Association between olfactory training and quality of life in patients with impaired sense of taste and smell following COVID-19
- a randomized controlled trial

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Introduction

Loss of the sense of taste and smell occurs in 65-88% of patients infected with new corona virus and is considered the most common symptom of COVID-19 (1). In contrast to previous post-viral olfactory loss, in coronavirus it is often younger patients, with milder course of COVID-19, who experience the combined taste and smell loss (1,2). The duration of the impaired sense of taste and smell ranges from a few days to weeks after the cessation of infection (3). 20-28% of the patients have persistently impaired sense of taste and smell (4), which is also one of the most frequently reported late sequelae after infection with COVID-19 (3).

Previous studies show that loss of the sense of smell is closely associated with a decline in quality of life (5,6). Smell training twice a day has been shown to be effective in other groups of patients with impaired sense of smell (7,8), whereas in patients with late sequelae of COVID-19, there is not yet evidence on the long-term effect of smell training and whether it can improve quality of life in this group of patients, and this should be investigated.

Background

Post-infectious olfactory loss is the second most common form of odour loss and occurs mainly after viral infections of the upper respiratory tract, such as influenza virus, rhinovirus, adenovirus and virus strains of the corona family (1). COVID-19, also a viral respiratory infection, was declared a pandemic by the WHO in March 2020 (3). COVID-19, which is caused by novel coronavirus (SARS-CoV-2), can present as anything from mild illnesses with mild colds to severe lower respiratory tract infections (3,9). SARS-CoV-2, like previous corona variants, is transmitted by droplet and contact transmission (9). One of the earliest and most frequent symptoms of COVID-19 is the combined loss of the senses of smell and taste, which, unlike previous post-viral odour losses, has been shown to frequently affect younger patients, as well as women, with milder disease courses (1,9).

The olfactory function

Odour molecules reach the olfactory epithelium along two pathways, the orthonasal and retronasal. In orthonasal olfaction, odours in the external environment reach the epithelium through inhalation via the nostrils. This happens when we breathe or sniff with our mouth closed. Retronasal olfaction is the perception of odours emanating from the oral cavity during eating and drinking (10).

The retronasal passage is essential for the sense of taste, as the taste buds' discrimination between the different tastes must be combined with olfactory stimuli to obtain differentiable sensations of tastes and aromas (10). The sense of taste and smell are therefore perceptually closely linked, as they both contribute to the experience of taste (8,10), which is why patients with an impaired sense of smell will often complain of an impaired sense of taste.

Olfactory dysfunction can be divided into quantitative and qualitative (1,8,11). The quantitative olfactory dysfunctions are categorized into hyposmia (reduced olfactory function) and anosmi (absence of all olfactory function). The qualitative olfactory dysfunctions are defined as disorders of odour identification, including parosmia (altered odour perception with odour present) and phantosmia (perception of smell without odour present) (1,8,11). The cause of the olfactory dysfunction caused by COVID-19 is thought to be comparable to previous post-viral olfactory dysfunction where the sensory loss is due to an effect on the mucosa and/or olfactory neurons (12). The olfactory dysfunction, as a late sequelae to COVID-19, can manifest both quantitatively and qualitatively as anosmia, hyposmia, parosmia and phantosmia (12).

Olfactory training

Olfactory training in patients with impaired sense of smell is often effective regardless of the etiology (8,11). However, the long-term effect is not yet known for the post-viral odour loss as a late follow-up to COVID-19. Olfactory training is performed by smell the same four different odours for 20 seconds in the morning and evening for three months, after which the patient is switched to a new set of odours (8,12). The scents should have a high concentration of fragrance molecules, so essential oils are recommended, for example, orange, lavender, peppermint and clove (13). It is thought that the effect of olfactory training is due to stimulation of the formation of new olfactory sensory neurons, but the effect may also be due to increased central registration of the olfactory stimuli themselves (8,11). Patients with loss of taste and smell will often experience an improvement in taste first, followed by a gradual improvement in smell (14). In the course after the postviral odour loss, parosmia is commonly known to occur and is considered a good prognostic factor (8,14).

Quality of life

International studies show that loss of the sense of smell is closely associated with deterioration in quality of life, as impaired sense of smell affects patients' eating experience, their sexual life and creates concerns about personal hygiene, which reduces participation in social life (5,6,11).

The loss of the sense of smell affects the patients' appetite, as the food is tasteless, and therefore reduces the pleasure of eating. The meal-related problems are not limited to the meal itself, but also to the tasting during preparation (5). Patients experience problems with tasting when the food burns, as well as smelling spoiled food, which can have an impact on their health (5,6). A common concern among patients with impaired sense of smell is the risk of not being able to smell smoke and gas, which can be a potential life-threatening hazard (5).

Personal hygiene has also been reported as a problem in patients with impaired sense of smell, as patients are concerned about not being able to perceive their own body odours such as sweat and bad breath (5,6). Loss of the sense of smell may have implications for working life, as this sense is essential in some types of occupation. Some patients may therefore experience problems in their working lives and have to ask for special accommodations, where others have to change profession (5). 25-33% of patients with loss of the sense of smell even show depressive symptoms, and international studies show that parosmia and phantosmia in particular are risk factors for high depression scores (5,6).

Aim

The aim is to investigate whether guided systematic olfactory training with essential oils to improve impaired sense of taste and smell following COVID-19, can improve patients' quality of life.

Hypothesis

The impaired quality of life in patients with impaired sense of taste and smell following COVID-19, can be significantly improved in patients performing olfactory training with essential oils, compared to patients performing olfactory training with placebo oils.

Primary outcome

To demonstrate improvement in quality of life measured by the QoL questionnaire ‘Taste and Smell Tool for Evaluation’, in patients diagnosed with anosmia, hyposmia og parosmia following COVID-19, randomised to three months of olfactory training with essential oils compared to control patients performing olfactory training with placebo oils.

Secondary outcome

To demonstrate whether three months of olfactory training with essential oils can improve the sense of taste and smell, measured objectively by TDI, in patients diagnosed with anosmia, hyposmia or parosmia after infection with COVID-19, compared to patients performing olfactory training with placebo oils.

To demonstrate whether three months of olfactory training with essential oils has an impact on depressive symptoms measured by the Major Depression Inventory (MDI), in patients with anosmia, hyposmia or parosmia after infection with COVID-19, compared to patients performing olfactory training with placebo oils.

Materials and methods

Study design

Patients with impaired or complete loss of taste and smell following COVID-19, will be block randomised to the intervention or control group using SPSS. At randomisation, the type of odour loss related to COVID-19 (hyposmia/anosmia/parosmia) and gender is stratified.

Patients in the intervention group receive four essential oils with scents of orange, lavender, clove, and peppermint. Patients in the control group also receive a fragrance kit, consisting of the same containers, but with fragrance-free oils added. Both the intervention and control groups are instructed to smell each of the four oils for 30 seconds in the morning and evening, over a three-month intervention period. Patients are given a diary in which to record their olfactory training and a weekly status of their olfactory function (VAS).

The nurse or medical student instructing the patients in the training and performing the TDI tests at the initial visit and at the follow-up visit after the intervention period is blinded. Patients receive a twice-weekly SMS reminder about olfactory training.

Study population and recruitment

The study population consists of patients referred to the Unit for Sense of Taste and Smell in the Department of Otorhinolaryngology Head & Neck and Audiology at Rigshospitalet. The referral criteria for the Unit are that the patients must have been assessed by a private practice otorhinolaryngologist who has performed an ENT examination (including endoscopy of the cavum

nasi and a prick test) and referral for MR regio olfactoria. Patients must have had complaints of taste and smell > 3 months and be diagnosed with hyposmia or anosmia based on Sniffin Sticks 12 (SIT12) or BSIT.

Inclusion and exclusion criteria

To be included in the intervention study, the patient must meet the following criteria:

Inclusion criteria:

- Impaired sense of taste and smell following COVID-19 > 3 months
- Hyposmia (15-30) or anosmia (<15) assessed by TDI test with Sniffin Sticks performed in the Unit for Sense of Taste and Smell or medical assessment of parosmia based on medical history
- > 18 years of age

Exclusion criteria:

- Cause of hyposmia, anosmia or parosmia other than COVID-19
- Impaired sense of taste and smell >24 months
- Does not read or speak Danish
- Lack of compliance to perform daily olfactory training

If patients meet the inclusion and exclusion criteria for participation in the intervention study at their initial visit in the Unit of Sense of Taste and Smell, they will receive information about the project from the investigator in her office, where the information can be given undisturbed. Patients are informed of all the advantages and disadvantages of participation in the study and based on this information, must give written informed consent prior to inclusion in the project. If patients wish to participate, they may be randomised at the initial visit to the intervention or control group and receive instruction in the performance of olfactory training. If patients wish to have further reflection time, they will be given the contact details of the study investigators and can then make enquiries if they are interested in participating in the study. These patients will be invited to a physical visit to the unit, where they will sign informed consent, be randomised, and receive instruction in the olfactory training.

Procedures

TDI test

To assess patients' sense of smell, the TDI test with Sniffin' Sticks is used, which is a validated tool with normative data (8,15). In practice, the TDI test is performed by a blinded nurse or medical student sitting with the patient in a room free of distracting factors and with the possibility of ventilation. The threshold test is performed first, followed by the discrimination test and finally the identification test (16,17).

Threshold test: the patient must smell 16 times three scent pens with different scent intensities of n-butanol. The test determines how strong the odour must be before the patient can detect it (16). Three scented pens are presented to the patient in randomised order; one scented pen contains n-butanol and two of the pens are odourless. The patient is asked to smell each of the three scent pens for four seconds with a five-second break between each pen. The next three pens are then presented to the patient for 30 seconds. During the threshold test, the patient is blindfolded and asked to identify which pen contains n-butanol. If the fragrance cannot be identified, the patient must make a guess. The score of the threshold test ranges between 1-16 (15).

Discrimination test: the patient must smell 16 times three scent pens, in randomized order, where two of the pens contain the same scent and the third contains a different scent. The patient must smell each of the three pens for four seconds with a five-second break between each pen, after which 30 seconds must elapse before the next three pens are presented to the patient. During this test, the patient is blindfolded and asked to identify which of the two scent pens smells different from the other two. If this pen cannot be identified, the patient is asked to make a guess (17). The score of the discrimination test ranges between 0-16 (15).

Identification test: the patient must smell 16 scented pens with common odours. The patient has to identify the odours in the scent pens using four answer options for each odour (16). For the identification test, a Danish validated answer sheet is used, which is adapted to the linguistic and cultural factors of the Danish population (18). The patient is asked to smell each of the 16 scent pens for four seconds followed by a 30-second pause before the next scent pen is presented to the patient. If the odour cannot be identified from the four response options, the patient must make a guess (17). The score of the identification test ranges between 0-16 (15).

The results of the three subtests makes a total TDI score (11,15). A score >30 indicates normal olfactory function, a score between 15-30 indicates hyposmia and a score <15 indicates anosmia in the form of severely impaired or complete loss of olfaction.

Taste test

To assess patients' sense of taste, taste sprays developed by XXX, are used. The sprays consist of the four basic tastes and a neutral resolution: 1) citric acid monohydrate resolution 5% (sour), 2) sucrose resolution 10% (sweet), 3) natriumchlorid resolution 7,5% (salty), 4) Quinine hydrochloride 0,05% resolution (bitter), and 5) purified water (neutral). In practice, the taste test is performed by a nurse or medical student who sprays each of the five sprays on the patient's tongue. The patient is then asked to indicate the perceived taste of either salty, sour, sweet, bitter og neutral. After each spray, the patient should rinse their mouth with water. The patient scores one point for each correct recognition and can therefore have a maximum score of five points.

Questionnaires

Taste and Smell Tool for Evaluation:

To investigate whether olfactory training can improve the quality of life in patients with anosmia, hyposmia or parosmia, the QoL questionnaire 'Taste and Smell Tool for Evaluation' is used. The questionnaire is Danish validated and aims to investigate the quality of life in this patient group.

Major Depression Inventory (MDI):

The Danish validated questionnaire, Major Depression Inventory (MDI), is used in the project to assess whether the patient is depressed and to make a possible assessment of the severity of depression.

Statistical analysis

The statistical analysis of the data is performed using IBM SPSS Statistics. Results are presented as mean, SD, range and 95% CI. The parametric data are compared by paired and unpaired tests, and the non-parametric data by Wilcoxon Signed-Ranks Test and Mann-Whitney Test. Categorical variables are tested by chi-square test. A P-value <0.05 is considered significant.

Power calculation

As the primary outcome of the intervention study is to demonstrate an improvement in patients' quality of life measured by the QoL questionnaire 'Taste and Smell Tool for Evaluation', the power

calculation will be based on this questionnaire, which is currently being developed. As the questionnaire is not yet published, a provisional MCID of 1 point and SD=1 is set. α-value <0.05 and β-value of 80%. Therefore, 16 patients in the intervention group and 16 patients in the control group are needed to demonstrate a change in quality of life related to olfactory training. With an expected dropout rate of 20%, 19 patients will be needed in each group. The final result of the power calculation will depend on the questionnaire when published from the Flavour Clinic Holstebro (expected end of November 2022). It is expected that approximately 75 patients will be included in each group.

Risk and side effects

There are no serious side effects associated with participation in the trial. However, as previous research shows that the best effect of olfactory training is achieved if it is started within 12 months of the onset of symptoms, there is a risk that patients in the control group may have a worse prognosis than patients in the intervention group. As one of the referral criteria for the specialised assessment in the Unit of Sense of Taste and Smell is that patients should have had an impaired sense of smell for >3 months, there is a risk that patients in the control group may start olfactory training later than recommended. To reduce this risk, patients in the control group will receive a paid olfactory training kit on equal terms with the intervention group, soon after the end of the trial. As the intervention study is carried out in a public hospital in Denmark, the public patient reimbursement scheme will cover any injury suffered by the study participants during participation in the research project.

Information from patient records and processing of personal data

No personal data will be collected from patient records for this intervention study. The data included in the study consists of data from patient completed questionnaires and results from the clinical objective tests of the sense of taste and smell. Data are obtained and entered the REDCap database only after patient consent, as patients are recruited during their initial visit to the Unit of Sense of Taste and Smell. Consent allows the trial investigator and any controlling authority to retrieve information from the patient's electronic medical record. The study is carried out in full compliance with the Data Protection Regulation and the Danish Data Protection Act. The data collected will be treated confidentially and used exclusively for internal purposes and will therefore not be shared with external data processors. If consent is given during the study, electronic reminders for olfactory training and diary completion (SMS and e-mail) may be sent to participants.

Economy

Patients do not receive payment or travel reimbursement for participating in the intervention study, as the visits to the Unit of Sense of Taste and Smell follow the normal control visits and thus do not require additional driving for patients. As this intervention study is a clinical trial that is part of the regular outpatient operation of the Department of Otorhinolaryngology Head & Neck and Audiology at Rigshospitalet, the evaluation of the patients, including the performance of the TDI test and taste test, is no extra cost. The nurse and/or medical student performing the clinical tests of patients' sense of taste and smell, as well as the investigator performing research as part of her employment as a clinical nurse specialist, are therefore paid by the Department. The purchase of the essential oils as well as placebo oils is covered by the department's Global Airways fund, which is administered by Professor, Vibeke Backer.

Conflicts of interest

There are no conflicts of interest to report related to this study.

Publication of results

The results of the study, both positive, negative, and inconclusive, will be published in relevant scientific journals and at scientific congresses, if possible. The results will also be published on ClinicalTrials.gov.

Ethical considerations

The study is conducted in accordance with the Helsinki Declaration (19). The study is conducted in accordance with the Helsinki Declaration (19). Patients who meet the study's inclusion and exclusion criteria will receive information about the research project at their initial visit to the Unit of Sense of Taste and Smell. If, based on the participant information, patients wish to participate in the study, they will be asked to sign a written informed consent. The project has been notified to and approved by the Capital Region's research registry, Pactius (P-2021-803). The project has also been approved by the Scientific Ethics Committee of the Capital Region (H-21074055).

References

1. Fjældstad AW, Ovesen T. Lugte- og smagstab ved COVID-19. 2020;1–7.
2. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Oto-Rhino-Laryngology [Internet]. 2020;277(8):2251–61. Available from: https://doi.org/10.1007/s00405-020-05965-1
3. Sundhedsstyrelsen. Senfølger efter COVID-19. Sundhedsstyrelsen. 2020;
4. Fjaeldstad AW. Prolonged complaint s of chemosensory loss aft er covid-19. Dan Med J. 2020;67(8):1–11.
5. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life-an updated review. Chem Senses. 2014;39(3):185–94.
6. Rochet M, El-Hage W, Richa S, Kazour F, Atanasova B. Depression, olfaction, and quality of life: A mutual relationship. Brain Sci. 2018;8(5).
7. Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: A meta-analysis. Rhinology. 2017;55(1):17–26.
8. Ovesen T, von Buchwald C. Lærebog i Øre-næse-hals-sygdomme og hoved-hals-kirurgi. 3. udgave. København: Munksgaard; 2020. 15–415 p.
9. Sundhedsstyrelsen. Retningslinjer for håndtering af COVID-19 i sundhedsvæsenet. Sundhedsstyrelsen. 2021;
10. Fjældstad AW, Clausen C, Kjærgaard T, Ovesen T. Lugtesansen har stor klinisk relevans. Ugeskr Læger. 2015;177(3):265–9.
11. Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, et al. Position paper on olfactory dysfunction. Rhinology. 2017;54:1–30.
12. Whitcroft KL, Hummel T. Olfactory Dysfunction in COVID-19: Diagnosis and Management. JAMA - J Am Med Assoc. 2020;323(24):2512–4.
13. Damm M, Pikart LK, Reimann H, Burkert S, Göktas Ö, Haxel B, et al. Olfactory training is helpful in postinfectious olfactory loss: A randomized, controlled, multicenter study. Laryngoscope. 2014;124(4):826–31.
14. Sundhedsstyrelsen. Senfølger ved COVID-. 2021; Available from: https://www.sst.dk/-/media/Udgivelser/2021/Corona/Senfølger/Anbefalinger-for-senfoelger-efter-covid-19.ashx?la=da&hash=77E0083548DBED190E3919EF9B71111409ED608A

15. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the “Sniffin’’ Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: An upgrade based on a group of more than 3,000 subjects.” Eur Arch Oto-Rhino-Laryngology. 2007;264(3):237–43.
16. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. “Sniffin” sticks’. Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses. 1997;22(1):39–52.
17. Wolfensberger M, Schnieper I, Welge-Lüssen A. Sniffin’Sticks®: A new olfactory test battery. Acta Otolaryngol. 2000;120(2):303–6.
18. Niklassen AS, Ovesen T, Fernandes H, Fjaeldstad AW. Danish validation of sniffin’ sticks olfactory test for threshold, discrimination, and identification. Laryngoscope. 2018;128(8):1759–66.
19. Assembly WG. WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS. 2013.

Informed consent for participation in a health science research project

Research project title:
Association between olfactory training and quality of life in patients with impaired sense of taste and smell following COVID-19 - a randomized controlled trial

Trial participant declaration of consent:
I have received written and oral information and I know enough about the purpose, the method, the advantages, and the disadvantages of the trial to give my consent to participate in the trial.

I know that it is voluntary to participate and that I can withdraw my consent at any time without losing my present and future rights to receive treatment.

I give my consent to participate in the research project and have received a copy of the declaration of consent, as well as a copy of the written information about the project.

Name of the trial participant: _____

Date: _____ **Signature:** _____

You will be informed if significant new information regarding your health is disclosed during the research project. If you request **to not be informed** about significant new information regarding your health that is being disclosed during the research project, please tick here: _____ (x)

Would you like to be informed about the results of the research project and any consequences it might have for you?
Yes _____ (x) **No** _____ (x)

Would you like to receive text messages from Department of Otorhinolaryngology, Head and Neck Surgery & Audiology with reminders to perform olfactory training and completion of the diary?

Yes _____ (x) **No** _____ (x)

Declaration from the person providing information:
I declare that the trial participant has received oral and written information about the trial.
I believe that sufficient information has been provided in order to make a decision regarding participation in this trial.

Name of the person providing information: _____

Date: _____ **Signature:** _____