ORIGINAL ARTICLE

CONTENTS

Assessment of olfactory and gustatory dysfunction in post-COVID dentists by a modified CCCRC

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ABSTRACT

Aim: This study aimed to evaluate the prevalence of sense loss and their deterioration within and post infection with COVID-19.

Materials and Methods: A systematic informative questionnaire was filled out for each participant. Chemosensitive symptoms were recorded by using n-butyl alcohol and environmentally realistic odorants and calculated in a modified way for the detection of olfactory function. The gustatory test scoring was done using the four standard primary tastes.

Results: Out of 133 participants, dentists were more commonly females (81, 61%) with the majority below 35 years of age (97, 72%). Half of the participants experienced smell and/or taste loss during the COVID-19 pandemic; whereas almost all reported having had olfactory dysfunction (132, 99.2%) and (105, 78.2%) gustatory dysfunction. Males reported a higher significant rate of taste loss (P=0.009) and females showed a higher recovery rate within the first two weeks after the onset than males. The Pfizer vaccine showed a significantly more frequent smell loss than other vaccinations (P=0.038).

Conclusions: Gender variation was noticed with taste and smell loss. Females recovered faster from dysfunction. Pfizer fully vaccinated participants were more prone to lose smell compared to others.

KEY WORDS: healed dentists, smell, and taste dysfunction, CCCRC

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ABBREVIATIONS

CCCRC: Connecticut Chemosensory Clinical Research Center
TLR: Toll-Like Receptors

INTRODUCTION

Hyposmia, anosmia, and hypogeusia, ageusia were some of the symptoms of COVID-19 infection [1]. The sudden onset of these symptoms was recognized by the European Centre for Disease Prevention and Control and WHO [2]. In Iraq, the first case of COVID-19 appeared in February 2020 [3] with a careless recording of these olfactory/gustatory symptoms. COVID-19 infected cells through the angiotensin-converting enzyme-2 protein (ACE-2) receptor, along with (Transmembrane protease, serine 2) TMPRSS2 [4]. Olfactory sensory neurons and mitral cells in the olfactory bulbs do not express ACE-2, but sustentacular and microvillar cells in the olfactory mucosa do. ACE-2 receptors are expressed in the basal region of filiform papillae on the tongue [5]. COVID-19 was caused by either conductive and/or sensorineural disorders. Obstruction anosmia occurs in 95% of patients and recovers within one month; while neuroinvasive anosmia related to coronavirus causes direct infection, injury, and death of neuronal cells [6]. In COVID-19, sustentacular cells are infected, leading to immune cell infiltration and desquamation of the olfactory epithelium, and cilia loss causing anosmia symptoms. Similarly, activation of toll-like receptors (TLR) and interferon (IFN) receptors in taste buds by inflammatory cytokines may limit taste cell regeneration, resulting in ageusia. However, positive ACE2 signals in inflammatory cells are expressed in less than 20% of cases [7]. Chemical senses during COVID-19 can be assessed subjectively using questionnaires or objectively using standardized tests like the Connecticut Chemosensory Clinical Research Center (CCCRC) through quantitative threshold determination and semiquantitative odor identification [8]. Olfactory and taste disorders in COVID-19 appear to differ from other post-viral olfactory disorders, with symptoms starting suddenly [9]. Dental and oral health

professionals are at greater risk for several occupational hazards and harmful agents, biological agents living in patients' saliva and blood, contaminated instruments, and bioaerosols in their working environment [10]. This study's hypothesis was to detect the deterioration of both senses after the pandemic and to assess the prevalence of this dysfunction among dentists even if this loss of sense had not occurred during early symptoms of infection using a modified CCCRC test.

AIM

This study aimed to evaluate the prevalence of sense loss and their deterioration within and post infection with COVID-19.

MATERIALS AND METHODS

SAMPLE COLLECTION

According to STROBE guidelines for cross-sectional studies [11], this study was conducted on Iraqi volunteer dentists after a thorough explanation of the study aims and procedures from Baghdad City working in health centers and clinics, from 9 March-21 September 2022 after receiving approval from the Ethics Committee for Research from the College of Dentistry, University of Baghdad, Baghdad, under protocol number (460722). A consent form was signed. Dentists with previous surgery, radiotherapy, pre-existing alterations of smell and taste, ahead trauma, allergic rhinitis, chronic rhinosinusitis, and psychiatric disorders were excluded by one examiner, a questionnaire (was validated by experts and included demographic information, medical history, COVID-19 infection status, onset, duration, chemo-sensitive symptoms, and vaccination date and type) was filled.

OLFACTORY FUNCTION ASSESSMENT

The CCCRC was used to assess the olfactory threshold using n-butyl alcohol (l-butanol) as the odorant [12], the average of both nostril scores was done. All scores 7 and higher were scored as 7 for each test and expressed as a composite threshold (0-50). Identification: environmentally realistic odorants are particularly suitable and have three necessary ingredients: odorants or trigeminal stimuli and distractors e.g., garlic [13]. The second correct answer canceled a previous error [14]. An average of both nostrils was recorded (0-7) and expressed as composite identification (0-50) [15]. When the average threshold or identification resulted in a number not recorded by (Cain, 1988) Ex. (average threshold=4.5; and identification score=3.5) in which composite score was put? For this reason, a modification in the threshold, identification, and sum scores was done in this study, to prevent the loss of accurate results for both nostrils reading and an accurate final score.

GUSTATORY FUNCTION

Four primary tastes: sweet, salty, sour, and bitter were used [16], scoring from 0-4; 0-ageusia and 4-normal [17].

STATISTICAL ANALYSIS

Data was expressed using mean/standard deviation and frequency/percent according to the type of the variable. Chi-square test and Fisher's exact test were used alternatively to assess the relationship between categorical variables. Correlation tests were used to assess the strength and direction of relationship between the studied variables. A confidence level of 95% with P-value equal or less than 0.05 was considered significant, by using SPSS version 26.

RESULTS

DEMOGRAPHY AND CLINICAL FINDINGS

Out of 133 Iraqi dentists who were included in this study, sex, age mean and groups, and habits like smoking were all recorded in Table 1, show the relation between Age and sex with social findings beside the descriptive data.

Information regarding infection status, frequency, duration from the last infection, loss of smell and taste as early signs and symptoms, and the recovery time were recorded from the questionnaire, Table 2.

Loss of smell and taste sensation as early symptoms of infection were found in 32% out of 67 participants with a history of loss, Table 3. A significant relation and positive correlation varied from weak to relatively strong were detected between variables, in Table 3.

CONNECTICUT CHEMOSENSORY CLINICAL RESEARCH CENTER TEST (CCCRC)

For all participants, an objective clinical assessment was done; the majority showed the score (2-3.9) of the olfactory threshold, and the score (1-2.9) of olfactory identification. The sum composite scores of both threshold and identification resulted in a score (>10-40). This was represented clinically as severe hyposomnia, Table 3.

Table 1. Demography and social findings

variable		Frequency	percent	p-value	p-value	p-value
Gender	Male	52	39%	Chi Seq. between gender systemic dis. & age groups	Chi Seq. between gender smoking & age groups	Chi Seq. between gender smoking status & age groups
	Female	81	61%			
Age	Mean	31years				
	SD	±9.09				
Age groups	<=35years	97	73%	0.59	0.33	0.29
	>35 years	36	27%	0.4	0.3	0.3
Systemic diseases	Yes	24	18%			
	No	109	82%			
Smoking	Yes	26	20%			
	No	107	80%			
smoking status	Cigarette <1 pack	11	8%			
	Cigarette ≥1 pack	10	11%			

Table 2. The infection status, loss of sense, and recovery time

Infection status	Total sample	Frequency of infection			Duration from the last infection				Loss of sense			Recovery time		
History of infection	N= 133	Once	Twice	< twice	≤6 months	>6 months-1 year	>1-2 years	>2 years	Smell	Taste	Both	1-15 days	>15-30 days	>30 days
Positive PCR	80 60%	45 34%	23 17%	12 9%	20 15%	30 23%	25 19%	5 4%	11 8%	8, 6%	48 36%	36 27%	15 11%	16 12%
Negative PCR	44 33%	53 (40%)			53 (39%)				66 (50%)			66 (50%)		
No. PCR	9 7%													
r & p-value		r=-0.73 P=0.000			r=-0.44 P=0.000				r=0.2 p=0.014			r=0.4 p=0.000		
			p=0.000 (Fisher Exact)			p=0.000 (Fisher Exact)								
		Frequency loss p=0.000 (Fisher Exact) Frequency Recovery P=0.000 (Fisher Exact) r=0.4 p=0.000												
		Duration loss p=0.000 (Chi-square), r=0.33 p=0.000 Duration Recovery p=0.000 (Chi-square), r=0.44, p=0.000												
Sex Female 61%	p-value								p=0.013 (Fisher Exact) r=0.19 p=0.028			p=0.038 (Fisher exact) r=0.22 p=0.010		
Sex Male 39%														

SMELL THRESHOLD AND IDENTIFICATION ACCORDING TO AGE AND SEX

Regarding the sex a weak positive correlation was determined between composite threshold and identification with sex (Pearson correlation=0.18, p=0.049), Table 3. The mean of both threshold and Identification of the female was higher than that of males, making the female more affected by olfactory dysfunctions than the male, Fig. 1.

Table 3. The modified CCCRC test scores

CCCRC composite threshold		CCRC composite identification		Composite score threshold+ identification		Clinically	
	N=133		N=133		N=133		
0-1.9	26 (19%)	0-0.9	6 (6%)	≤10	14 (10%)	Anosmia	
2-3.9	27 (20%)	1-2.9	57 (43%)	>10-40	57 (43%)	Severe	
4-4.9	26 (20%)	3-3.9	38 (29%)	>40-60	43 (32%)	Moderate	hyposomnia
5-5.9	18 (18%)	4-4.9	18 (13%)	>60-80	18 (14%)	Mild	
6-6.9	12 (9%)	5-5.9	10 (7%)	>80-100	1 (1%)	Normo-sonmia	
≥7	24 (18%)	6-7.	4 (3%)				
Sex	Female 61%			Pearson r=0.18 p=0.049		Pearson r=0.17 p=0.041	
Sex	Male 39%						

Table 4. Gustatory dysfunction according to age and sex

Variables Severe		Hypogeusia				p-Value
		Moderate	Mild	Normal		
Age	≤ 35	11 (69%)	25 (66%)	40 (82%)	20 (69%)	0.436[1]
	>35	5 (31%)	13 (34%)	9 (18%)	9 (31%)	
Sex	Male	10 (63%)	20 (53%)	17 (35%)	5 (17%)	0.009[1]
	Female	6 (37%)	18 (47%)	32 (65%)	24 (83%)	
Infection	pos. PCR	13 (81%)	18 (47%)	35 (71%)	14 (48%)	0.012[1]
	neg. PCR	3 (19%)	14 (37%)	14 (29%)	12 (41%)	
	no PCR		6 (16%)		3 (10%)	
Frequency of infection	once	5 (31%)	11 (29%)	19 (39%)	10 (35%)	0.03[1]
	twice	3 (19%)	3 (8%)	13(27%)	4 (14%)	
	>twice	5 (31%)	4 (10%)	3 (6%)		
	none	3 (19%)	20 (53%)	14 (29%)	15 (52%)	
Duration from last infection	≤ 6 month	4 (25%)	7 (18%)	9 (18%)	5 (17%)	0.863
	6mon-1 year	6 (38%)	6(16%)	14 (29%)	8 (28%)	
	>1-2 years	3 (19%)	10 (26%)	11 (22%)	5 (17%)	
	>2 years	1 (6%)	1 (3%)	2 (4%)	1 (3%)_	
	none	2 (13%)	14 (37%)	13 (27%)	10 (35%)	
Recovery time	1-15 days	6(38%)	8 (21%)	16 (33%)	6 (21%)	0.566
	>15-30days	1 (6%)	2 (5%)	9 (18%)	3 (10%)	
	>30days	2 (13%)	5 (13%)	4 (8%)	5 (17%)	
	none	7 939%)	23 (61%)	20 (41%)	15 (52%)	

[1] Significant relation between infection, frequency of infection, and gustatory dysfunction (p=0.012, 0.03), respectively.

Regarding age, no significant correlation was detected between both age groups in this study and both threshold and identification. The mean of both threshold and identification of the age group >35 years were higher than those of the age group ≤ 35; Fig.2. The threshold and identification tests had a validity between (0.51-0.82) which was within an acceptable range of validity (0.3-0.7) and high reliability as (Alpha Cronbach's=0.879). The clinical expression of olfactory function: is shown in, Table 3. The mean of olfactory dysfunction within this study was (41.43), 95% CI= (37.92-44.94). The prevalence of olfactory dysfunction was 99.2%. A weak significant correlation was detected between olfactory dysfunction and sex, Table 4. Concerning infection status, loss of sense, and recovery no significant relation was detected with olfactory dysfunction.

TASTE SCORING

Regarding gustatory dysfunction, Table 4.

The mean taste score was (2.66), 95% confidence interval (2.50-2.84). The prevalence of the taste disorder

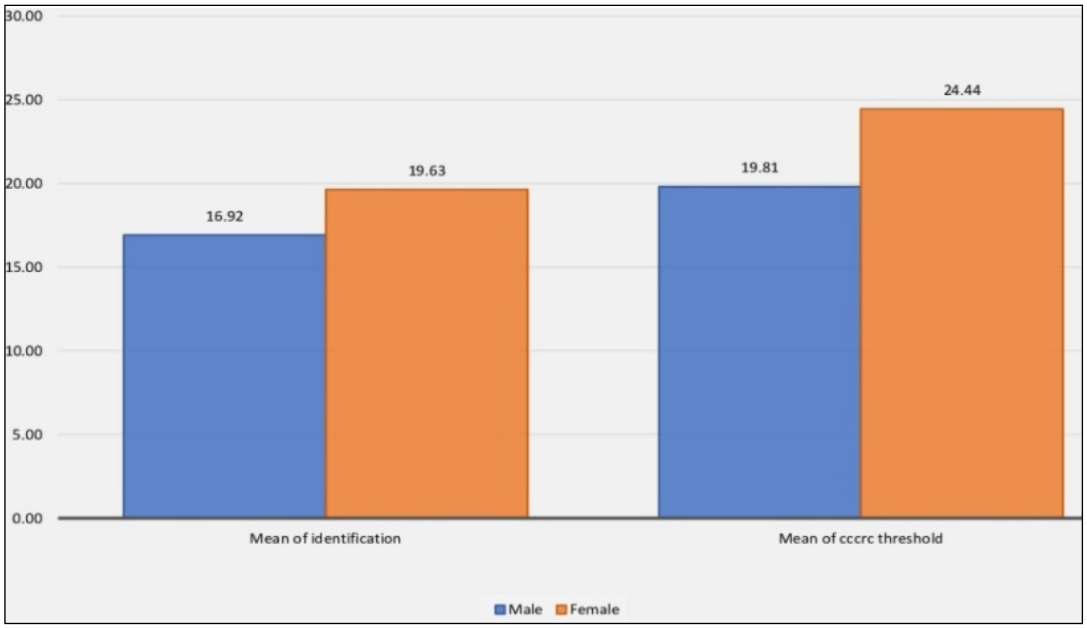

Fig. 1. Threshold and identification composite mean according to sex.

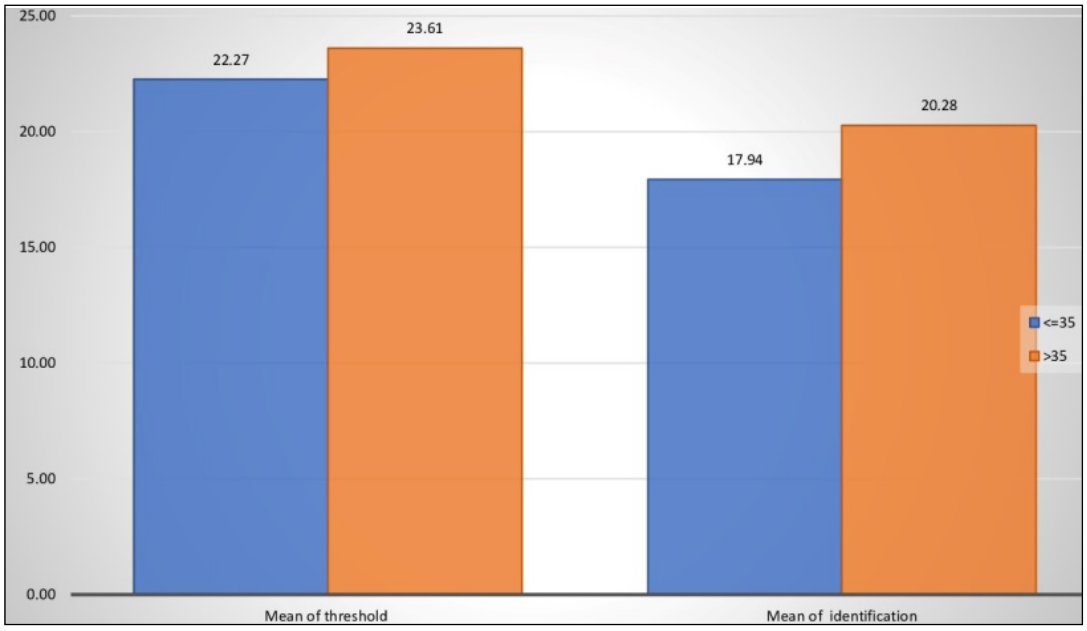

Fig. 2. Threshold and identification mean according to age.

in this study was 78.2%. There was a significant relation between taste disorder and gender (p =0.009); the male gender experienced moderate and severe hypogeusia more than the females. Age is not significantly related to taste disorder although; all types of hypogeusia in the first age group were more. There was no significant correlation between smell and taste dysfunction.

RECOVERY PERIOD WITH GUSTATORY AND OLFACTORY DYSFUNCTION:

There was a significant relation between time to recovery of both olfactory and gustatory disorder and sex (p=0.034) high percentage of the female gender recovering within the first 2weeks; Fig 3.

TYPES OF VACCINES

Medical staff received Pfizer type rather than other types of vaccines, a significant relation between Pfizer type and olfactory dysfunction (p=0.038) while no such relation with gustatory dysfunction was shown as in Table 5.

DISCUSSION

Dentists are in a high-risk group for being infected, once infected [18]. In contrast to a systematic review involving over 4000 participants from 40+ countries, our study included 133 participants from a single region. Both studies independently indicated a reduced sense of smell associated with the onset of infection

Table 5. Compare between olfactory and gustatory in relation to vaccine type

Dysfunction			Type of vaccine		
			Pfizer (83)	AstraZeneca (23)	P--Value
Olfactory	Hypo-somnia	Ansonia	6	2	0.038(Chi-Seq.)
		Sever	37	5	
		Moderate	29	10	
		Mild	10	6	
		Normal	1	0	
Gustatory	Hypoge-usia	Agusia	0	0	0.88(Chi-Seq.)
		Sever	9	3	
		Moderate	25	7	
		Mild	30	9	
		Normal	19	4	

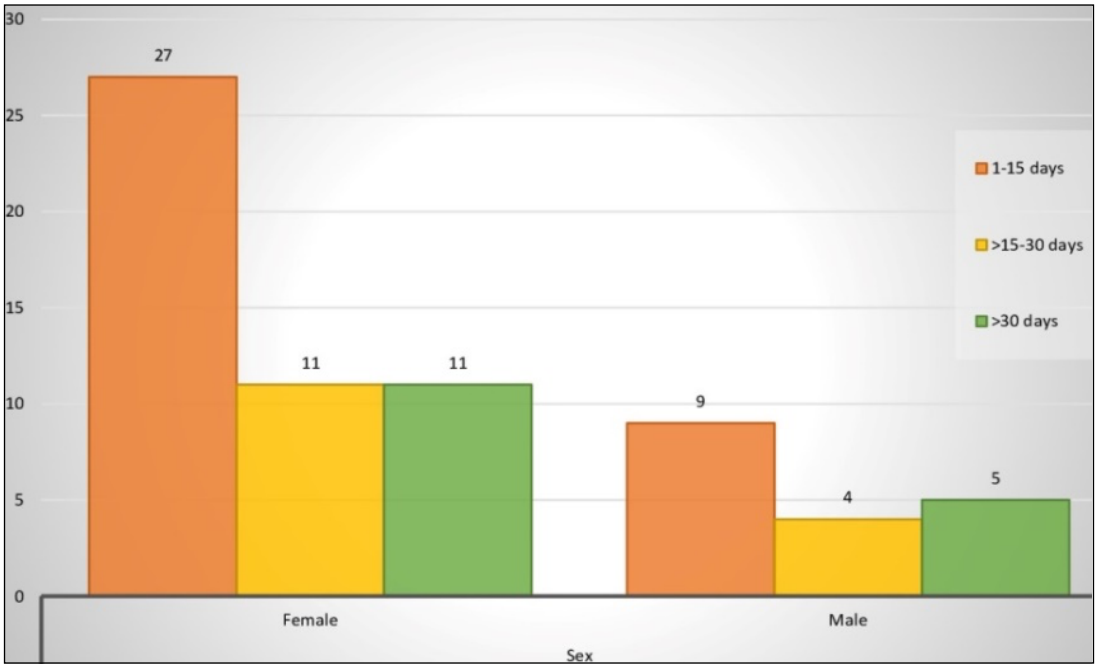

Fig. 3. Recovery time according to sex.

signs and symptoms [8]. In a post-infected study, 102 participants with demographics similar to this study (mean age: 39.1± 9.09 years, 60.9% women) were included [19]. Variation may result from differences in ethnicity, sample size, and categories like "children or adults, hospitalized, non-hospitalized, with nasal symptoms, subjective, objective assessment, and disease severity" [20]. The prevalence of olfactory and gustatory dysfunctions in this study was similar to (83%; 89%) [21], (85.6%; and 88%) [22], respectively; but was higher than that of the multi-centric case (41% and 61.2%) [21]. Objective methods 77% show higher prevalence than subjective (44%), suggesting subjective measures may miss critical COVID-19 symptoms, resulting in lower reported prevalence [1]. Geographical differences may affect symptom prevalence [23]. Higher ≤ 35 prevalence, more dysfunction in younger, non-hospitalized; younger age predisposes symptoms' appearance [24]. Milder infections in high immunity; symptoms more common in milder patients [23]; Older patients report lower CCCRC, taste scores, influenced by age-related chemoperception reductions [2].This study revealed females preferred smell and taste disturbance, with males having lower threshold anosmia. More females experienced mild dysfunction, while severe COVID-19 conditions were linked to males, possibly influenced by social factors [26]. This study identified a significant relationship between sex and gustatory dysfunction, potentially attributed to the predominantly female study population. Hyposmia significantly relates to reduced taste scores [27]. Viral invasion impairs taste buds retrogradely from an infected nerve. Anosmia results from direct virus impact on the olfactory epithelium and ACE2, expressed outside taste papillae [7]. The high prevalence of olfactory compared to gustatory is

due to the higher renewal and faster turnover rate of taste buds than olfactory neuron receptors [28]. Using odorless and colorless agents for 'Sweet', 'Sour', 'Salty', and 'Bitter' indicates viral invasion to the gustatory system, avoiding retro-nasal aroma taste due to taste bud dysfunction [27]. Smoking hurts and severe the clinical outcome, lower study smokers agrees with the study [21]. No significant association was found regarding olfactory dysfunction. Olfactory dysfunction was more common in positive COVID-19 infections, coinciding with Kurdistan Iraqi study [29]. No significant link between dysfunction and COVID-19's three waves (Jan. 2021-2022) [30]. In contrast, a significant relation was found between gustatory dysfunction and COVID-19 infection frequency, coinciding with milder forms that do not require hospitalization [31]. COVID-19 may cause dysgeusia, like ACE2 inhibitors, and cause additional damage to the olfactory epithelium [32] initiated by cytokine and antiviral storms, causing apoptosis of olfactory receptor neurons and loss of cilia and sense dysfunction [33]. Both sense's dysfunction prevalence was higher than [34] and lower than [19]. Mild COVID-19 is linked to a significant relation between this dysfunction and infection or its frequency [31]. Smell and taste disorders seem to be an early symptom, in agreement with Lauer and colleagues [18] becoming warning signs even in oligosymptomatic individuals. This aligns with Heidari et al but at a higher percentage [35], suggesting the olfactory epithelium's role as the first line of defense against viruses. In milder cases, sense defects prevent viral spread into the lower respiratory system [34]. Most participants recovered within two weeks, aligning with studies reporting a rapid symptom recovery within the same timeframe [31]. However, it is yet to occur in others [1]. In Europe and the USA, olfactory dysfunctions persisted in half of the patient's even 8 weeks post-symptom onset [20]. Virus near CNS leads to potential long-term neurological effects. Younger ages recover faster; over 40, prolonged effects, influenced by increased transmembrane serine protease 2 with age [36]. Females recover from sense loss 2:1 faster than males within two weeks. Other studies suggest longer recovery for females. Anosmia and ageusia in males usually resolve within 7 days [37]. Controversial results arise from diverse assessment methods for smell and taste dysfunction, potential sex-related inflammatory differences, ethnic variations, faster recovery in Asia, and genetic influences [38]. ACE-2 invasion causes mild temporary anosmia, while NRP1-mediated damage causes more persistent loss. Viral binding with oral mucosal cells induces inflammation, abnormal turnover, and reduced taste bud sensitivity, resulting in sensorineural dysgeusia after COVID-19 [39]. Pfizer vaccine recipients showed a significant association with olfactory dysfunction, similar to the initial finding with influenza vaccine in 0.19% of patients [40]. Post-vaccine inflammation may cause transient smell disorder. Virus presence in neuroepithelium or olfactory bulbs could lead to antibody-related inflammation, causing temporary anosmia. Serum antibodies are higher in severe COVID-19, while nasal antibodies are higher in milder cases. Investigation in vaccinated individuals is essential [41]. The study's strength is in the precise, unbiased assessment with the objective CCCRC method, ensuring accuracy through blind testing, however, the pandemic complicated finding unaffected control participants. Further studies are needed to explore sense dysfunction recovery time relating to COVID-19.

CONCLUSIONS

1. High olfactory dysfunction prevalence was found in this study in comparison to other previous studies
2. Olfactory dysfunction prevalence was higher than the gustatory one within the same sample.
3. Although there were no significant changes regarding age groups and olfactory threshold and identification, the mean of both were higher in age group >35 years old.
4. Sex disparity was detected as more severe scores of olfactory dysfunctions shown in males but higher proportion and milder form of this dysfunction in females.
5. Fast recovery from the dysfunction occurred in females.
6. High significant correlation was detected between hypogeusia and female sex, beside the positive PCR tested participants with one time of infection showed a significant relation with hypogeusia.
7. Pfizer may be more related to olfactory dysfunction as one of its complications.

LIMITATION AND STRENGTH

Study strength was that use of the objective modified CCCRC assessment for this dysfunction is more accurate and with decreased bias results due to the blind testing of the participants and precise scoring values.

Study was limited by the pandemic making it very difficult to find normal, non-infected control participants for comparison purposes.

Follow-up the sense dysfunction recovery time related to COVID-19 by using repeatable CCCRC test could be a very valuable step.

Dentists as a sample not selected in the previous studies to compare these study findings with.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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