

Evaluation of Olfactory and Gustatory Functions in Patients With Fibromyalgia Syndrome: Its Relationship With Anxiety, Depression, and Alexithymia

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ABSTRACT

Objectives: This study aims to evaluate smell and taste functions in patients with fibromyalgia syndrome (FMS) and the relationship between smell and taste functions, anxiety, depression, alexithymia, and quality of life (QoL).

Patients and methods: This cross-sectional study included 30 patients with FMS (3 males, 27 females; mean age 46.0±8.5 years; range, 18 to 70 years) and 20 age- and sex-matched healthy participants (2 males, 18 females; mean age 45.7±10.0 years; range, 18 to 70 years). Fibromyalgia Impact Questionnaire (FIQ) was applied to FMS patients. Hamilton Anxiety Scale, Depression Scale, Toronto Alexithymia Scale, and EuroQoL Questionnaire Five-Dimensions (EQ-5D) were applied to all participants. Sniffin' Sticks test was used for olfactory function analysis while taste strips were used for gustatory function analysis.

Results: The FMS patients had higher anxiety, depression, and alexithymia while lower QoL scores. Olfactory and gustatory function test scores were lower in FMS patients. Total olfactory function scores were 25.96 and 36.40 for FMS and control groups, respectively. For taste function, they were 9.93 and 13.55, respectively. These scores were negatively correlated with anxiety, depression, and alexithymia scores whereas positively correlated with EQ-5D index score. There was no significant correlation with FIQ score.

Conclusion: Anxiety and depression are common symptoms of FMS. Patients with FMS had altered olfactory and gustatory functions and these impairments were correlated with their anxiety and depression. Further studies with larger sample sizes including functional magnetic resonance imaging evaluation should be performed.

Keywords: Anxiety, depression, fibromyalgia, gustation, olfaction.

Fibromyalgia syndrome (FMS) is characterized by chronic widespread musculoskeletal pain and a variety of symptoms including fatigue, sleep disturbances, anxiety, depression, and cognitive dysfunction.^{1,2} Psychiatric disorders are more common in FMS compared to the general population.^{3,4} Anxiety and depressive disorders are the most common psychiatric comorbidities with frequencies of 13-63.8% and 20-80%, respectively.⁴

Depression and fibromyalgia have similar pathophysiology and pharmacological therapy. Thus many authors stated that FMS and depression are differential symptom presentations of a single underlying condition.⁵ Recent studies showed that olfaction is altered in depression and olfactory bulb volume is reduced.⁶⁻⁸ Since there is a strong relationship between depression and FMS, olfactory bulb volume was studied in FMS and decreased volume of the olfactory bulb

Received: September 29, 2019 **Accepted:** December 08, 2019 **Published online:** March 26, 2020

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Citation:

Özsoy-Ünüböl T, Kullakçı T, İlhan İ, Yılmaz F. Evaluation of Olfactory and Gustatory Functions in Patients With Fibromyalgia Syndrome: Its Relationship With Anxiety, Depression, and Alexithymia. Arch Rheumatol 2020;35(4):584-591.

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was detected.⁹ Although olfaction was tested in FMS, to our knowledge, there was no study evaluating both smell and taste functions in FMS and assessing its relationship with psychiatric parameters such as anxiety and depression.¹⁰ Olfactory and gustatory functions were assessed in patients with rheumatoid arthritis, and a significant decrease was found both in the olfactory and gustatory functions.¹¹ Therefore, in this study, we aimed to evaluate smell and taste functions in patients with FMS and the relationship between smell and taste functions, anxiety, depression, alexithymia, and quality of life (QoL).

PATIENTS AND METHODS

This cross-sectional study was conducted in a tertiary care center between January and June 2019. The study included 30 patients with FMS (3 males, 27 females; mean age 46.0 ± 8.5 years; range, 18 to 70 years) diagnosed according to 2016 revised American College of Rheumatology (ACR) criteria^{1,12} and 20 age- and sex-matched healthy participants (2 males, 18 females; mean age 45.7 ± 10.0 years; range, 18 to 70 years). Neurologic disorders, rheumatologic and endocrine diseases, diabetes mellitus, traumatic brain injury, psychiatric disorders, chronic rhinitis/sinusitis/rhinosinusitis, history of head trauma or operation, malignancies, and pregnancy were defined as exclusion criteria. Besides, patients taking any antidepressants, pregabalin or gabapentin were also excluded. The study protocol was approved by the University of Health Sciences, Hamidiye Ethics Committee (28.12.2018-18/88). A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

G*Power version 3.1.9.2 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was used for sample size estimation. The study performed by Lötsch et al.¹⁰ was used as a reference. According to their data (FMS patients: 14.6 ± 1.3 , controls: 15.5 ± 0.6), effect size was calculated as 0.888 to achieve 90% power with $\alpha=0.05$, (1.5/1 allocation ratio) 29 FMS patients and 19 controls were needed. Uneven allocation was used to decrease the cost.¹³

According to 2016 revised ACR criteria, widespread pain index (WPI), symptom severity scale (SSS) score, and fibromyalgia severity scale (FSS) score, which is the sum of WPI and SSS, were calculated.¹ Fibromyalgia Impact Questionnaire (FIQ) which measures patient status was applied to FMS patients and the total score was derived from all 10 items.

EuroQol Questionnaire Five-Dimensions (EQ-5D) was applied to all participants to assess QoL. Hamilton Anxiety and Depression Scales were administered by a psychiatrist who was unaware of the diagnosis. Toronto Alexithymia Scale (TAS-20) was used for the measurement of alexithymia which refers to trouble in identifying and describing emotions.^{14,15} Cut-off scores were as follows: ≤ 50 =no alexithymia, 51-60=borderline alexithymia, and ≥ 61 =alexithymia.¹⁶ After all psychiatric tests, a second psychiatrist who was unaware of the diagnosis and participants' psychological condition performed olfactory and gustatory function tests.

Olfactory function was assessed by Sniffin' Sticks test which consists of odor threshold (T), discrimination (D), and identification (I) subtests.¹⁷ For testing, odorants were presented to the participants via felt-tip pens. The cap was removed for three seconds and placed at 2 cm in front of the nostrils. Each odorant was presented with at least 30-second intervals. All participants were advised not to eat/drink anything except for water and not to smoke 15 minutes before the test.

For threshold test, phenylethyl alcohol (PEA, a rose-like odor) diluted in propylene glycol was used with 16 available dilution steps while participants' eyes were closed with sleep masks. Two pens contained an odorless solvent (propylene glycol) and one pen was filled with PEA in a certain concentration. The test was performed with a staircase procedure. The participant was asked to find the pen containing the odor. If the participant was unsuccessful, then the concentration was increased. If the odor was detected twice, then the concentration was decreased. After seven turns, the average of the last four turns was used in order to determine the threshold score.

Discrimination test was performed with three sets of odorants, two of them containing the same odor, one containing a different odor.

The participant was tested while eyes closed with a sleep mask and asked to identify the different odor.

For identification test, 16 common odors were used and the participant was asked to identify the odor from a list of four descriptors. The total number of correct answers represented the identification test score.

Total score for threshold, discrimination and identification (TDI) is the sum of the three subtests. TDI scores ≤ 15 refer to functional anosmia, between 16 and 30 refer to hyposmia, and ≥ 31 refer to normosmia.¹⁸ The test was validated for the Turkish population.¹⁹

Gustatory function was evaluated with taste strips test (Burghart Medical Technology, Wedel, Germany) which consists of 16 filter paper taste strips.²⁰ Four different concentrations of each taste strip (sweet, sour, salty, and bitter) were applied randomly starting with the lowest concentration. After each strip, the mouth was

rinsed with water. Total number of correct answers represented the total taste score with a range of 0 to 16. One hour before the test, all participants were advised not to smoke or eat/drink anything except for water. Scores below 9 refer to hypogeusia.^{21,22}

All participants were asked to rate their own olfactory and gustatory functions on a three-point scale (1=below average, 2=average, 3=above average).

Statistical analysis

The IBM SPSS Statistics version 22.0 software (IBM Corp, Armonk, NY, USA) was used for statistical analysis. The normality of the parameters was assessed with the Shapiro-Wilk test. Mean, median, standard deviation, and frequency were used as descriptive statistical methods. Mann-Whitney U test was used to compare means between two independent groups. The chi-square test, Fisher's exact test, and Yates

Table 1. Demographical and clinical data of participants

	Fibromyalgia syndrome (n=30)			Control (n=20)			p
	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			46.0±8.5			45.7±10.0	0.898*
Body mass index (kg/m ²)			28.1±5.4			26.0±4.2	0.145*
Sex							-
Female	27			18			
Male	3			2			
Education							0.551**
Primary-Secondary School	18	60		9	45		
High School	4	13.3		3	15		
University	8	26.7		8	40		
Smoking							0.339**
None	19			11			
Active	9			9			
Past history	2			0			
Amount of smoking (pack-year)			5.3±8.7			5.90±7.6	0.531†
Alcohol consumption							0.672‡
Yes	27			17			
No	3			3			
Symptom duration (month)			49.9±40.9			-	-
Disease duration (month)			11.8±19.4			-	-
Widespread pain index			11.1±3.2			-	-
Symptom severity scale			9.4±1.6			-	-
Fibromyalgia severity score			20.5±3.8			-	-
Fibromyalgia impact questionnaire			61.4±10.7			-	-

SD: Standard deviation; * Student t-test; ** Chi-square test; † Mann-Whitney U test; ‡ Fisher's exact test.

continuity correction were used to compare the qualitative data. Spearman test was performed for the analysis of the correlation between the parameters. Significance was assessed at $p < 0.05$ level, with 95% confidence interval.

RESULTS

There was no statistically significant difference in demographic data of study participants ($p > 0.05$) (Table 1). Clinical characteristics of FMS patients were presented in Table 1.

Patients with FMS had significantly higher scores of anxiety, depression, and TAS-20. Besides, FMS patients had lower EQ-5D index and visual analog scale (VAS) (general health status) scores (Table 2).

Patients with FMS had lower test scores for smell and taste functions. Although FMS patients'

self-assessment for smell function was significantly different, there was no difference compared to healthy controls for their taste function (Table 3).

Olfactory and gustatory function test scores were negatively correlated with anxiety, depression, and alexithymia scores whereas positively correlated with EQ-5D index and VAS score. Although FIQ score was negatively correlated with smell score, no significant correlation was detected with taste score (Table 4).

DISCUSSION

The FMS patients had higher anxiety, depression, alexithymia scores, and lower QoL. Olfactory and gustatory function scores were lower compared to healthy subjects. Although olfaction had a strong negative correlation with anxiety and depression, it had a strong positive correlation with EQ-5D index and VAS (general

Table 2. Comparison of anxiety, depression, alexithymia, and quality of life scores between patients with fibromyalgia syndrome and healthy subjects

	Fibromyalgia syndrome		Control		<i>p</i>
	%	Mean±SD	%	Mean±SD	
Hamilton Anxiety Scale					
Score		21.2±9.2		5.5±4.2	0.0001*
No anxiety	23.3		95		
Mild anxiety	10		0		0.0001**
Moderate anxiety	20		0		
Severe anxiety	46.7		5		
Hamilton Depression Scale					
Score		18.0±7.8		5.7±6.0	0.0001*
No depression	10		85		
Mild depression	30		5		0.0001**
Moderate depression	53.3		10		
Severe depression	6.7		0		
Toronto Alexithymia Scale					
Score		57.2±13.1		46.8±11.3	0.006†
Non-alexithymia	40			70	
Borderline alexithymia	16.7			15	0.078**
Alexithymia	43.3			15	
EQ-5D index					
Score		0.452±0.288		0.916±0.109	0.0001*
EQ-5D VAS (general health status)					
		45.3±11.4		79.5±19.0	0.0001*

SD: Standard deviation; EQ-5D: EuroQol Questionnaire Five-Dimensions; VAS: Visual analog scale; * Mann-Whitney U test; ** Chi-square test; † Student t-test.

Table 3. Smell and taste function scores in patients with fibromyalgia syndrome and healthy subjects

		Fibromyalgia syndrome		Control		p
		%	Mean±SD	%	Mean±SD	
Smell	Sniffin' Sticks test score					
	Threshold		5.6±3.6		11.2±2.5	0.0001*
	Discrimination		10.1±2.6		12.3±1.6	0.002*
	Identification		10.3±1.6		13.5±1.4	0.0001*
	Total		26.0±6.5		36.4±4.5	0.0001*
	Functional anosmia	3.3		0		
	Hyposmia	80		15		0.0001**
	Normosmia	16.7		85		
	Self-assessment for smell function					
	Below the average	30		10		
Average	36.7		85		0.003**	
Above the average	33.3		5			
Taste	Taste function test score					
	Total		9.9±2.7		13.6±1.8	0.0001*
	Hypogeusia	36.7		0		0.002†
	Normogeusia	63.3		100		
	Self-assessment for taste function					
	Below the average	10		0		
Average	76.7		100		0.066	
Above the average	13.3		0			

SD: Standard deviation; * Mann-Whitney U test; ** Chi-square test; † Fisher's exact test.

health status). Smell function had a moderate negative correlation with TAS-20 and FIQ scores. Taste function had a moderate negative correlation with anxiety and depression and it had a moderate positive correlation with EQ-5D index and VAS score. On the other hand, it had a weak negative correlation with TAS-20 score and no significant correlation with the FIQ score.

Anxiety and depression prevalence differs in various studies because of the differences in the socioeconomic or psychosocial characteristics of the patients.²³ In the current study, high prevalence (90%) of depression was detected in the FMS group consistent with the literature.^{24,25} The prevalence of anxiety in FMS ranges from 13 to 63.8%.⁴ However, in a recent study, it has been found as 87.5%, which is similar to our result (76.7%).²³ FMS patients had higher TAS-20 scores compared to healthy subjects. In the current study, mean TAS-20 scores were 57.2 and 46.8 for FMS and control groups, respectively. The TAS-20 scores were similar to those reported in

the literature.^{26,27} The differences in prevalence may be related to the test, which was used to diagnose anxiety, depression, and alexithymia. Moreover, cultural differences may affect the prevalence. Since antidepressants can affect the olfactory function and reverse the alterations, patients taking any antidepressants were excluded from the study. Because of these exclusion criteria, FMS patients might have had high rates of anxiety and depression.

Lötsch et al.¹⁰ studied olfactory function in patients with FMS and found that FMS patients had lower scores in the identification test. The participants were asked to rate their own smell function and FMS patients judged their function as better than average. In this study, anxiety, depression, and alexithymia have not been evaluated. However, these psychiatric conditions are common in FMS and it has been shown that olfactory function can be affected in depression and anxiety disorder.^{6,28}

Table 4. Correlation analysis between smell and taste function scores and clinical parameters

	Smell total score	Taste total score
Age		
p	0.021	0.487
r	-0.325	-0.101
Fibromyalgia impact questionnaire		
p	-0.481	-0.108
r	0.007	0.571
Fibromyalgia severity score		
p	0.821	0.421
r	0.043	0.152
Hamilton Anxiety Scale		
p	0.0001	0.0001
r	-0.615	-0.550
Hamilton Depression Scale		
p	0.0001	0.0001
r	-0.625	-0.530
Toronto Alexithymia Scale		
p	0.003	0.038
r	-0.413	-0.294
EQ-5D index score		
p	0.0001	0.0001
r	0.610	0.534
EQ-5D VAS score		
p	0.0001	0.001
r	0.641	0.465

EQ-5D: EuroQol Questionnaire Five-Dimensions; VAS: Visual analog scale; Spearman test.

Olfactory deficits have been evaluated in depression because the affected brain areas in depression are essential for olfactory processing and bilateral olfactory bulbectomy in rodents was organized to create a depression model.²⁹

Association between major depressive disorder and odor identification impairment has been assessed and the authors concluded that odor identification impairment is evident in major depressive disorder with first-time high symptom severity and in patients with more severe disease.³⁰

It has been shown that olfaction is related to emotional processing. In depressed mood, prefrontal limbic network alterations are seen and these areas are also involved in olfactory processing.³¹ Deviant limbic functionality in depressed people is associated with an altered chemosensory perception. Olfactory threshold tests give information about former processing, while identification and discrimination tests measure later levels. Thus smell function allows us to investigate limbic functions.³² One theory

suggests that in depression, reduced attention to olfactory stimuli causes decline in olfactory receptor turnover rate, resulting in impairment in olfactory threshold. The second theory is about the impairment of cognitive functioning which is supported by the knowledge that olfactory identification is related to executive function and semantic memory.³³ In fibromyalgia, the same neuroanatomical regions are affected.¹⁰ Besides, cognitive impairment is common in FMS and associated with olfactory impairment.³⁴

Since the majority of the FMS patients in our study had depression and patients taking antidepressants were excluded, we could not establish whether the impairment was associated with depression or not. In either case, olfactory impairment was detected in FMS. In addition, when evaluating whether FMS severity or impact correlated with smell function, we found that FIQ had a moderate negative correlation with smell function, and FSS had no significant correlation with smell function. Further studies should be performed in patients with FMS without depression.

Olfactory abnormalities have been studied in anxiety disorders with the Sniffin' Sticks test. Although there was a significant deficit in discrimination test, there was no significant deficit in threshold and identification tests.²⁸ In our study, 76.7% of FMS patients had anxiety and anxiety scores had a negative correlation with the smell and taste function scores.

The normal olfactory system is necessary to distinguish food flavors and 90% of individuals having altered taste function had primarily smell disorder.³⁵ So, it is important to evaluate the taste and smell together. In the current study, 80% of FMS patients had hyposmia and 36.7 had hypogeusia. We can expect a lower rate of hypogeusia since the main reason for the decrease in taste is the decrease in smell function.

The strengths of the study are the comprehensive approach to FMS patients and the objective evaluation of both the olfactory and gustatory functions. To the best of our knowledge, this is the first study evaluating smell and taste in FMS patients together with their psychiatric status.

The limitations of this study are the lack of a follow-up period as well as the lack of an analysis to identify whether FMS medications (duloxetine or pregabalin) have any effect on smell and taste functions. Since it has been shown that altered olfactory performance can be improved with treatment, we excluded FMS patients taking medications like duloxetine and pregabalin.²¹ On the other hand, the value of the study could be increased if patients could be evaluated by functional magnetic resonance imaging (MRI).

In conclusion, FMS patients had higher anxiety, depression, and alexithymia scores and worse smell and taste functions. Assessments for olfactory and gustatory functions should be included in FMS patients' comprehensive evaluation and multimodal treatment strategies. Further prospective studies with larger sample sizes and including evaluation with functional MRI are needed.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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