after systemic HRT.

A few studies have been published about the oral status of menopausal women. Ben Aryeh et al.¹⁷ and Laine and Virtanen²⁰ found no statistical changes in periodontal conditions between menopausal and non-menopausal women by using the Gingival Index. In this study, by using CPITN, the periodontal status of menopausal women was found to be worse than the control group. The same authors¹⁷ also examined the general health of the teeth (DMF) and reported no difference between the groups. Laine and Virtanen²⁰ examined the oral status of menopausal and non menopausal women according to WHO criteria and reported lower DMFT values in non-menopausal women. In this study DMFT and DMFS values were found to be higher in the menopausal women.

In the literature the data on the effect of menopause on salivary flow rate are confusing. Increased, decreased, or no changes of salivary flow rate have been reported.^{17, 18, 20, 21-23} Using the unstimulated flow rate, which was found the most reliable method for the measurement of hypo salivation²⁵, we found salivary flow rate was significantly lower in the menopausal women in comparison with the non-menopausal women. HRT, ALN, and calcium supplements increased the salivary flow rate. Although in most of the studies stimulated saliva was used, in this study unstimulated saliva was preferred. Saliva collected without any masticatory or gustatory stimulus just by passive drooling into a cylinder is a more reliable indicator of reduced salivary flow rate and hyposalivation than the stimulated saliva.²⁵

Kullander and Sonesson¹⁹ and Laine and Virtanen²⁰ reported lower secretion rates in menopausal women than in menstruating women.

Ship et al.²² and Ben Aryeh et al.¹⁷, however, found the salivary flow rate did not significantly change during menopause.

Hietala et al.¹⁸, Laine and Virtanen²⁰, Virtanen et al.²³, and Sewon et al.²¹ found menopausal women receiving HRT showed higher saliva flow rates than untreated controls.

In this study salivary flow rate was significantly lower in the menopausal women but was increased by using HRT. It can be concluded estrogen treatment has a beneficial effect on salivary flow rate.

However, Ship et al.²² found no difference in flow rates between menopausal women receiving HRT and not receiving HRT, but they used lower dosages of estrogens. Estrogens vary greatly in their biological activities, which partly may explain the conflicting results.

No significant difference was found in pH values between the menopausal women or untreated control group in this study. This agrees with earlier observations by Laine and Virtanen²⁰ but disagrees with Sewon et al.²¹ who showed pH values increased during HRT.

Sodium, potassium, and chlorine are the most important ions for maintaining the ionic strength of saliva. Hormonal changes may also affect the composition of saliva.²³ In this study the concentration of potassium was decreased in menopausal women, whereas, the sodium concentration was significantly higher. No significant difference was found between the chlorine values of the menopausal women and the women in control group.

Sewon et al.²¹ also found increased sodium concentration, while no change was observed in the potassium concentration in the menopausal women having HRT.

Ben Aryeh et al.¹⁷ found no statistical difference between the levels of sodium and potassium in the menopausal and healthy women.

Among the electrolytes of whole saliva, the concentration of salivary calcium may be associated with both dental and periodontal health. Sewon et al.²¹ reported decreased calcium concentration in the menopausal women getting HRT, and they concluded this may indicate the individual salivary calcium concentration is modified and/or regulated by factors other than salivary flow. Such a factor could be the amount of salivary protein, which

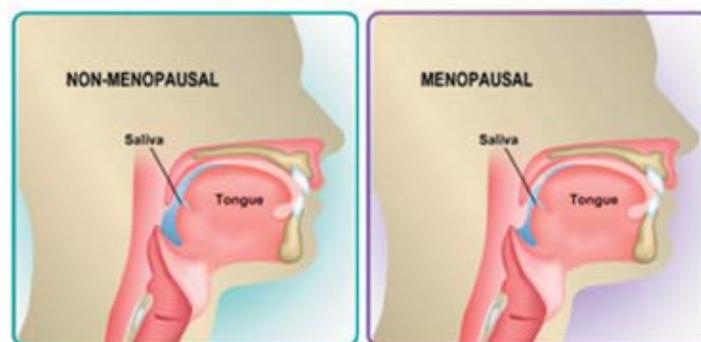
is known to form complexes with calcium and, hence, can cause changes in the amount of soluble calcium.

In this study the calcium concentrations did not show any significant difference between the menopausal women and the controls. Also, HRT did not make any difference. This may be due to the calcium supplement given in HRT to the menopausal women.

In the literature no data showing an effect of ALN on saliva was found. However, Povoroznjuk and Mazur⁷ reported daily administration of ALN with calcium for 3-4 months was effective in the management of patients with periodontal diseases. Mazur and Povoroznjuk⁶ also showed the efficiency of ALN in the treatment of patients with advanced alveolar bone loss.

Conclusion

This study was undertaken to establish a correlation between menopause, HRT (supplemented with ALN and calcium), and some salivary components. The effects of changes in salivary components induced by HRT with ALN and calcium on saliva remains to be determined. When diagnostic tests based on saliva are used in clinical practice, the influence of HRT and ALN should not be ignored.



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