Omega-3 supplementation in postviral olfactory dysfunction: a pilot study*

Anna Kristina Hernandez#, Dorothea Woosch#, Antje Haehner, Thomas Hummel

Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany

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#both authors contributed equally

Abstract

Background: This study aimed to examine whether omega-3 supplementation would support olfactory recovery among postviral olfactory dysfunction patients.

Methodology: Patients with postviral olfactory dysfunction were included in this non-blinded, prospective pilot study. Structured medical history was taken from the patients, including the following: age, sex, history of COVID-19 infection, and duration of symptoms. Patients were randomly assigned to receive olfactory training only (control group) versus olfactory training with omega-3 supplementation (treatment group). All patients exposed themselves twice a day to four odours (phenyl ethyl alcohol [rose], eucalyptol [eucalyptus], citronellal [lemon], and eugenol [cloves]). Olfactory function was measured before and after training using "Sniffin' Sticks", comprised of tests for odour threshold, discrimination, and identification. The average interval between olfactory tests was 3 months.

Results: Fifty-eight patients were included in the study, 25 men and 33 women. Generally, an improvement in olfactory scores was observed. Compared to the control group, the improvement in odour thresholds was more pronounced in the omega-3 group. Age, sex, and duration of symptoms had no effect on olfactory scores among both control and treatment groups.

Conclusion: Overall, the present results indicate that omega-3 supplementation may be an option for adjunct therapy with olfactory training in patients with postviral olfactory dysfunction.

Key words: smell, odour, nose, olfactory, omega-3, postviral

Introduction

Olfactory dysfunction (OD) has received increasing interest in the past years, more so since anosmia has become part of the defining symptoms of coronavirus 2019 disease (COVID-19). However, compared to the impairment of hearing and vision, there are relatively fewer studies done on the impaired human sense of smell. This may be because the sense of smell some may be perceived by some as something that is not as essential in terms of daily life, and also because of the limited treatment options for these conditions. This paucity of studies is also remarkable given that approximately 22.2% of the general population is thought to be affected by olfactory dysfunction[1]. OD has a negative impact on quality of life[2,3], potentially leading to inability to detect health hazards such as fire or toxic fumes[4,5], decreased nutrition from inability to enjoy food[2,4,5], social isolation due to environmental and social anxiety, depression[2], and even an increased risk for mortality[5,6].

Apart from aging, various etiologies have been identified for OD, including infections of the upper respiratory tract, head trauma, chronic rhinosinusitis, iatrogenic causes, and idiopathic cases. Post-infectious causes are frequent, commonly occurring after an upper respiratory tract infection[2,7]. The pathophysiology of this condition is still poorly understood but is known to involve

damage at the olfactory mucosa, olfactory nerve or olfactory-related areas in the central nervous system; with viruses as the most common infectious cause[2,7]. OD is attributed to virally induced atrophy of the olfactory sensory neurons and replacement of olfactory epithelium with respiratory epithelium. Several drugs have been investigated in relation to postviral olfactory dysfunction (PVOD), including systemic corticosteroids, intranasal corticosteroids, sodium citrate, insulin, antibiotics, theophylline, oral antibiotics, vitamins, and antioxidants (vitamin A, zinc sulfate, alpha-lipoic acid), acupuncture, or omega-3[4]. However, olfactory training (OT) remains to have the strongest evidence as appropriate therapy for PVOD[3,8-13]. The main challenge to the investigation of possible therapies is that most studies lack control groups and have limited sample sizes[4]. Due to only a few high-quality studies present, there is room for studies that evaluate adjunct treatments that can furtheer improve outcomes, among PVOD patients.

Omega-3 has been reported to have protective, neuro-regenerative, and anti-inflammatory properties that may be beneficial in olfactory loss in a trial on OD after endoscopic sellar and parasellar tumor resection[3]. The goal of this study was to examine the effect of omega-3 supplementation on olfactory function among PVOD patients. A secondary, exploratory aim was to determine if benefits from supplementation varied between those who had a history of COVID-19 infection and those who did not.

Materials and methods

The prospective study design was approved by the Institutional Review Board (IRB) of TU Dresden and was conducted according to the principles expressed in the Declaration of Helsinki. Possible risks and benefits related to participation in the study were explained to patients during the initial consultation. All participants provided their written informed consent.

Patients

The study included adult patients of at least 18 years of age, who were seen for PVOD at the Smell and Taste Clinic, Department of Otorhinolaryngology at the University Clinic in Dresden. A standardised structured history was taken[14] followed by nasal endoscopy. For this study, results were analysed with specific attention towards age, sex, and duration of symptoms.

PVOD is defined as an olfactory dysfunction that immediately follows an upper respiratory tract infection in the absence of any other etiology[15]. For this study, patients who presented with a history of upper respiratory tract infection accompanied by sudden olfactory loss associated with unremarkable nasal endoscopy and absence of findings related to chronic rhinosinusitis or tumors (e.g., nasal congestion/obstruction, rhinorrhea), those who tested positive for COVID-19, or those who had positive viral antibody tests were considered to have PVOD. Patients with other causes of OD, such as chronic rhinosinusitis, head trauma or idiopathic causes, those with incomplete data, and those who did not follow up after training were excluded.

Patients were randomly assigned to 2 treatment groups: 1) OT only, or 2) OT with omega-3 supplementation.

Olfactory training

OT was done over a period of 12 weeks. Training patients received four brown glass jars with one of four odours in each: phenyl ethyl alcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves). A cotton pad soaked with 2.5 ml of each odourant was placed inside the jars to prevent possible spilling. All jars were labelled with the odour name. Patients were asked to sniff the odours for approximately 30 seconds in the morning and in the evening, making sure that they focused their attention on the training and the odours while doing so.

Omega-3 supplementation

The patients were advised to use omega-3 supplements (Eicosapentaenoic acid + Docosahexaenoic acid, "1400 Omega-3", Doppelherz), 2 capsules, 2 times a day (in the morning and evening), for a total of 2 grams per day, to be taken for 12 weeks. During the follow-up consultation after 12 weeks, patients were asked whether or not they took the omega-3 supplements.

Olfactory testing

Olfactory testing was performed before and after a training period of 12 weeks using the Sniffin' Sticks test kit, which involves tests for odour threshold, discrimination and identification (Burghart Messtechnik, Holms, Germany)[8,16]. Using odour dispensers like felt-tip pens, the odourants were presented at approximately 2 cm in front of both nostrils. For olfactory thresholds, a single-staircase, three-alternative forced-choice method was used. For odour discrimination, the same three-alternative forced choice method was used. For odour identification, participants were asked to identify the odour among a set of 4 verbally labeled pictures. Details of the process of olfactory testing may be read in detail in earlier studies[16-18]. The composite TDI Score was the sum of scores for threshold, discrimination, and identification subtests. Scores can range from 1 to 48 points, with a maximum score of 16 for all 3 subtests. The first test was done during the first consultation at the clinic. The second test was done on follow-up, at least 3 months after the first consultation. Patients were, likewise, asked to give a rough self-rating for their olfactory function on follow up (i.e., worse, better, or same).

Data collection and statistical analysis

Patient records were assigned codes and anonymised. Data were encoded into a Microsoft Excel Office 365 version 2107 database

Table 1. Clinicodemographic data.

Variables		Frequency			Mean (SD)			p-value
		Omega-3	No Omega-3	Total	Omega-3	No Omega-3	Total	
Age (in years)					46.1 (15)	53 (16.5)	49.6 (16)	0.099
Sex	Men Women	16 (55%) 13 (45%)	9 (31%) 20 (69%)	25 (43%) 33 (57%)				0.065
Group		29 (50%)	29 (50%)	58 (100%)				
Omega-3 reliability	Yes No	24 (83%) 5 (17%)						
History of COVID-19	Yes No	18 (62%) 11 (38%)	9 (31%) 20 (69%)	27 (47%) 31 (53%)				0.017
Duration of symptoms (in months)					9.2 (7.2)	13.3 (25.8)	11.3 (18.9)	0.409
Olfactory testing interval (in months)					3 (0.2)	3.2 (0.4)	3.1 (0.3)	0.059

Table 2. Mean scores for threshold, discrimination, identification, and composite TDI.

	Threshold (p = 0.040)		Discrimination (p = 0.871)		Identification (p = 0.666)		Composite TDI Score (p = 0.397)	
	Omega-3	No Omega-3	Omega-3	No Omega-3	Omega-3	No Omega-3	Omega-3	No Omega-3
Pre-training	3.1 (2.2)	2.4 (2.2)	8.9 (3.2)	9.2 (3.3)	9.4 (3.3)	8.4 (3.5)	21.4 (7.6)	20.1 (7.5)
Post-training	4.9 (3.5)*	2.9 (2.5)*	11.1 (3.2)	11 (2.6)	10 (3.2)	10.3 (2.6)	26.1 (8.1)	24.2 (6.2)

*Omega-3 group had significantly higher threshold score after training, compared to olfactory training only.

(Microsoft Corp., Redmond, WA, USA) and checked for accuracy of encoding. Data analysis was done using SPSS ver. 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). Means and proportions were used to describe the study variables.

Multivariate and repeated measures analysis of variance, two-tailed t-test, Pearson's r, and Spearman's rho were computed for the variables, with a p value of <0.05 considered significant. Using G*Power Version 3.1.9.6(19), sample size was calculated with an alpha level of 0.05 and a power of 0.80. Our study aimed for an effect size of 24% based on a previous study on Vitamin A as an adjunct treatment for postinfectious OD[20]. We aimed to enroll 102 patients for this study, with 51 patients per treatment group.

Results

A total of 30 men and 40 women initially participated in the study, with ages ranging from 19 to 83 years old and a mean age of 50 years. Patients who were lost to follow-up with incomplete data for olfactory testing (n = 12) were excluded from the analysis. Fifty-eight patients with OD were randomly assigned to receive OT (n = 29) or OT with omega-3 supplementation (n = 29). Post-hoc power analysis using G*Power Version 3.1.9.6[19] resulted in an effect size of 0.33 with an alpha level of 0.05 in a sample size of 58.

Demographic data are outlined in Table 1. Mean age was 53 and 46 years for the control and treatment groups, respectively. The mean duration of symptoms was 11 months, while the mean olfactory testing interval was 3 months. Twenty-seven patients (47%) had a history of COVID-19 infection. Twenty-four (83%) of the participants from the treatment group took omega-3 supplementation reliably, 5 patients indicated non-reliable intake of omega-3.

Threshold, discrimination, identification, and composite TDI scores generally increased for most patients in both treatment and control groups (Table 2, Figure 1). More patients from the treatment group improved in threshold, discrimination, and composite TDI scores, but not identification (Table 3). It is also worth noting that no patient had a worse composite TDI score classification (from hyposmia to functional anosmia or normosmia to hyposmia/functional anosmia) in both the treatment and control groups after OT.

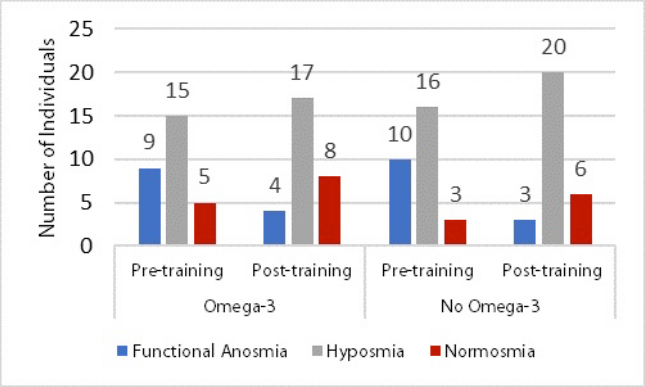

Figure 1. Summary of pre- and post-training olfactory function among omega-3 and no omega-3 groups.

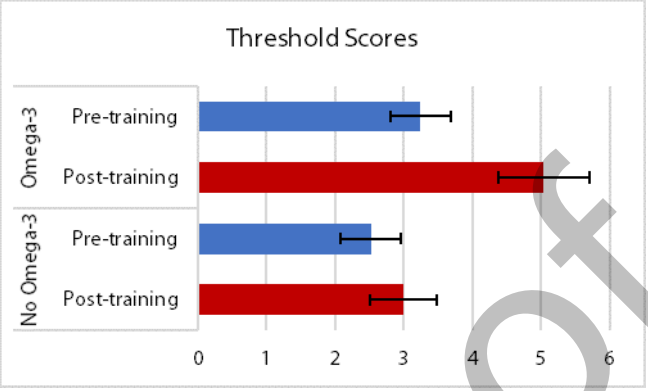

Figure 2. Pre- and post-training odour threshold scores among omega-3 and no omega-3 groups.

There was a significantly higher score difference for threshold subtest among patients in the omega-3 group, $F(1,56) = 6.81$, $p = 0.012$ (Figure 2). When factoring in clinically significant differences in threshold scores based on the cut-offs defined in a study by Gudziol et al.[18], results remained significant, $F(1,56) = 5.93$, $p = 0.018$. Five patients reported unreliable intake of omega-3. On re-analysis of the data, not including these 5 patients, a significantly higher score difference for threshold subtest ($F(1,51) = 4.81$, $p = 0.033$), as well as clinically significant differences in threshold scores ($F(1,51) = 5.09$, $p = 0.028$) were still observed in the omega-3 group. Age, sex, duration of symptoms had no significant effects on measured olfactory function (T, D, I, TDI Scores) between the treatment and control groups.

Three patients from the treatment group experienced diarrhea, constipation, or abdominal pain after a few days of taking omega-3. They discontinued taking omega-3 and were transferred to the control group afterwards. Symptoms improved after discontinuation of the drug and none of the participants required hospitalization.

Discussion

There are very limited studies on the effect of omega-3 supplementation on olfactory loss. If any, the studies available were mostly done on animals and involve peripheral nervous system injury[21,22]. In a study by Figueroa & De Leon[21], they found that long-chain omega-3 polyunsaturated fatty acids were prophylactic against spinal cord injury and improved functional recovery.

Omega-3 polyunsaturated fatty acids (particularly Eicosapentaenoic acid and Docosahexaenoic acid have been found to also regulate inflammatory responses[23]. In humans, varying strength of evidence exists for clinical benefits of omega-3 in certain inflammatory diseases such as: rheumatoid arthritis (strong evidence), asthma and inflammatory bowel disease (weak evidence)[24]. Viral infections of the upper respiratory tract may result in OD through a local inflammatory response that impairs signal transduction at the area of olfactory receptors or the olfactory sensory neurons[23,25]. A study by Yan et al.[3] hypothesised that omega-3 may have benefits through neural regeneration or anti-inflammatory protection on the olfactory mucosa. It is through these neuroprotective effects and increased antioxidant and anti-inflammatory amino acid production that omega-3 may have a potential effect on OD [21].

In our study, only threshold scores increased among patients given omega-3 supplementation. Among patients with PVOD, threshold scores are usually most sensitive to olfactory dysfunction, mainly as discrimination and identification subtests are both suprathreshold tests[16]. In addition, threshold scores also appear to reflect the condition of the peripheral olfactory system relatively better than odour identification or odour discrimination and may confirm the effects of omega-3 on the peripheral nervous system. However, the exact site and mechanism of this observed improvement, whether it is from neuroprotection or anti-inflammation, is unclear.

Although the number of patients with history of COVID-19 is significantly different among the treatment and control groups, we noted a tendency for an increase in threshold scores in this subset of patients, which did not reach the level of statistical significance, $F(1,54) = 3.85$, $p = 0.055$.

The rate of spontaneous recovery after PVOD remains varied and unclear. Published reports likely exclude those who have transient smell loss, capturing only those who present with smell loss for longer than a couple of weeks[26,27]. Hendriks[28] reported a spontaneous recovery rate of 35% (n = 9) over a period of 12 months, based on a sample of 26 individuals reported in literature from 1870-1977. Duncan & Seiden[29] found 90% (n = 19) of patients with higher UPSIT scores after a mean follow-up of 37 months. Reden et al.[30] found one-third (32%) of 262 patients

Table 3. Summary of changes in threshold, discrimination, identification, and composite TDI scores.

	Threshold[a] (p = 0.028)		Discrimination[b] (p = 0.605)		Identification[b] (p = 0.396)		Composite TDI[c] (p = 0.421)	
	Omega-3	No Omega-3	Omega-3	No Omega-3	Omega-3	No Omega-3	Omega-3	No Omega-3
Worse	0 (0%)	1 (3.4%)	1 (3.4%)	0 (0%)	2 (6.9%)	1 (3.4%)	0 (0%)	0 (0%)
Same	19 (65.5%)	25 (86.2%)	14 (48.3%)	17 (58.6%)	20 (69%)	18 (62.1%)	17 (58.6%)	20 (69%)
Better	10 (34.5%)	3 (10.3%)	14 (48.3%)	12 (41.4%)	7 (24.1%)	10 (34.5%)	12 (41.4%)	9 (31%)

Scores were classified as "worse" or "better" when changes were greater or equal to the following: [a] 2.5 points, [b] 3 points, [c] 5.5 points [22].

to improve over 1 year. Rombaux et al.[31] found 26% (n = 7) of patients improve over a period of approximately 9 months. Most studies have small sample sizes, assessing olfactory change for a short period, using varying testing procedures[27]. Given that spontaneous recovery may occur in as much as 1/3 of postviral patients, and our sample was only observed for a short term, we are unsure as to what degree this may have influenced our results.

Limitations to the study include the relatively low sample size, lack of placebo control group, and the short follow up period at 3 months. Considering the exploratory analyses between COVID-19 and non-COVID-19, it is also important to mention the baseline significant difference between the 2 groups in terms of sample size (treatment, corona: n = 18, control, corona: n = 9). This baseline difference may have contributed to the result with only a tendency for increased threshold scores in the treatment group. Future double blind randomised controlled trials may explore a larger sample size, a placebo control group, longer follow up, longer duration of treatment with omega-3, and improved randomization to account for history of COVID-19 infection as a variable.

Conclusion

A significant increase in odour threshold scores was observed among PVOD patients in the treatment group. Omega-3 supplementation may be a possible option as adjunct treatment with OT for patients with PVOD.

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None.

Authorship contribution

AKH[#]: data analysis, writing, review and editing; DW[#]: conceptualization, data collection, review and editing. AH: conceptualization, supervision, review and editing. TH: conceptualization, supervision, writing, review and editing.

[#] AKH and DW contributed equally and both should be written as first authors

Conflict of interest

The authors do not have any conflict of interest to declare.

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Anna Kristina Hernandez
Smell & Taste Clinic
Department of Otorhinolaryngology
TU Dresden
Dresden
Germany

Tel: +49 351 458 4189
Fax: +49 351 458 4326
E-mail:
akmhernandezmd@gmail.com