

Is there a relationship between olfactory dysfunction and duration of menopause?

Fatma Atalay¹, Zeynep Yavuz²,
Ayhan Kars³, Murat Yaşar¹

¹ Kastamonu University Faculty of Medicine, Department of Otorhinolaryngology, Head and Neck Surgery, Kastamonu, Turkey; ² Hitit University Faculty of Medicine, Department of Biostatistics, Çorum, Turkey; ³ Erzincan Binali Yıldırım University Faculty of Medicine, Department of Otorhinolaryngology, Head and Neck Surgery, Erzincan, Turkey

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Correspondence

Ayhan Kars
E-mail: drakars25@hotmail.com

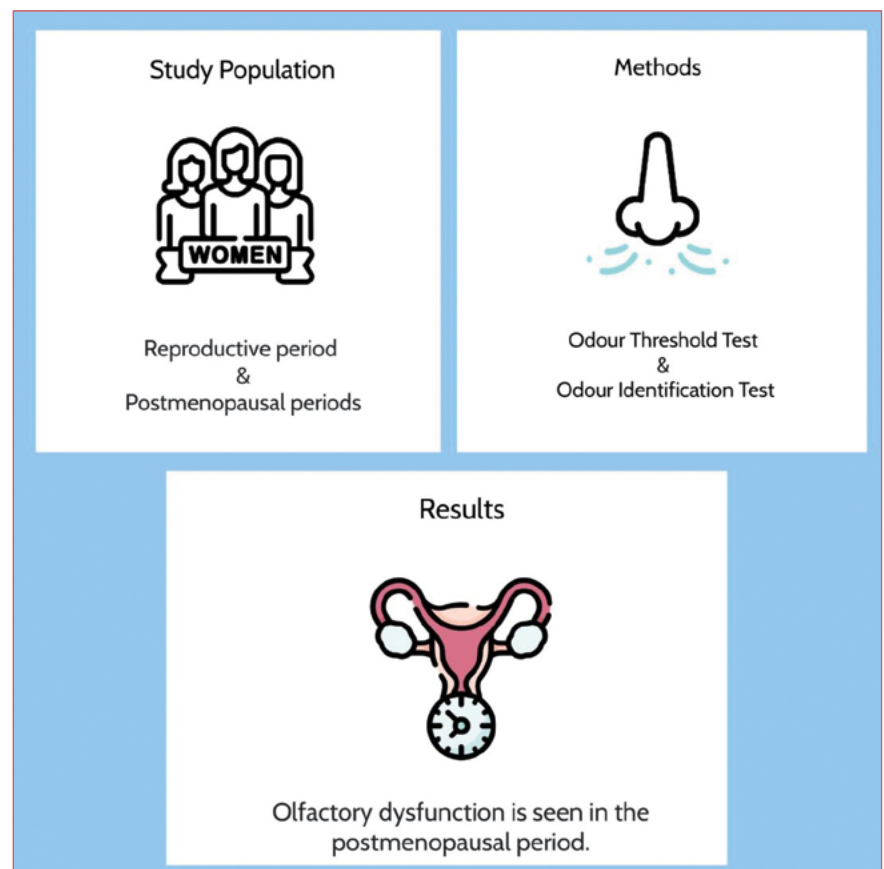
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Cover figure. Examining the relationship between duration of menopause and olfactory dysfunction by comparing odour threshold and odour identification tests of women of reproductive age and postmenopausal women.

Summary

Objective. The aim of this study is to compare the odour threshold and odour identification tests of women of reproductive age and postmenopausal period and to examine the relationship between the duration of menopause and olfactory dysfunction.

Methods. Eighty women of reproductive age and in the postmenopausal period were included in this prospective study. These were divided into four groups of 20 women each: Group 1, reproductive period; Group 2, postmenopausal period (0-5 years); Group 3, postmenopausal period (6-10 years); and Group 4, postmenopausal period (more than 10 years). All the women enrolled underwent complete ear, nose, and throat examinations, followed by odour threshold test and odour identification test. The results were then compared among the groups.

Results. There was a statistically significant difference between the groups in terms of age, odour threshold test and odour identification test ($p < 0.001$, $p = 0.016$, and $p < 0.001$, respectively). Age adjusted

results indicated that there were no statistically significant difference in odour threshold test scores between groups compared to the reference group 1. However, women in group 3 were 90% less likely to have higher odour identification test scores compared to women in group 1 [OR (95% CI): 0.10 (0.01-0.73); $p = 0.025$]. **Conclusions.** Olfactory dysfunction is seen in the postmenopausal period. However, this is correlated with age. Olfactory dysfunction in the postmenopausal period appears to be the result of aging together with hormonal changes.

Key words: menopause, olfactory dysfunction, oestrogen, odour threshold test, odour identification test

Introduction

Olfaction is an important sensory function with a direct effect on quality of life. Olfactory disorders can lead to loss of appetite and a weakening of social relationships. They can also damage physical and mental health by affecting defense mechanisms against harmful substances¹. Numerous agents capable of leading to olfactory disorders have been described in the literature, particularly sinonasal diseases, infections, head trauma, metabolic causes, toxins, drugs, neurological and endocrine disorders, psychiatric diseases, advanced age, and idiopathic and iatrogenic causes^{2,3}. The prevalence of olfactory disorders is higher in males⁴.

Menopause is a physiological aging process leading to decreased oestrogen release that results in the termination of the menstrual cycle due to ovarian reserve depletion⁵. The period after 12 months of no menstrual cycle is called the postmenopausal period⁶. Women undergo numerous physical and psychological changes when they enter this period. The principal effects of menopause are associated with oestrogen deficiency and involve vasomotor symptoms, cognitive decline, cardiovascular disease, osteoporosis, genitourinary system atrophy, and sexual problems⁷. Psychological problems such as irritability, anxiety, sleep problems, forgetfulness, and depression also increase around menopause⁶. The risk of depression has been shown to rise during this period, with various studies reporting that 26-33% of women experience first depressive attacks during menopause.⁷ There are studies showing that women experience olfactory perception changes following the menopause, a decrease in oestrogen levels being thought to cause a decline in olfactory perception acuity^{8,9}.

Since the olfactory system is directly exposed to the external environment, there is a high possibility of contact with pathogens and toxins. Olfactory dysfunction also increases the risk of pathogens and toxins penetration into the brain via the olfactory system by reducing awareness of various harmful elements in the environment. A correlation has been found between olfactory dysfunction and increasing mortality in the elderly. A study examining the effects of olfactory disorders on general quality of life and depression reported that mental health problems including anxiety, depression, and other negative states were related to olfactory dysfunction¹⁰.

Despite the frequency of olfactory disorders and their adverse impacts on quality of life, the sense of smell does not receive

due attention from either patients or physicians, and has been less studied than the other senses. Although studies have reported a weakening of olfactory functions in the postmenopausal period, none has shown an association between the menopausal duration and olfactory dysfunction.¹ The aim of this study is to compare the odour threshold and odour identification tests of women of reproductive age and postmenopausal period and to examine the relationship between the duration of menopause and olfactory dysfunction.

Materials and methods

Eighty women of reproductive age and in the postmenopausal period were included in this prospective study. These were divided into four groups of 20 women each: Group 1, reproductive period; Group 2, postmenopausal period (0-5 years); Group 3, postmenopausal period (6-10 years); and Group 4, postmenopausal period (more than 10 years). Women with sinonasal pathologies capable of leading to olfactory disorders, with histories of head trauma or sinonasal surgery, with neurological or psychiatric diseases, with endocrine disorders, or receiving hormone replacement therapy were excluded. All the women enrolled underwent complete ear, nose, and throat examinations, followed by odour threshold test and odour identification test. The results were then compared among the groups (Cover figure).

Odour threshold test

Nine series were established with 1:3 dilutions, commencing with the highest 4% butanol. Distilled water was employed for dilution. The highest concentration was labelled vial 9 and the lowest vial 1. Different concentrations of butanol solution were held 1-2 cm in front of both nostrils for approximately 3 seconds, the subjects being asked to confirm when they were sure they smelled the odour concerned. The odour presentation commenced with the lowest concentrations and continued with higher levels. Odour presentation was then performed with decreasing concentration series, the point of intersection at which the odour was perceived in the two series being adopted as the threshold value¹¹.

Odour identification test

Scents were obtained from 20-ml aromatic oils obtained from herbalist stores (Biovitals, Alfazen, Istanbul, Turkey). Seven

odours determined in odour identification studies for Turkish society were selected (rose, lemon, orange, lavender, mint, cinnamon, and clove)². The participants were asked to smell scents sequentially placed onto absorbent at a distance of 1-2 cm without coming into contact with the nose. The procedure was performed separately for each patient and each odour. The tests were conducted by the same physician in an odour-free room at 22°C. One point was added to the score section for each correct response. Tests were not performed consecutively in the same environment, and the room was ventilated before and after each test to eliminate additional odours that might affect the test.

Statistical analysis

Descriptive statistics for the numerical variables are presented as median (minimum-maximum) values. Assumption of normality was assessed using Shapiro-Wilk test. Numerical variables are compared with Kruskal-Wallis test between groups and followed by Bonferroni corrected Dunn's test for post-hoc comparisons. The effect of group on the variables odour threshold test and odour identification test was evaluated with the proportional odds logistic model considering the ordinal nature of these variables, and since the variable age differed between groups, age was included into the model as a covariate. Thus the effect of group on odour threshold test and odour identification test was age adjusted. Brant's test was used to assess the assumption of proportionality for the proportional odds model. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) (Version 22.0. Armonk, NY: IBM Corp.), uJamovi (Version 2.3.18.0) and R (RStudio 2022.02.1+461 "Prairie Trillium" Release for Windows; package="brant"). P values less than 0.05 were considered statistically significant.

Results

There was a statistically significant difference between the groups in terms of age, odour threshold test and odour identification test ($p < 0.001$, $p = 0.016$, and $p < 0.001$, respectively; Table I). Age adjusted comparisons between groups in terms of odour threshold test and odour identification test are presented in Table II. Age adjusted results indicated that there were no statistically significant difference in odour threshold test scores between groups compared to the reference group 1. However, women in group 3 were 90% less likely to have higher odour identification test scores compared to women in group 1 [OR (95% CI): 0.10 (0.01-0.73); $p = 0.025$] (Tab. II).

Discussion

Olfactory dysfunction, defined as a partial or total loss of

the ability to perceive smells, is more common in the community than is generally thought. Despite its severe effects on quality of life, including physical and mental health, it is not sufficiently recognised¹². Since weakening in odour perception, particularly that which is associated with systemic diseases, develops gradually and over a long-term process, individuals may be unaware or insufficiently troubled by it. Olfactory dysfunction is therefore not identified as quickly as other sense system function disorders^{13,14}. Statistically, only about one-quarter of individuals with olfactory disorder are reported to be aware of the problem before being tested¹⁵. None of the patients to whom we applied the odour threshold test and odour identification test in this study complained of olfactory disorders before the test.

Individual performance in terms of odour identification is known to be highly affected by social and cultural history¹⁶. Odour threshold tests largely evaluate the peripheral olfactory pathways, while odour identification and discrimination tests are thought to involve complex and highly cognitive olfactory processes¹³. In order to obtain reliable findings from odour tests, the materials employed must be appropriate for the geographical region involved and must be prepared according to the cultural values of that region¹⁶. Accordingly, in the present study we employed seven odours determined in odour identification studies for Turkish society (rose, lemon, orange, lavender, mint, cinnamon, and clove)².

The nasal mucosa is affected by changes in sex hormones, and studies have suggested that this effect occurs via oestrogen receptors and neuropeptides in the nasal mucosa⁵. The nasal mucosa has been reported to be affected and rhinitis symptoms to emerge under conditions in which oestrogen levels rise for physiological reasons or if oestrogen is absorbed from the outside. In addition, squamous metaplasia in the nasal mucosa, interepithelial oedema, hyperplasia in the tunical glands, histiocytic penetration, and accumulation of fibrous tissue have been detected in women using oral contraception. These changes are also thought to be related to oestrogen¹⁷. In their research into fullness and hyperactivity occurring in the nasal mucosa during the menstrual cycle, Haeggström et al. used rhinometric measurements to demonstrate the nasal hyperactivity that develops when oestrogen concentrations reach peak levels¹⁸. The condition of the nasal mucosa also affects the function of the nervus olfactorius. Optimal odour perception is possible in the presence of moderately congested, moist, and red nasal mucosa¹⁹. Topical oestrogen preparations have been used to improve mucosal congestion in patients with atrophic rhinitis, and these have been shown to be therapeutically effective⁵. Since the nasal mucosa can be affected by oestrogen via receptors located on the cell surface, their presence must be dem-

Table I. Comparison of demographic and clinical parameters between groups.

	Group 1 (N = 20)	Group 2 (N = 20)	Group 3 (N = 20)	Group 4 (N = 20)	p value*
Age (year)	41.5 (24-53) ^a	53 (47-62) ^b	58 (47-63) ^{b,c}	65.5 (53-76) ^c	< 0.001
Odour Threshold Test	1 (1-2) ^a	2 (1-3) ^{a,b}	1.5 (1-3) ^{a,b}	2 (1-3) ^b	0.016
Odour Identification Test	7 (6-7) ^a	6 (4-7) ^b	4 (3-7) ^{b,c}	4 (1-6) ^c	< 0.001

*: Kruskal-Wallis Test; ^{a,b,c}: Different superscripts indicate a significant Bonferroni corrected Dunn's test result between groups at the 0.05 significance level.

Table II. Age adjusted proportional odds logistic model results.

	Odour Threshold Test		Odour Threshold Test	
	OR (%95 CI)	p value		p value
Age (year)	1.07 (0.98-1.18)	0.157	0.89 (0.81-0.97)	0.008
Group		0.764		0.116
2 vs 1	2.12 (0.36-13.95)	0.414	0.33 (0.06-1.77)	0.207
3 vs 1	1.29 (0.17-10.62)	0.805	0.10 (0.01-0.73)	0.025
4 vs 1	1.59 (0.11-24.37)	0.734	0.09 (0.01-1.07)	0.060

OR: odds ratio, CI: confidence interval; * Proportionality assumption for parallel regression lines hold (Brant Test).

onstrated in order to confirm that oestrogen is impacting the nasal mucosa ⁵. Wolstenholme et al. investigated female sex hormone receptor levels in the nasal mucosa and detected oestrogen β receptors in 25 of 26 women. However, they observed no oestrogen α or progesterone receptors. In addition, they determined a correlation between oestrogen β receptor numbers and rhinitis quality of life questionnaire scores ²⁰.

Since olfactory perception is a chemical-sensory process carried out by special sensory cells, changes in olfactory functions are thought to represent early biomarkers of neurodegeneration ¹⁰. Caruso et al. reported that oestrogen may affect neuronal plasticity and neuronal conduction time to the olfactory system and that decreasing postmenopausal oestrogen may cause a decrease in olfactory acuity ⁹. A study comparing the odour perception and identification thresholds of women who had been in the menopause for at least 5 years and women in the reproductive period reported that olfactory function decreased significantly in the postmenopausal period ¹.

Aging is also known to have an adverse effect on olfactory perception. A significant decrease in olfactory perception function occurs by the sixth decade of life. A greater age-related decrease in olfactory perception has been shown in men than in women ²¹. Savović et al. compared olfactory perception ability in peri- and postmenopausal women from the same age group and observed a greater decline in olfactory perception in postmenopausal women. Researchers have concluded that this significant postmenopausal decrease in olfactory perception ability in women may be attributable to a decline in oestrogen levels ⁸. Doty et al. measured oestradiol, progesterone, testos-

terone, and follicle stimulating hormone levels and reported that hormone replacement therapy exhibited beneficial effects on olfactory and cognitive measurements, and that this could be recommended since it would improve the quality of life, albeit to a limited extent, of postmenopausal women ²². Odour threshold and odour identification tests, a non-invasive, simple, and low-cost method for the early detection of olfactory disorders, particularly in neurodegenerative diseases associated with olfactory defects, will allow oestrogen replacement therapy to be planned for suitable patients ^{10,22}.

Significant differences were determined between our study groups in terms of age, and odour threshold test and odour identification test results. However, examination of the results corrected for age revealed no significant difference between the menopausal groups compared to the reproductive period in terms of odour threshold results. The odour identification test results only differed significantly between the reproductive period and Group 3. In the light of these findings, it may be concluded that there is no significant relationship between an increased duration of menopause and olfactory dysfunction. The menopause results in olfactory dysfunction irrespective of its duration. Age increases in parallel with menopause duration, and olfactory dysfunction is thought to increase in line with age, rather than with endogenous oestrogen deficiency. It may therefore be concluded that olfactory dysfunction in the postmenopausal period is a consequence of both aging and a decrease in oestrogen levels.

The principal limitation of this study is that correlations between our odour threshold and odour identification test re-

sults and oestrogen and follicle stimulating hormone levels were not examined. Also, despite statistical adjustments, age differences between groups could still influence the findings related to olfactory dysfunction. It is recommended that future studies compare women in the same age group but at different postmenopausal periods. Another limitation of the study is that the tests used only provide a basis for possible comparisons between groups. The tests used did not allow for a classification of olfactory function nor did they determine whether a disorder is present. The relatively small sample size and cross-sectional study design are other limitations. More extensive studies can be carried out in the future.

Conclusions

In conclusion, olfactory dysfunction is seen in the postmenopausal period. However, this is correlated with age. In summary, olfactory dysfunction in the postmenopausal period appears to be the result of aging together with hormonal changes.

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Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

FA, AK, MY: conceptualization, writing-original draft, project administration; FA, ZY, AK: data curation; FA, ZY: formal analysis. All authors: methodology, visualization, writing-review editing.

Ethical consideration

This study was approved by the Institutional Ethics Committee (Kastamonu University Clinical Research Ethical Committee) (Decision No: 2022-KAEK-3, Date: 23.03.2022). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each participant/patient for study participation and data publication.

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