Smell Dysfunction in Patients with Primary Sjögren's Syndrome: impact on quality of life

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Research Article

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Abstract

Objectives

Patients with primary Sjögren's Syndrome (pSS) often report smell and taste disturbance. However, a correlation between the smell impairment and mucosal dryness is not well understood. The objectives of this study were to investigate: 1) The prevalence of smell hypofunction in patients with SS. 2) The impact of smell hypofunction on the quality of life (QoL) 3) Whether the smell is corelated to xerostomia. 4) Whether the smell function is affected by taste hypofunction, disease duration, age, smoking or with self-reported neuropathy.

Methodology:

An ethically approved cross-sectional study was conducted on 65 female patients with SS and 62 sex-matched healthy controls. The smell was assessed using the University of Pennsylvania Smell Identification Test. The taste acuity was assessed using Taste Strips Test. Visual analogue scale was used for self-assessment of the smell and taste functions. Xerostomia was assessed by salivary flow rate, the clinical oral dryness score and Xerostomia Inventory. The QoL and mental health well-being were assessed using validated questionnaires.

Results

In the SS group, the smell function was impaired in 27/65 compared with controls (15/62 $p < 0.05$) and it did not correlate with the severity of xerostomia, taste acuity ($r = 0.05$, $p = 0.6$) or with the self-reported nasal dryness ($r=-0.02$, $p = 0.7$). In the patients group, the smell hypofunction was not correlated with disease duration ($\beta = 0.1$, 95% CI=-0.07-0.1), or smoking ($\beta=-0.02$, 95% CI=-8-7). Age was not correlated with the smell function in the patients' group ($\beta=-0.1$, $P = 0.5$), but correlated significantly with the smell in the healthy participants group ($\beta=-0.3$, $P = 0.02$). Neuropathy affected 81.2% of the patients group. The QoL and mental health well-being were not affected by the smell hypofunction.

Conclusion

Smell hypofunction appears to be a clinical manifestation in patients with SS, but it does not seem to be associated with the severity of mucosal dryness or with taste disturbance.

Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease of unknown aetiology that primarily affects the exocrine glands, leading to functional impairment and dryness of mucosal membranes. Patients

diagnosed with SS frequently report dryness of the nasal passages and olfactory disorders but only a few studies have addressed this problem in these patients.

Smell and taste dysfunction have been previously reported in patients diagnosed with SS [1,2], but the number of recruited participants was limited in these studies.

However, there are other studies which do not support that the smell is impaired significantly more in patients with SS[3,4]. The findings of studies of the aetiology of smell dysfunction has also been contradictory. Some studies correlated the smell disturbance to mucosal dryness of the nasal cavity [1,2]. Others suggested that the systemic inflammatory process in SS as the aetiological factor for the smell dysfunction in patients with SS[5], contradicting a previous study where no association was found between the impaired smell function and the inflammatory markers of the syndrome [6].

Peripheral neuropathy is a well-documented symptom in patients with SS[7,8]. Some studies reported that the integrity of the neurological function of olfaction is important for smell acuity[9,10]. In addition, smell impairment has been recognised as an early feature in patients with neurodegenerative and age-related disorders such as Alzheimer and Parkinson's Disease[11,12,13]. However, whether there is a neurological basis for smell dysfunction in patients with SS has not been studied. In the current study, we investigated whether patients who have peripheral neuropathy, also demonstrate impaired smell, in an attempt to provide preliminary data for future studies.

It is recognised in the literature that patients diagnosed with SS may have smell and taste problems[14,15], but it is unclear whether the smell dysfunction is influenced by the taste disturbance in these patients or correlated with the dryness of mucosal membranes or with neuropathy. Therefore, the primary aims of this study was to assess the prevalence of smell dysfunction in a cohort of patients with SS, to evaluate the impact of smell dysfunction on the QoL, to investigate whether the smell function is correlated with the severity of mucosal dryness or with a taste dysfunction. The secondary aims were to investigate whether the smell function is correlated with the taste, disease duration (the onset of the symptoms), age, smoking or with self-reported neuropathy. This study is part of a larger project where persistent dryness of the mucosal membranes in patients diagnosed with pSS was hypothesised to compromise the senses of smell, taste and sexual function which can affect the quality of life and mental health well-being[16].

Study Group

The study was based in the Multidisciplinary Sjögren's Clinic, Institute of Dentistry, Queen Mary University of London, UK. One researcher (MA) performed the recruitment procedure during the period between 2nd March and 30th November 2016 and investigations were performed daytime (10am-4pm) based on participants' conveniences. Eligible patients were defined as women diagnosed with pSS according to the AECG criteria[24]. Sixty-Five patients were recruited from the above clinic or identified by screening 337 patients records on the clinical database. The database was reviewed and suitable patients who have

given consent in the past and met the eligibility criteria were sent an invitation pack in the post with full information of the research project. Additionally, the research project was announced on the British Sjögren's Syndrome Association (BSSA) website and interested pSS members were invited to contact the research team.

For comparison, healthy participants were recruited from the general population. The project was advertised in the Institute of Dentistry with contact details of the research team for interested people to take part. Sixty-two sex-matched healthy individuals aged 18 years or more, who were capable to provide informed consent and who were able to understand verbal and written information in English, with the support of the researcher, were recruited to the control group.

Participants were excluded if they had current cold/blocked nose or have had head and neck radiation, chemotherapy treatment, chronic salivary gland disease or swelling, secondary SS, asthma, allergic sinusitis, uncontrolled diabetes, pregnancy, breast feeding, candidiasis, lichen planus, severe gum disease and dental caries that can interfere with the taste function and QoL. A record of current medications taken by the study participants was kept, to assess whether there is an association with the smell or taste function.

Methodology

A cross-sectional study was given an ethical approval by a Research Ethics Committee to be carried on 65 primary SS (pSS) female patients diagnosed according to the American European Consensus Group (AECG) criteria, and 62 sex-matched healthy volunteers[24]. All study protocols were approved by Research Ethics Committee of London Bridge (Reference number: 15/LO/2064, 10/02/2016). One investigator performed all assessments in no particular order for both groups. Information of oral and general health, medications smoking habits were obtained from all participants by history taking and/or medical records.

The smell function was assessed by the University of Pennsylvania Smell Identification Test (UPSIT-40) (Sensonics, USA), which is a forced choice test for the quantitative assessment of the smell function[17]. The test comprises of a standardized 40-item distributed into four booklets; each booklet has ten boxes of embedded microencapsulated odours with four different choices provided for each box. Participants had to scratch each box with the provided pencil, sniff the released smell and then select an appropriate match out of the provided options on the relevant page of the booklet. A score was then calculated for the final recognition of each subject. A special version of this test was ordered to match the British cultural norms. The smell test results were calculated collectively to indicate acuity of smell in each individua. There was no gradient, and each smell was given a binary value (one of two scores, i.e., yes or no) then added as a total value at the end. A cut off point for smell dysfunction for all participants was given at ≤ 30. Taste Strips Test (TST) (Burghart Medical Technologies, Wedel, Germany) was used to assess the threshold of the taste function of four primary tastes: sweet, sour, salt and bitter. These strips were placed

on three sites on the anterior 2/3 of the tongue; tip, right and left sides[14]. The taste test results were grouped according to each individual test tested; sweet, sour, salt and bitter.

Nasal dryness was assessed subjectively by asking patients whether they suffer from this symptom, which is part of 11 items in the Xerostomia Inventory that was used to assess xerostomia[20]. The xerostomia severity was assessed clinically, by stimulated (SSFR) and unstimulated (USSFR) salivary flow rate (SFR), and by clinical oral dryness score (CODS)[18,19,20,21]. World Health Organisation Quality of Life-BRÉF (WHOQOL- BRÉF) and Hospital Anxiety and Depression Scale (HADS) were used to assess the general QoL and mental health well-being[22,23]. A Visual Analogue Scale (VAS) was used for self-rating the smell "How do you rate your sense of smell?" by all participants with an arbitrary cut-off value of < 50 over a 100 graded scale. The study group were asked open ended questions to assess symptoms of neuropathy. These questions are routinely used in neurology clinics at the Royal London Hospital, for the clinical assessment of neurological impairment:

-Have you lost feeling in your hands and/or feet?

-Do you have tingling in your hands and/or feet (pins and needles)?

-Do you have numbness in your hands and/or feet?

-Have you suffered from clumsiness?

Statistical analysis

Data were analysed using the latest version of Statistical Package for Social Sciences, IBM Corporation, SPSS Inc., Chicago, IL, USA version-23 statistical software. A pilot study was conducted to help estimate the sample size calculation, which was based on a mean difference of the smell and taste outcome of a larger study. The power was set at 90% and the level of significance at 5%. It was concluded that a total of 75 participants (patients with SS and healthy volunteers) would be enough to detect that level of difference. The sample was inflated by 20% to give a total of 90 participants (45 patients and 45 healthy volunteers) to account for any potential dropout. Continuous variables were expressed as mean difference followed by P-value or 95% confidence interval (CI). Independent t-test, Chi-square and multiregression analysis tests were used. Residual plots were used to assess quality of regression. Frequency analysis was used to determine the rate of the self-reported neuropathy symptoms by patients.

Results

Sixty-five patients and sixty-two sex-matched healthy volunteers gave consent and participated in the study. All literate with different levels of educational attainment with age mean, (± SD) of patients 59 ± 13 (Patients' age range 24–83 years) and healthy volunteers 43 ± 15 (Volunteers' age range 21– 93 years) (Table 1). Smoking was reported in 6% of participants in each groups (n = 4 patients, n = 4 healthy participants), whilst chewing betel leaves was only reported in 3% of the healthy participants group (n =

2). The medications reported by the participants were: hydroxychloroquine,pilocarpin, supplements, antidepressants, immunosuppressants, anticoagulants, antihistamine, antihyperthyroids, antihypothyroids, antibiotics, angiotensin, pain relief, antiacid drugs, hepoglycaemic, inhalers, primary biliary cirrhosis drugs, overactive bladder drugs, topical medicines (Eye drops, Eye gels, Viscotears –liquid gel-, Skin creams and Telmesteine) and gabapentine. Multiregression analysis was used to assess the effect of these medicines on the smell and taste in the patients group.

Table 1
Characteristics of patients and healthy volunteers.

Characteristics	**Patients**	**Volunteers**
	n = 65	**n = 62**
Age	Mean ± SD	Mean ± SD
	59 ± 13	43 ± 15
Smoking	2 ± 0.2	4 ± 1
Smokeless tobacco	1 ± 1.4	2 ± 0.1
Alcohol	1.3 ± 1.2	1.6 ± 0.5
Mouthwash	1.2 ± 1	1.5 ± 0.5
USFR*	0.13 ± 0.1	0.6 ± 0.4
SSFR*	0.6 ± 0.7	11.8 ± 26
CODS*	16 ± 30	0.7 ± 1
Xerostomia Inventory	48 ± 5	16.6 ± 5
VAS* smell	7.5 ± 17	11.2 ± 25
Disease duration	17.2 ± 16	---
*USFR: unstimulated salivary flow rate, cut-off value is ≤ 1.5 ml of saliva in 15 minutes.		
*SSFR: stimulated salivary flow rate, cut-off value is ≤ 0.6 ml/min of the whole stimulated salivary		
*CODS: clinical oral dryness scale. Mild dryness was indicated to scores ranged one to three. Moderate dryness was referred to scores ranged four to six and sever dryness when the score ranged seven to ten.		
*VAS: visual analogue score, cut-off value was specified at < 50 for poor rating.		

The smell function was statistically significantly impaired in the patients' group (30 ± 7) compared with the controls (34 ± 5). The mean difference (4, 95% CI = 1.8–6.1) and percentage difference (17.4, P = 0.03) of the smell function between the two groups were both statistically significant. Individuals with hyposmia comprised 41.5% (n = 27/65) of patients with SS vs 24.1% (n = 15/62) healthy controls. In the self-assessment of the smell quality using VAS, a significant positive correlation was found between the

smell function and VAS smell in the patients' group (r = 0.7, p = 0.00). Interestingly, only 7.3% (n = 10) of the patients' group were aware of the loss of their smell acuity (Table 2).

Table 2
Comparison of the dysfunction rate of the study outcomes in pSS patients compared with healthy volunteers

Test	pSS group Mean age: 59 95% CI = 59–62	Healthy volunteers group Mean age: 43 95% CI = 39–47	Mean difference (95% CI)	P-value	Type of test
Smell function[1]	41.5% (n = 27/65)	24.1% (n = 15/62)	3.9 (1.8-6)	< 0.05	Clinical
Taste function[2]	54% (n = 34/63)	8.3% (n = 5/60)	4.3 (3.4–5.2)	< 0.05	Clinical
Quality of life[3] Psychological domain (D2)	47.7% (n = 31/65)	9.8% (n = 6/61)	11.8 (6.9–16.6)	< 0.05	Questionnaire
Quality of life[3] Social domain (D3)	44.6% (n = 29/65)	21.3% (n = 13/61)	11.9 (5.2–18.7)	< 0.05	Questionnaire
Quality of life[3] Environmental domain (D4)	21.5% (n = 14/65)	9.8% (n = 6/61)	6 (0.9–11.2)	< 0.05	Questionnaire
Mental health well-being[4] Anxiety	58.5% (n = 38/65)	21% (n = 13/61)	2.8 (1.5–4)	< 0.05	Questionnaire
Mental health well-being[4] Depression	32.3% (n = 21/65)	8.2% (n = 5/61)	3.5 (2.3–4.6)	< 0.05	Questionnaire
1: Calculated as normal smell function of ≥ 30 in 0–40 scale; 2: Normal taste function of ≥ 9 in 0–16 scale;					
3: Overall QoL ≥ 60 in a scale of 0–100; 4: Normal HADS scores < 8.					

In the patients' group, xerostomia was found in 78.4% (n = 51/65) using USFR, 64.6% (n = 42/65) using SSFR and 84.6% (n = 55/64) using CODS assessments (Table 1). The multiregression analysis revealed that the severity of xerostomia, assessed by USFR and CODS did not contribute to the smell dysfunction in pSS group (Table 3).

Table 3
Coefficients' table of the multiregression analysis of the impact of xerostomia assessed by USFR, SSFR and CODS on the smell function in pSS group.

Xerostomia tests	Standardized coefficients	95% CI for B	R^2
USFR	0.03	-11.2–15	0.19
SSFR	0.1	-1.6–4	0.2
CODS	-0.1	-1.1–0.8	0.19

The impairment of the smell function in the SS group was not correlated with the QoL in any of the assessed domains; Physical (β=-0.02, 95% CI=-1.4-1.3), mental (β = 0.1, 95% CI=-0.9-1.4), social (β = 0.1, 95% CI=-0.9-1.6) or environmental (β = 0.1, 95% CI=-1-1.3). Also, the mental health well-being in its both domains; anxiety (β = 0.1, 95% CI=-0.2-0.3) and depression (β=-0.1, 95% CI=-0.3-0.2) were not associated with the smell dysfunction (Table 4).

Table 4
Coefficients' table of the impact of the smell dysfunction on QoL and mental health well-being in pSS group.

QoL	Standardized Coefficients (B)	95% CI for B	R^2
Physical domain (WHOQoL-BRÉF)	− .018	-1.4–1.3	0.35
Psychological domain (WHOQoL-BRÉF)	0.1	− .9–1.4	0.31
Social domain (WHOQoL-BRÉF)	0.1	-0.9–1.6	0.51
Environmental domain (WHOQoL-BRÉF)	0.06	-1–1.3	0.31
Anxiety (HADS)	0.1	-0.3–0.4	0.39
Depression (HADS)	-0.1	-0.4–0.2	0.47

Smell And Taste

When the data of both groups were pooled (total population n = 127), a significant positive correlation was found between the smell and taste function (r = 0.3, P = 0.05). However, the smell function was not a good predictor of the taste acuity in the total population of the study (β = 0.09, 95% CI=-0.03-0.1).

In the SS group, no significant correlation was found between the smell and taste function (r = 0.05, p = 0.6), unlike in the healthy group, where a significant positive correlation was established between the smell and taste (r = 0.2, P = 0.05). In the regression model, the smell function was not with a predictor of the taste acuity neither in the SS (β=-0.06, 95% CI=-0.1-0.08) or in the control group (β = 0.2, 95% CI=-0.03-0.2) (Fig. 1).

No significant correlation was found between the self-reported nasal dryness that was assessed by one of the Xerostomia Inventory items, and the smell function (r=-0.02, P = 0.2) in the study group. Similarly, the smell function in the patients' group was not correlated with disease duration (β = 0.1, 95% CI=-0.07-0.1), or smoking (β=-0.02, 95% CI=-8-7). Age did not seem to influence the smell function of the patients' group (β=-0.1, P = 0.5), but there was significant negative correlation between age and smell in the healthy participants group (β=-0.3, P = 0.02).

Effect Of Medicines On The Smell Function And Mucous Membrane

In the patients' group, topical medicines correlated with the smell function and were a good predictor of its impairment (β=-0.4, 95% CI=-9 - -0.7) and the severity of xerostomia (β = 0.4, 95% CI = 0.3–2.2) that was assessed by CODS. Nasal dryness that was assessed by item 11 of the Xerostomia Inventory, correlated significantly with hydroxychloroquine (β = 0.4, 95% CI = 0-2.1) and supplements (β=-0.3, 95% CI = 0- -2). Pain relief (Aspirin, Codeine, Co-codamol, Diclofenac, Fentanyl, Naproxen, Painkiller, Paracetamol) associated significantly with the impairment of taste function (β = 0.3, 95% CI = 0.1–3.8). Gabapentin (β=-0.2 95% CI=-6.4–0.3) and inhalers (β=-0.2. 95% CI=-8.8-1.2) correlated with the taste function but not significantly.

Discussion

This study was designed to assess the smell function in patients diagnosed with SS and its correlation with the dryness of the mucous membrane. We investigated the effect of smell impairment on the QoL and mental health well-being in patients with a confirmed diagnosis of SS. Our results demonstrated that patients with SS are more likely to have smell dysfunction compared with healthy controls. The dryness of the mucosal membranes was not the key indicative factor for smell impairment as it was previously suggested in the literature [1,2].

In this study, the statistically significant mean difference of the smell function between both groups was small. In the SS group, 41.5% exhibited disturbance in the smell function compared to the healthy

volunteers (24%), which may indicate that SS can cause smell dysfunction. It is worth noting that the overall prevalence of the olfactory dysfunction in the general population which was reported in a recently published systematic review and meta-analysis (22.2%) is comparable with our findings of the smell dysfunction in the control group (24.1%)[30].

Interestingly, the majority of patients with SS who had abnormal UPSIT results, were unaware of any smell problems and reported no change in their smell function or acuity. Perhaps this is attributed to coping mechanisms that patients with SS develop over time.

Henkin et al. (1972) and Kamel et al. (2009) suggested a correlation between the deteriorated of smell function and the dryness of the nasal mucosa in patients with SS. However, our results did not support the aforementioned studies and revealed no correlation between smell dysfunction and the dryness of the mucosal linings in SS. Our findings, however, are in line with a study by Rasmussen et al (1986), which demonstrated that the smell threshold is not associated with the severity of the dryness of the nasal mucosa in patients diagnosed with SS.

Due to the rarity of patients diagnosed with SS, it was difficult to exclude those on medications, which would otherwise limit the pool of patients required for the current investigations. When confidence intervals are reported, the interpretation is aided by the knowledge of range of possible results rather than a single p-value. Therefore, Bonferroni correction is recommended for consideration in the future.

Age was not correlated with smell in our SS group, which contradicts a previous statement of the negative correlation between age and smell in patients with SS[2]. However, in our healthy group, there was significant negative correlation between age and smell, which is an anticipated regression of the smell function with age[25,26,27].

Smoking a had weak association with the smell function in the patients and healthy volunteers groups. This finding supports previous evidence which demonstrated an association between heavy smoking and smell deficit[2,28,29]. Interestingly, our data showed that the highest score of the smell test (39/40) was recorded by a heavy smoker healthy participant, who reported smoking 20 cigarettes per day. This participant reported that the smell acuity has not been changed, which may be due to the continuous renewing process of the nasoepithelium due to the exposure to the smoke particles.

Disease duration did not influence the smell function in the patients group. This was a surprising finding as it is anticipated that with time, disease would progress and therefore patients with longer disease duration would be more likely to be symptomatic. We are unaware of a study that has investigated the association of the disease duration with the smell function in patients diagnosed with SS, therefore, studies for comparison are not applicable.

Within the SS group, patients who were on topical medicines (e.g., Eye drops, Eye gels, Skin creams) had significantly more smell disturbance, (β=-0.4, 95% CI=-8.6 - -0.7) than those who did not report using

topical preparations. It is presumed that patients with more severe SS symptoms are the ones who are more likely to have the smell dysfunction and more likely to be on topical medications.

Correlation Between Smell And Taste

The evidence in the literature is conflicting on whether a correlation between smell and taste exists. Our study revealed that smell and taste functions were correlated in the study population as a whole (n = 127) and in the control group (n = 62) but not in the patients' group (n = 65). This can be attributed to the presence of underling factors that impeded the correlation of both variables in this SS group. In the current study the prevalence of the neuropathy, was 81.2% in our pSS population. The symptoms that were reported ranged from "lost feeling" to "tingling", "numbness" or "clumsiness". Our results support previous findings of smell disturbance in patients with polyneuropathic symptoms, in which neurological function integrity was found to be important for olfaction acuity[9,10]. Therefore, neuropathy should be considered as a possible factor compromising the smell function in patients diagnosed with SS. However, assessing the nerve function of the smell sensation was beyond the remit of the present study. Furthermore, factors such as, mucosal oedema or nasal crusting may potentially be possible contributing factors that can compromise smell in patients with SS. The data in this preliminary study suggest that including CT scan and endoscopy in studies investigating smell disturbance, would lead to a more robust results and stronger evidence for the aetiology of olfactory dysfunction.

We concluded that the smell dysfunction did not compromise the QoL or the mental health well-being in patients diagnosed with SS. This finding was similar to our findings reported in a previous publication showing that taste impairment in patients with SS did not compromise the QoL or mental health well-being[14]. These findings indicate that the smell and taste problems were not identified as significant health issues by patients with SS. Our results contradicted others who suggested that the impairment of smell and taste contributed to a diminished QoL in patients with SS[2].

Conclusion

Irrespective of age, the smell function was affected in patients diagnosed with SS but not influenced by the dryness of the mucosal linings, neuropathy or by taste. It appears that these patients can cope with reduced smell function without any impact on the QoL and mental health well-being.

Declarations

Acknowledgement: Not applicable.

Ethics approval and consent to participate: All methods were carried out in accordance with the Research Ethics Committee of London Bridge (Reference number: 15/LO/2064, 10/02/2016). All procedures were performed in accordance with relevant guidelines, and the Declaration of Helsinki. Informed consent as defined by the Mental Capacity Act 2005 to participate and to publish was obtained from all participants.

Consent for publication**:** Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contribution:

ME: Contributed to the design of the study, data acquisition and interpretation, performed all statistical analyses, drafted and critically revised the manuscript

AT: Contributed to the conception and design of the study, contributed to the results interpretation, drafting and the critical revision of the manuscript

KK: Contributed to conception, design, data interpretation and critical revision of the manuscript.

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Figures

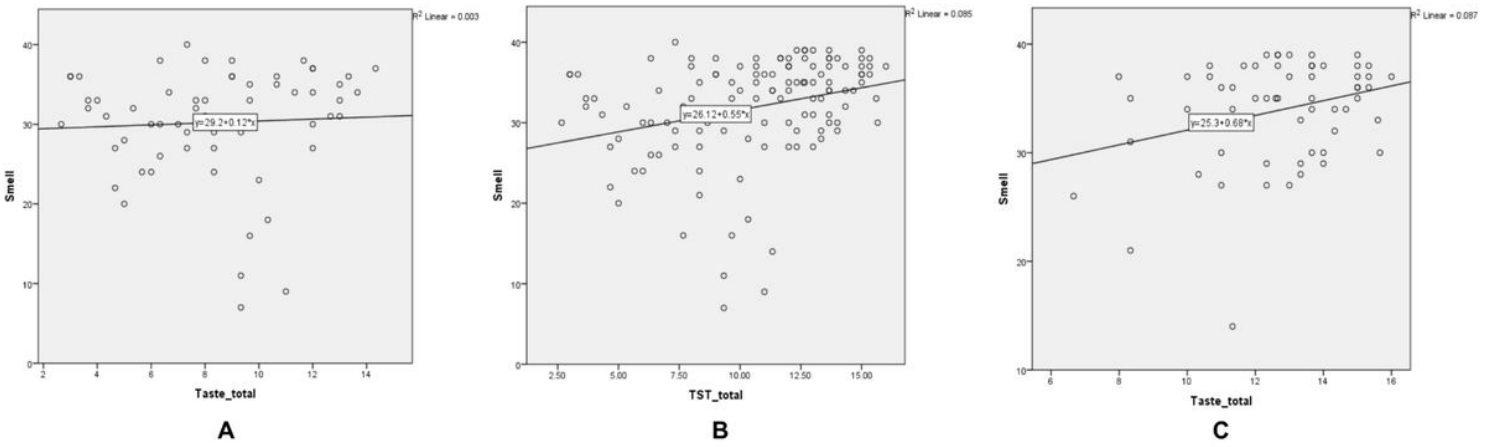

Figure 1

Correlation of the smell and taste in the study

(A) Patients' group (B) Control group (C) Total population of the study (patients and controls).